Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia

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ABSTRACT

Background: Neurophysiologic studies on human and nonhuman primates implicate an orbitofrontal-insular-striatal circuit in high-level regulation of feeding. However, the role of these areas in determining feeding disturbances in neurologic patients remains uncertain.

Objective and Methods: To determine brain structures critical for control of eating behavior, we performed a prospective, laboratory-based, free-feeding study of 18 healthy control subjects and 32 patients with neurodegenerative disease. MR voxel-based morphometry (VBM) was used to identify regions of significant atrophy in patients who overate compared with those who did not.

Results: Despite normal taste recognition, 6 of 32 patients compulsively binged, consuming large quantities of food after reporting appropriate satiety. All six patients who overate were clinically diagnosed with frontotemporal dementia (FTD), a disorder previously associated with disordered eating, while the nonovereaters were diagnosed with FTD, semantic dementia, progressive aphasia, progressive supranuclear palsy, and Alzheimer disease. VBM revealed that binge-eating patients had significantly greater atrophy in the right ventral insula, striatum, and orbitofrontal cortex.

Conclusion: Binge eating can occur despite reported satiety and is associated with damage to a right-sided orbitofrontal-insular-striatal circuit in humans. These findings support a model in which ventral insular and orbitofrontal cortices serve as higher-order gustatory regions and cooperate with the striatum to guide appropriate feeding responses. *Neurology*® 2007;69:1424–1433

GLOSSARY

AD = Alzheimer disease; **FTD** = frontotemporal dementia; **GCRC** = General Clinical Research Center; **MMSE** = Mini-Mental State Examination; **OFC** = orbitofrontal cortex; **PA** = progressive aphasia; **PSP** = progressive supranuclear palsy; **ROI** = region of interest; **SemD** = semantic dementia; **VBM** = voxel-based morphometry.

Many studies implicate orbitofrontal-insular-striatal circuits in the regulation of feeding and satiety. However, studies in patients with damage to these brain areas are needed to determine which areas are critical for regulation of human feeding behavior. Single case studies have suggested that lesions to ventromedial hypothalamus, third ventricular region, and frontotemporal cortical sites (particularly on the right) may lead to abnormal feeding behavior.[1,2] Psychiatric diseases with prominent eating abnormalities, such as obsessive compulsive disorder and bulimia, have also been associated with orbitofrontostriatal circuit dysfunction, with a suggestion of right laterality.[3,4] However, previous case studies have lacked the power to precisely localize critical brain regions for normal feeding and have relied on subjectively reported clinical histories and questionnaires for quantification of eating behavior.

Frontotemporal dementia (FTD) is a neurodegenerative disorder defined by progres-

Supplemental data at www.neurology.org

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From the University of California at San Francisco.

Supported by grant no. UL1 RR024131-01 from the National Center for Research Resources, a component of the NIH, and NIH Roadmap for Medical Research and by the following grants: NIH/NIA P01-AG019724, P50-AG03006 AD Research Center, M01-RR0079 General Clinical Research Center; DHS 03-75271 (Miller, Johnson); and National Institute of Neurological Disorders and Stroke R01-AG22985 and DHS 04-35516 (Gorno-Tempini).

Disclosure: The authors report no conflicts of interest.

The content of the paper is the responsibility of the authors and does not necessarily represent the official view of the National Center for Research Resources or NIH.

sive behavioral abnormalities, and gray matter atrophy is commonly seen in frontal, insular, and temporal cortices.[5] Anecdotal and questionnaire-based studies indicate that FTD causes striking abnormalities in eating behavior, including early changes in appetite, food preference, eating habits, and other oral behaviors.[6-8] Given the prominent alterations in eating and the characteristic pattern of atrophy, patients with FTD provide a unique opportunity to investigate the neural substrates of human feeding and food choice.

Here we report a laboratory-based, controlled, prospective study of eating behavior in patients with neurodegenerative disease. Our results demonstrate that "gluttonous" overeating is associated with right insular, orbitofrontal, and striatal atrophy and suggest that these structures are necessary for normal control of eating behavior.

METHODS

Feeding procedure. Patients and control subjects were recruited from the University of California, San Francisco, Memory and Aging Center, a tertiary dementia clinic and research program. Clinical diagnosis in both patients and controls was determined after a detailed clinical history, neurologic examination, a 1-hour neuropsychological battery,[9] laboratory screening, and 1.5 T brain MRI. Only cases with a consensus diagnosis of a neurologist, a neuropsychologist, and a nurse were included in the current study. Patients diagnosed with FTD, semantic dementia (SemD), and progressive aphasia (PA) met Neary criteria,[10] and patients with Alzheimer disease (AD) met AD probable National Institute of Neurological and Communication Disorders/Alzheimer's Disease and Related Disorders Association criteria.[11] All patients required a reliable caregiver to be in the study. Exclusion criteria for the feeding protocol included symptomatic ageusia, anosmia, severe swallowing deficits, or relevant food allergies. Exclusion criteria for research evaluation included a previous history of Korsakoff encephalopathy, alcohol abuse or dependence (within 5 years of onset of dementia), substance abuse, head trauma (with loss of consciousness greater than 30 minutes), brain tumor, multiple sclerosis, epilepsy, Parkinson disease, communicating or noncommunicating hydrocephalus, schizophrenia, bipolar affective disorder, intracerebral hemorrhage, B12 deficiency, hypothyroidism, HIV, renal failure, liver failure, and respiratory failure (requiring oxygen). Likewise, dementia due to other than frontotemporal lobar dementia, corticobasal dementia, or AD, extra-axial brain tumor (with visible compression of the brain parenchyma), cerebral infarct, large confluent white matter lesions, and significant systemic medical illnesses such as deteriorating cardiovascular disease excluded participation. Subjects taking benzodiazepines, amitriptyline, doxepin, lithium, first-generation neuroleptics, narcotics, anticonvulsants (outside of therapeutic ranges), and antihistamines were also ineligible.

All patients received in-patient care at the University of California, San Francisco, General Clinical Research Center (GCRC) for 4 to 5 days; during this time, the patients' cognitively normal caregivers also stayed at the GCRC. While at the GCRC, patients received extensive cognitive and behavioral testing along with a structural MRI. Neurodegenerative patients (13 FTD, 4 SemD, 11 AD, 3 PA, and 1 progressive supranuclear palsy [PSP]) and their caregivers (n = 18) were studied in the following paradigm. During the course of their stay in the GCRC, two successive lunches were manipulated to investigate the subjects' sensitivity to variety. Subjects refrained from eating for at least 2 hours prior to the lunch. At one lunch, subjects were allowed to pick their favorite type of sandwich among seven different types of sandwiches (variety condition). The subjects were given as many of their favorite type of sandwich as they wished until either they were full or 1 hour had passed. At a second lunch, subjects were given access to all seven types of sandwiches and were allowed to eat as much as they chose (nonvariety condition). A constant volume of food (seven quarter sandwiches) was maintained in front of the subject for the entire hour at both lunches. We continued to bring sandwiches to the subjects, irrespective of their requests, until 1 hour had elapsed. If the subject said that they were finished, we informed them they could stop at any time but that the food would be kept in the room for testing purposes. The sandwiches were Nutella and banana, jelly, tomato and mayonnaise, turkey and lettuce, roast beef and mustard, cream cheese, and cheddar cheese. They were made with identical bread and cut into quarters but were not matched for energy content. While the lunches were labeled "variety" and "nonvariety," their temporal order was randomized to prevent order effects. Height, weight, and waist to hip ratio were also measured.

All subjects underwent a separate taste test during which they were required to taste and name the sandwiches to assess for gross taste or memory deficits. Similarly, subjects ranked basic taste solutions: salt (0.032 M, 0.1 M, 0.32 M, 1 M), sugar (0.032 M, 0.1 M, 0.32 M, 1 M), quinine (0.000032 M, 0.0001 M, 0.00032 M, 0.001 M), and sour (0.001 M, 0.0032 M, 0.01 M, 0.032 M) on intensity and palatability to determine whether they had normal taste sensitivity.

Neuropsychological testing. All patients underwent detailed, standardized cognitive and behavioral testing as a part of their assessment. The Clinical Dementia Rating Scale was completed for each patient based on an interview with their primary caregiver-informant. Face-to-face neuropsychological testing included the Mini-Mental State Examination (MMSE), an abbreviated form of the Boston Naming Test that included 15 of the 60 items (a format which has been verified to be a psychometrically valid equivalent to the full form)[12]; the Trail Making test, Color-Word Interference Test, and FAS verbal fluency test from the Delis-Kaplan Executive Function Scale; the Wechsler Adult Intelligence Scale, 3rd ed., Block Design and Digit Span Tests; the Wechsler Memory Scale, 3rd ed., Visual Reproductions I and II; and the California Verbal Learning Test, Mental Status Edition. Differences between overeaters and nonovereaters were analyzed using PROC TTEST in the SAS statistical package (Cary, NC).

Table 1 Anatomical coordinates for areas of atrophy

	x, y, z (mm)	Voxel number	T value	Z value
Right ventral insula	43, 1, −7	907	6.03	5.38
	40, 13, −13		5.63	5.09
Right striatum	16, 18, 3	1,734	5.86	5.26
	26, 15, 6		5.39	4.91
	18, 9, 11		5.14	4.72
Rt. anterior orbitofrontal cortex	19, 65, −18	435	5.17	4.74
	26, 65, −12		4.89	4.52

MRI scanning. Twenty-seven of the 32 patients in the current study received an MRI scan of sufficient quality for analysis within 3 months of testing. MRI scans of the 27 patients and 47 control subjects were obtained on a 1.5 T Magnetom VISION system (Siemens, Iselin, NJ) equipped with a standard quadrature head coil. The control subjects did not participate in the eating paradigm. Structural MRI sequences included a volumetric magnetization prepared rapid gradient echo MRI (repetition time/echo time/inversion time = 10/4/300 milliseconds) to obtain T1-weighted images of the entire brain, 15° flip angle, coronal orientation perpendicular to the double spin echo sequence, 1.0 × 1.0 mm^2 in-plane resolution, and 1.5-mm slab thickness. These images were used for the voxel-based morphometry (VBM) analysis.

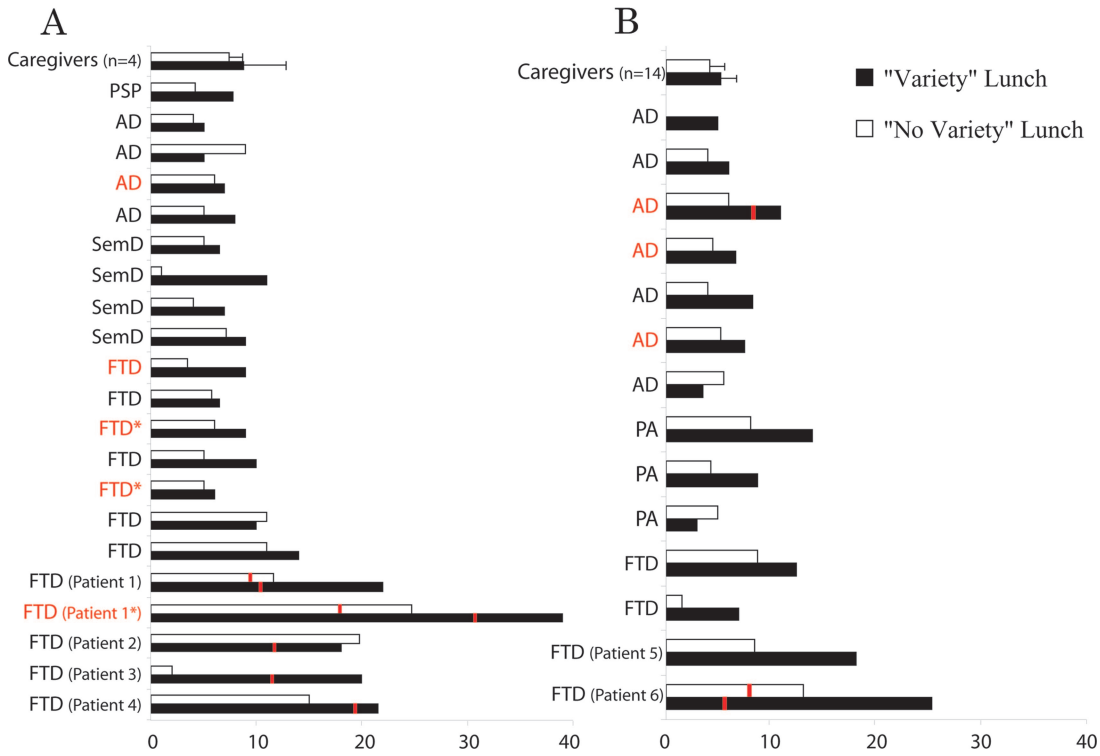
VBM. VBM is a technique for the detection of regional brain atrophy by voxel-wise comparison of gray matter volumes between groups of subjects.[13,14] The technique comprises an image preprocessing step (spatial normalization, segmentation, modulation, and smoothing) followed by statistical analysis. Both stages were implemented in the SPM2 software package (www.fil.ion.ucl.ac.uk/spm) using standard procedures.[14] Spatially normalized, segmented, and modulated gray matter images were then spatially smoothed with a 12-mm full width at half-maximum isotropic Gaussian kernel. This step allowed intersubject anatomic comparison and application of the theory of Gaussian fields. Six overeaters' scans were compared with 21 nonovereating patients and 47 age-matched control subjects. Age, total intracranial volume, and gender were entered into the design matrix as nuisance variables. Regionally specific differences in gray matter volumes were assessed using the general linear model and the significance of each effect was determined by using the theory of Gaussian fields. To identify areas that are more atrophied in overeaters compared with controls and nonovereaters, we performed the following contrast: Overeaters (as established by the behavioral feeding study) vs controls inclusively masked with overeaters vs nonovereaters. This inclusive masking procedure serves to identify voxels that are significant in both contrasts of overeaters against controls and overeaters against nonovereating patients. Consequently, only a single set of comparative statistics are reported in table 1. Blinded to the results of the current study, we used the Wake Forest University Pick atlas to define one a priori region of interest (ROI) including the entire insular, frontal and temporal-polar cortices (posteriorly limited by the uncinate fasciculus and defined by the temporal pole mask from the Anatomical Automatic Labeling atlas) as well as the basal ganglia bilaterally. This ROI was chosen because these brain regions are affected in FTD[5] as well as being implicated in taste,[15-17] hunger,[18] and taste-reward modulation.[19,20] We accepted a level of significance of $p < 0.05$ corrected for multiple comparisons within this ROI.

RESULTS Feeding behavior and biometrics. Of the 32 patients investigated, 6 (of 13) patients with FTD (4 men and 2 women) each consumed enough sandwiches during the variety lunch to be at least 1.5 SD above the mean consumption for all subjects (greater than 17.5 quarter sandwiches for men and 14 quarter sandwiches for women). These six overeating patients showed a greater preference for the sweet jelly sandwich (33.0 ± 22.1%) than non-FTD patients (9.2 ± 15.6%, $p < 0.01$), nonovereating patients with FTD (11.5 ± 17.3%, $p < 0.1$), or caregivers (3.3 ± 7.0%, $p < 0.0001$). Age was not different between the overeaters (60.8 ± 4.6), nonovereaters (59.2 ± 10.0), and caregivers (57.2 ± 8.1). Five of the six overeating patients spontaneously reported "fullness" to the experimenter after consuming a quantity of sandwiches similar to, or slightly more than, the other subjects. However, the overeating patients continued to consume sandwiches (figure 1, red bars). For example, one female patient with FTD (Patient 6) ate five more sandwiches after reporting fullness while the other overeating patients made comments such as, "You don't need to bring anymore," "I really am finished," "Don't bring anymore, please." In response to such comments, it was explained that the subject was not required to continue eating and could stop at any time. Surprisingly, the six overeating patients were not more obese than other subjects (see figure E-1 on the *Neurology*® Web site at www.neurology.org). The overeating patients showed no impairment in sandwich naming and recognition, and all patients accurately ranked taste solutions based on intensity.

One of the overeating (Patient 1) and two of the nonovereating patients with FTD returned after 1 year and were restudied using the same paradigm. Patient 1 showed identical behavioral patterns to the previous year, despite remembering the experimenters and test procedures. He persistently reported being "full" but continued to consume sandwiches; remarkably, he did not gain weight during the intervening year (figure E-1). The other returning patients consumed approximately the same amount of food as recorded in the previous year.

Representative case history. Patient 6 was a 61-year-old right-handed woman with a 1.5-year history of insidious behavioral changes. She had

Figure 1 Number of sandwiches consumed during lunches with and without variety is shown for men (A) and women (B)



Some patients with frontal variant frontotemporal dementia (FTD) show compulsive overeating. Total number of quarter sandwiches is shown on the *x*-axis and subjects are arranged on the *y*-axis by diagnosis. Red lines indicate a spontaneous claim of fullness with placement on the *x*-axis indicative of how many sandwiches had already been consumed at that time point. Subjects were never asked if they were full or if they wanted more food. Subjects labeled by patient number refer to FTD patients described in the text. *Second visit for that subject after a 1-year interval. Subject labels in red denote individuals who were excluded from the imaging analysis due to lack of an appropriate scan or a second visit. "Caregivers" are cognitively normal caregivers of patients with dementia. Their consumption data are presented as a mean. Error bars signify SD. SemD = semantic dementia (otherwise known as temporal variant fronto-temporal dementia); AD = Alzheimer disease; PSP = progressive supranuclear palsy.

gone to an elite university where she majored in English, receiving excellent grades. She then worked as an editor for several years until the birth of her first child, after which she did not work outside the home.

Initially, her daughters noticed that she called them less frequently and was less interested in their lives. She became less social, often sitting alone at family gatherings. Apathy ensued, and she lost interest in crossword puzzles, instead spending her days smoking and watching television. Eight months prior to evaluation, while driving to a wedding, she took a detour along the coast. She ran out of gas three times and called roadside assistance on each occasion. That night she stayed in a hotel but left without paying. Eventually, her family filed a missing persons report and the police found her driving around a small town with a hitchhiker she had picked up. At the wedding, she ate with her hands and spoke openly with guests about her marital problems. She showed no regret and no understanding of the distress her behavior was causing her family. She also developed sexual disinhibition.

While she had never been neat, her room became highly disordered and she lost interest in personal hygiene, seldom bathing and wearing dirty clothes with burn holes. She urinated in a cup by her bed instead of walking to the bathroom at night. She developed a "sweet tooth" and ate quickly, often spilling her food. On several occasions, she stole food from stores, mostly candy. She gained 30 lbs and developed type 2 diabetes and hyperlipidemia. From typically smoking two to three cigarettes per day, over the course of 1 year her interest in smoking dramatically increased. Similarly, she opened many cans of Diet Coke throughout the day but would only drink part of each one. The patient and her family noted no specific neuropsychological deficit.

Past medical history was unremarkable and there was no family history of dementia. On examination, her speech was fluent, without word-finding pauses or paraphasic errors, but lacked spontaneity. She had little insight into her disease, although she did endorse decreased inhibitions,

Table 2 Cognitive and functional neuropsychological scores of overeaters vs nonovereaters

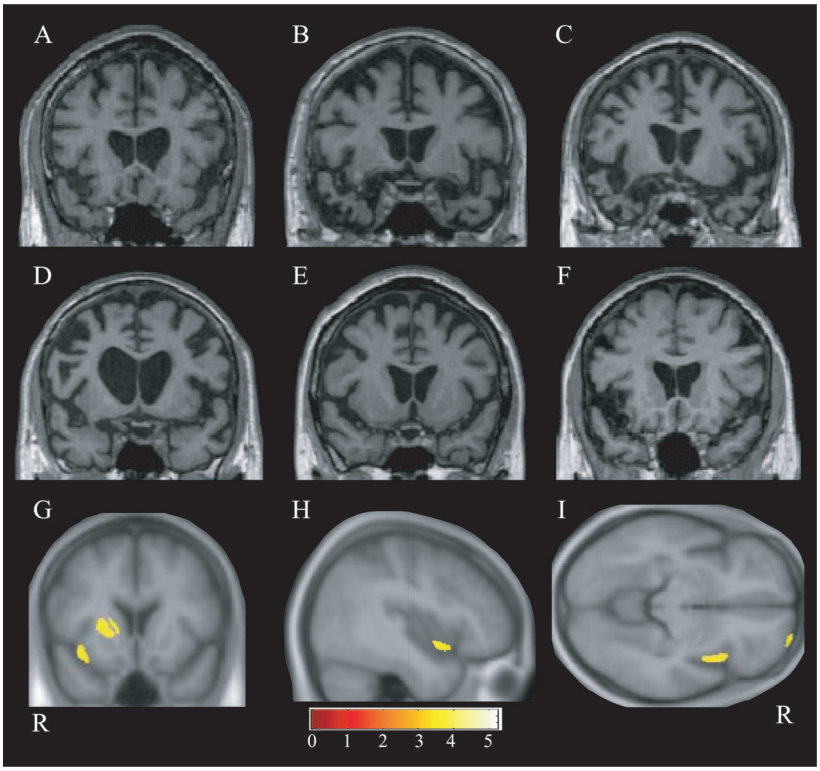
Test (max possible score)	Overeaters, n = 6 Score, mean (SD)	Nonovereaters n = 26 Score, mean (SD)	*T* value	*p* Value
MMSE (30)	22.3 (4.2)	21.1 (7.3)	0.38	NS
Clinical Dementia Rating				
Total score (3.0)	1.6 (0.7)	1.0 (0.6)	218	0.0365
Total of box scores (18)	9.7 (3.0)	5.5 (3.2)	2.93	0.0060
Abbrev. Boston Naming Test (15)	8.8 (5.6)	10.4 (5.1)	0.64	NS
D-KEFS FAS	7.6 (5.0)	5.0 (3.4)	1.48	NS
WAIS-III Block Design	5.4 (3.8)	6.3 (3.4)	0.54	NS
WMS-III Visual Reproductions				
Immediate Delay I	4.8 (4.5)	5.4 (3.6)	0.34	NS
Long Delay II	5.6 (1.9)	7.4 (3.8)	1.01	NS
CVLT-MS 10′ Free Recall (9)	1.0 (1.4)	2.9 (3.1)	1.31	NS
WAIS-III Digit Span	8.6 (2.9)	7.9 (3.4)	0.39	NS
D-KEFS Design Fluency Filled Dots	7.6 (4.8)	7.0 (3.1)	0.39	NS
D-KEFS Trail Making Number-Letter	3.8 (3.8)	4.4 (4.1)	0.28	NS
D-KEFS Color-Word Interference	6.5 (6.4)	3.9 (3.6)	1.11	NS
NPI				
Delusions	0.7 (1.6)	0.1 (0.4)	1.66	NS
Hallucinations	0.7 (1.6)	0.1 (0.4)	1.52	NS
Agitation	3.3 (4.1)	2.1 (2.6)	0.96	NS
Anxiety	2.2 (3.7)	2.4 (3.1)	0.13	NS
Depression	2.0 (4.9)	1.6 (2.9)	0.24	NS
Euphoria	3.3 (3.0)	0.6 (1.1)	3.98	0.0004
Apathy	9.3 (3.2)	4.2 (4.1)	2.85	0.0076
Disinhibition	9.7 (2.7)	3.7 (4.7)	2.95	0.0061
Irritability	2.3 (4.8)	2.3 (2.7)	0.03	NS
Aberrant motor	7.3 (3.9)	1.8 (3.2)	3.65	0.0009
Aberrant sleep	5.0 (3.0)	1.4 (2.7)	2.92	0.0064
Aberrant eating	8.0 (3.6)	3.9 (4.0)	2.29	0.0285
Total NPI score	53.8 (19.7)	23.9 (18.5)	3.55	0.0012

Scores are reported as scaled scores except where max possible score is noted, in which case raw scores are reported.
CVLT-MS = California Verbal Learning Test, Mental Status Edition; D-KEFS = Delis-Kaplan Executive Function Scale; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; WAIS = Wechsler Adult Intelligence Scale.

stating that she often "blurted things out." Her affect was flat, but she described her mood as "fabulous" and stated "I never ever feel depressed or sad" and "if this is a disease, it's the one to get." Her MMSE score was 30 of 30. Her general physical and neurologic examinations were normal. Detailed case histories for the other five overeating FTD patients are provided as supplementary material at www.neurology.org.

Neuropsychological and functional correlates of abnormal eating. A general linear model (proc GLM) in the SAS statistical program (Cary, IN) was used to compare overeaters with nonovereaters on a number of cognitive, functional, and behavioral neuropsychological measures. The overeating FTD patients did not differ significantly from nonovereating patients with dementia on any cognitive variables including tests in the domains of language, visuospatial skills, verbal and nonverbal memory, attention, and executive functioning (table 2). The overeating FTD patients did have significantly worse functional and behavioral impairment as rated by the Clinical Dementia Rating Scale total and box scores as well as the neuropsychiatric inventory including the euphoria,

Figure 2 Structural MRI coronal sections of overeating patients and VBM



The overeating patients with frontotemporal dementia (FTD) have significantly more atrophy in the right ventral insula, striatum, and anterior orbitofrontal cortex (OFC). (A through F) Comparable structural MRI coronal sections obtained from the six overeating patients (Patients 1 through 6) are presented in native space. (G through I) Voxel-based morphometry (VBM) on high-resolution T1-weighted MR images was used to identify brain regions that showed significantly greater voxel-wise volume loss in the 6 overeating patients with FTD compared with 21 nonovereating patients with dementia and 47 control subjects. We defined an a priori region of interest including the insular, frontal, and temporal cortices as well as the basal ganglia bilaterally. The right inferior insula, striatum, and anterior OFC of overeating patients were significantly atrophied compared with controls and nonovereating patients ($p < 0.05$ corrected for multiple comparisons in the region of interest). Areas of significant atrophy are displayed on coronal (G), sagittal (H), and axial (I) sections of the mean of all subjects' brains and thresholded at $p < 0.05$ corrected for multiple comparisons (coordinates: $x = 41$, $y = 12$, $z = -13$).

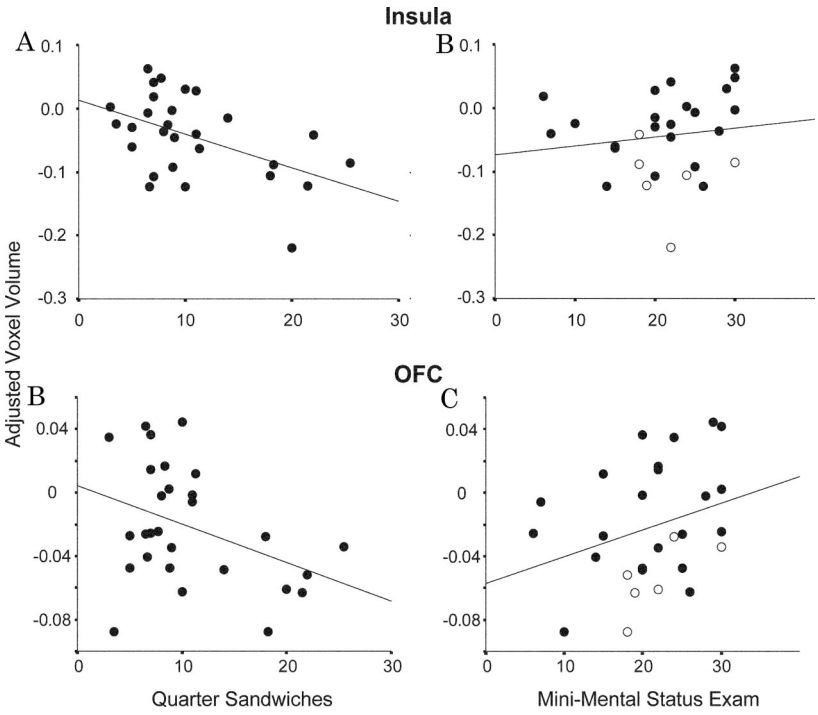
apathy, disinhibition, aberrant motor, aberrant sleep, and aberrant eating behavior subscales.

Anatomic correlates of abnormal eating. Using VBM, we identified brain regions that showed greater atrophy in the six overeating patients when compared with controls and to nonovereating patients. The right ventral insula (including the anterior portion), the right striatum, and the right rostral orbitofrontal cortex (OFC) were more atrophied in overeaters than nonovereaters and controls ($p < 0.05$ corrected for multiple comparisons within the ROI) (table 1; figure 2). In addition to these group effects, the number of sandwiches consumed was correlated with atrophy of the right ventral anterior insula ($R^2 = 0.24$, $p < 0.01$) and OFC ($R^2 = 0.15$, $p < 0.05$) (figure 3, A and C) but not Clinical Dementia Rating box score ($R^2 = 0.08$). Atrophy in these regions did not, however, correlate with the MMSE (figure 3, B and D).

DISCUSSION Using a prospective, experimental feeding paradigm, we identified six patients who compulsively overate in spite of reported satiety. These patients showed normal primary taste processing and reported appropriate fullness, yet continued to eat long after consuming food quantities that prompted other subjects to stop. On tests of language, memory, and executive function, the overeating patients were no more impaired than patients who did not overeat. Anatomically, what differentiated these subjects from nonovereating patients was atrophy in the right ventral insular cortex, striatum, and rostral OFC. Furthermore, atrophy within the right ventral anterior insula and OFC correlated with the amount of food consumed. The findings suggest that damage to a right orbitofrontal-insular-striatal circuit is associated with overeating behavior in humans and support the hypothesis that these regions integrate internal satiety signals with environmental food cues to produce adaptive eating behavior.

Case reports of patients with focal brain lesions and eating disorders have suggested that disruption of right-sided frontal, temporal, and insular cortices is associated with development of eating abnormalities,[1] but these associations have remained anatomically unrefined. Similarly, in Gourmand syndrome, a benign eating disorder characterized by behavioral symptoms similar to those of FTD, preoccupation with food and a preference for fine dining are associated with unilateral lesions of right anterior cortico-limbic regions including the insula.[2] One study correlating eating disturbances quantified by questionnaire with patterns of brain atrophy found that development of a "sweet tooth" was associated with damage to the right anterior insula and the bilateral posterior OFC.[21] Functional imaging studies of healthy subjects also suggest a right lateralization of food-related processing in humans. For example, more taste-related activations are found in the right than left insula[15] and olfactory[22] and flavor[23] processing occurs predominantly in the right hemisphere including the right OFC. Thus, our finding that the right ventral insula, striatum, and OFC are critical for the control of feeding behavior converges with previous lesion and functional imaging experiments (for review see ref. [24]). Furthermore, a wealth of animal studies have implicated the striatum[25] and OFC[19] in feeding behavior. The existence of parallel cortical

Figure 3 Atrophy of the right anterior, ventral insula, and the orbitofrontal cortex (OFC) correlates with the quantity of sandwiches consumed but not with Mini-Mental State Examinations (MMSE)



Voxel volumes within the right anterior, ventral insula ($x = 43$, $y = 1$, $z = -7$) and the right OFC ($x = 19$, $y = 65$, $z = -18$) are plotted against the number of sandwiches consumed during the variety lunch (A and C) and the MMSE scores (B and D). Filled circles denote non-overeating patients and open circles denote overeating patients. Correlations between voxel volumes and number of sandwiches consumed were significant for the right anterior, ventral insula ($p > 0.01$), and the right OFC ($p > 0.05$), while there were no significant correlations between voxel volumes and MMSE in either brain area.

feedback loops passing through the striatum may allow functionally distinct corticostriatal circuits to activate one another and pair reward determination with goal directed action (for review see ref. [26]). Damage to the striatum could impair integration of these functions, leading some FTD patients to eat despite awareness of satiety signals. Supporting this view, lesions of the dorsomedial striatum often render otherwise goal-directed actions habitual.[26] Finally, right striatal dysfunction is a consistent finding in patients with obsessive compulsive disorder,[3] suggesting that striatal atrophy may partly explain the compulsiveness of overeating in FTD.

Previous neurophysiologic studies provide clues to how the orbitofrontal-insular-striatal network may regulate feeding behavior. The ventral insula is homologous to a secondary gustatory cortex[15] assigned to the caudolateral OFC of nonhuman primates.[19,27,28] This area has taste responsive neurons that are sensitive to reward and satiety manipulations in monkeys[19,29] and shows taste-induced activations on the right side in some,[30,31] but not all,[32,33] human fMRI experiments (for review see ref. [15]). While more posterior insular regions track taste intensity irrespective of preference, caudolateral OFC/anterior insular activations are coupled to dynamic changes in food's palatability[34-36] and track preference irrespective of intensity.[37] Furthermore, the ventral insula is crucial in linking sensation with visceromotor output.[38] In particular, it is part of both the "orbital" network that integrates input from different sensory modalities[19,20,39] and the "medial" network that provides the major cortical output to the visceromotor structures in the hypothalamus and brainstem.[27] More anterior regions within the OFC contain neurons that respond to multimodal stimuli (taste, smell, vision, texture, and temperature), rapidly reverse in visual discrimination learning, and often respond to food only if the animal is hungry.[19,40,41] These properties have led to the proposal that the rostral OFC is critical for the integration of multimodal information with visceral homeostatic information to guide eating behavior.[19] Taken together, our lesion study and previous physiologic findings suggest that a right orbitofrontal-insular-striatal circuit integrates highly processed sensory and motivational information regarding food. The increased consumption of our six overeating patients may be explained by disruption of this integrative system, leading to inflexible, stimulus-driven feeding behavior.

Satiety is not sufficient to suppress eating. This fact was illustrated by our overeating FTD patients, who continued to eat despite claiming to be full. This striking dissociation may relate to sparing of more dorsal and posterior parts of the insula. Gustatory information maps specifically to the dorsal anterior insula (i.e., primary gustatory cortex),[24,42,43] while gastrointestinal, cardiovascular, and respiratory afferents project to the dorsal insula in an anterior to posterior topography. All homeostatic afferent information (i.e., pain, temperature, itch, visceral sensation, and sensual touch) is topographically relayed to the dorsal posterior insula through a pathway that is well developed in humans, less well developed in nonhuman primates, and absent in nonprimate mammals.[24] These orderly representations of the body's physiologic state make up the "primary interoceptive cortex,"[24,42] and it may be that relative sparing of this system allowed for preserved food-relevant primary sensations in our overeating patients. The fact that the overeating patients were not more obese is surprising given their robust feeding phenotype. Compensatory mechanisms

such as hyperactivity or altered resting metabolic efficiency might explain this finding. Alternatively, these patients may not grossly overeat at home owing to their caregivers' control of their access to food. Further study of compensatory mechanisms may provide insight into normal factors affecting the development of obesity.

Impaired serotonin function has been implicated in the pathogenesis of depression, anxiety, obsessive compulsive and eating disorders,[44,45] as well as disorders of aggression.[46] Decreases in serotonin receptors[47-49] and serotonergic innervation from the nucleus Raphe dorsalis[50] have been described in FTD, and selective serotonin reuptake inhibitors have shown some efficacy in treating the behavioral symptoms found in FTD[51,52] (but see ref. 53). Similarly, in vivo quantification of 5-HT_{2A} receptor density in FTD using a selective ligand and PET found decreased receptor binding in the orbitofrontal, frontal medial, and cingulate cortices.[54] Previous questionnaire data suggest that FTD patients exhibit carbohydrate cravings,[55] thought by some to reflect low serotoninergic tone.[48,55] In a controlled environment, FTD patients in the current study preferred sweet jelly sandwiches over all others, suggesting carbohydrate craving is not a mere consequence of the ubiquity of such snacks in the home setting. Inhibition of serotonin receptors or depletion of serotonin levels can lead to increased consumption as well as increased preference for carbohydrates[56] and transgenic mice lacking 5-HT_{2c} receptors exhibit chronically elevated food intake and obesity.[57,58] Though not addressed specifically by our study, serotoninergic deficits in FTD may be reflected in a consistent preference for carbohydrates.

In summary, the ventral anterior insula and OFC are considered higher-order "interoceptive cortices" where context, motivational state, and previously learned associations can be integrated to guide a choice of action (or inaction). We have shown that disruption of a right orbitofrontal-insular-striatal circuit leads to stereotyped, pre-potent responses to food stimuli. Patients with atrophy of this circuit continue to perceive satiety but fail to translate satiety signals into appropriate action plans. The results suggest that a right orbitofrontal-insular-striatal circuit ties information about the taste of consumed food to satiety and counterbalances environmental and internal cues that promote eating. Controlled behavioral and anatomic studies in patients with neurodegenerative disease offer a new window into the neurobiology of eating and other drive-related behaviors.

Received January 13, 2007. Accepted in final form April 23, 2007.

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