Citation

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The handle http://hdl.handle.net/1887/54684 holds various files of this Leiden University dissertation

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Title: Obesity and type 2 diabetes : cardiovascular and cerebral aspects
Issue Date: 2017-09-05

Chapter 8

Increased amygdalar and hippocampal volumes in elderly obese individuals with or at risk of cardiovascular disease

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ABSTRACT

Background

The basal ganglia, hippocampus, and thalamus are involved in the regulation of human feeding behavior. Recent studies have shown that obesity [body mass index (BMI; in kg/m^2) > 30] is associated with loss of gray and white matter. It is unknown whether the subcortical brain structures that are actually involved in feeding behavior also show volume changes in obesity. Therefore, the purpose of this study was to evaluate the volumes of the basal ganglia, hippocampus, and thalamus in obesity.

Methods

Three-dimensional T1-weighted magnetic resonance imaging scans of the brain were analyzed by using automatic segmentation to measure volumes of the nucleus accumbens, globus pallidus, amygdala, putamen, caudate nucleus, thalamus, and hippocampus in 471 subjects (mean age: 74.4 y; 56% men).

Results

Obese subjects had larger left ($P = 0.013$) and right ($P = 0.003$) amygdalar volumes and a larger left hippocampal volume ($P = 0.040$) than did normal-weight subjects (BMI < 25). None of the other subcortical structures differed in size between these groups. After correction for age, sex, smoking, hypertension, and pravastatin use, BMI was associated with left ($\beta = 0.175$, $P = 0.001$) and right ($\beta = 0.157$, $P = 0.001$) amygdalar volumes and with left hippocampal volume ($\beta = 0.121$, $P = 0.016$).

Conclusions

This study showed that the amygdala and hippocampus are enlarged in obesity. In consideration of the function of these structures, this finding may indicate that hedonic memories could be of major importance in the regulation of feeding. Because of the cross-sectional design, cause and effect could not be discriminated in this study.

INTRODUCTION

Obesity is a major public health issue strongly associated with chronic diseases, including diabetes mellitus and cardiovascular disease[1, 2]. It is well recognized that many brain structures are functionally involved in the regulation of food intake, including internal and external sensory inputs[3]. Regulation of food intake is controlled by multiple cognitive factors, including memorial representations of foods and their environmental context, and emotional and rewarding properties of such representations and their hedonic effects[3]. These factors are regulated by signaling molecules through the corticolimbic brain systems, in which the basal ganglia have an important role[4].

In addition to homeostatic regulation of food intake driven by inputs of the basal ganglia, thalamus, and hippocampus, generic morphometric changes of the brain have been described as well. There is growing evidence that an increased body mass index (BMI) is independently associated with whole-brain atrophy[5, 6]. Other studies have shown an evident correlation between obesity and loss of cortical gray matter[7-10]. On the other hand, cortical gray and white matter volume loss has also been described in patients with a very low BMI, as in anorexia nervosa[11-15]. Mechanisms behind these relations have not yet been clarified.

To our knowledge, the relation between obesity and the anatomy of subcortical structures that play a role in human food regulation have not been investigated previously. In the present study we aimed to investigate whether the basal ganglia, hippocampus, and thalamus are different between obese subjects and overweight and normal-weight subjects.

METHODS

Subjects

All subjects were derived from the magnetic resonance imaging (MRI) substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER was a double-blind, randomized, placebo-controlled trial aimed at assessing the effect of therapy with 40 mg pravastatin on vascular events in 5804 men and women from Scotland, Ireland, and the Netherlands aged 70-82 y with vascular disease or at risk of vascular disease[16]. The PROSPER study was initiated in 1997. In the Netherlands, all consenting subjects were enrolled beginning in May 1998. The inclusion criteria for this study were as follows: men or women aged 70-82 y; total cholesterol of 4.0-9.0 mmol/L; stroke, transient ischemic attack, myocardial infarction, arterial surgery, or amputation for vascular disease > 6 mo before study entry; or one or more of the following risk factors for vascular disease: current smoking, hypertension, current drug treatment, known diabetes mellitus, or fasting blood glucose > 7 mmol/L. The institutional ethics review boards of all centers approved the protocol, and all participants gave written informed consent. The protocol was consistent with the Declaration of Hel-

sinki. All subjects had a Mini-Mental State Examination score of ≥ 24. Effects of dementia and/or Alzheimer disease on the volumes of the basal ganglia were hereby automatically eliminated[16, 17]. Weight and height data for all participants were collected. The results were compared between subjects on the basis of BMI (in kg/m^2) groups: normal-weight subjects (BMI < 25), overweight subjects (BMI = 25-30), and obese subjects (BMI > 30).

Magnetic resonance acquisition

Of the 1100 Dutch participants in PROSPER, 494 subjects underwent a high-resolution three-dimensional (3D) T1-weighted (T1-w) MRI. All imaging was performed on an MR system operating at a field strength of 1.5 Tesla (Philips Medical Systems, Best, Netherlands). Three-dimensional T1-w scans were obtained by using the following parameters: repetition time = 30 ms, echo time = 4.6 ms, flip angle = 30°, slice thickness = 1.5 mm, 120 slices, no interslice gap, field of view = 220 × 220 mm, matrix = 256 × 256, and in-plane resolution = 1.12 × 1.12 mm.

MRI processing

Segmentation of the various subcortical structures was performed on the original data set (*n* = 494) and on the same data set of which the left and right hemispheres were mirrored in the lateral plane. This approach was chosen to overcome potential systematic lateralization bias in preferential volume determinations by the algorithm FIRST (FMRIB's Integrated Registration and Segmentation Tool). To calculate the individual left and right volumes of the separate basal ganglia, the original volume and the corresponding mirrored volume of that particular intracranial structure were averaged.

   FIRST was applied to estimate the volumes of left and right structures separately in 7 subcortical regions: nucleus accumbens, globus pallidus, amygdala, putamen, caudate nucleus, thalamus, and hippocampus. FIRST is part of FSL (FMRIB's Software Library) and performs both registration and segmentation of the mentioned subcortical regions[18, 19]. During registration, the input data (3D T1 images) are transformed to Montreal Neurological Institute (MNI) 152 standard space. For intrasubject comparison studies, the algorithm uses 12 df to transform the image (i.e., 3 translations, 3 rotations, 3 scalings, and 3 skews). After registration, a subcortical mask was applied to locate the different subcortical structures, followed by segmentation based on voxel intensities. Absolute volumes of subcortical structures were calculated, taking into account the transformations made in the first stage. The software was set to archive all single-structure segmentations. Border correction was used to increase the accuracy of the volumetric measurements[20]. Border-corrected segmentations were archived as well. Volumetric data were obtained from the archived segmentations and normalized to MNI space. Incorrect segmentation of individual structures (volume greater or less than the mean group volume ± 3 × SD, usually with the value of "0") was excluded for analysis based on Tukey's rule[21].

The single time point measurement technique SIENAX was performed to obtain estimates of gray and white matter volumes as well as brain volume. SIENAX starts by extracting brain and skull images from the single whole-head input data. The brain image is then affine-registered to MNI 152 space (by using the skull image to determine the registration scaling), done primarily to obtain the volumetric scaling factor to be used as normalization for head size. Next, tissue-type segmentation with partial volume estimation is carried out to calculate total volume of brain tissue (including separate estimates of volumes of gray matter, white matter, peripheral gray matter, and ventricular cerebrospinal fluid)[19]. Atrophy was defined as intracranial volume: parenchymal volume / intracranial volume × 100%. All volumetric data were normalized to standard space, thereby correcting for interindividual differences in brain size. All MRI scans were reviewed by M.A.v.B. (> 15 y of neuroradiologic experience) for incidental findings.

Statistical analysis

Statistical analysis was performed by using SPSS for Windows (version 16.0.2; SPSS, Chicago, Ill). All descriptive data were expressed as means ± SDs or n (%). To compare group data, a one-factor analysis of variance was used, followed by a Scheffe's post hoc test to correct for multiple comparisons. For categorical variables, the chi-square test or Fisher's exact test was used. The association between basal ganglia volumes and BMI was determined by using a multiple linear regression analysis, with age, sex, smoking, hypertension, and pravastatin use as covariates. β regression coefficients and P values are reported. P values < 0.05 were considered significant.

RESULTS

Three-dimensional T1-w MRI of the brain was performed in 494 subjects. Except for age-related changes, none of our subjects had unexpected findings on MRI. After exclusion of cases with poor segmentation, 471 subjects (mean age: 74.4 y; 56% men) remained for volume calculation. The BMI of our sample population was 26.8 ± 3.6, with a minimum of 15.8 and a maximum of 43.5. The distribution of all BMIs is shown in **Figure 1**. On the basis of BMI, 140 subjects were classified as normal-weight (BMI = 23.2 ± 1.6), 256 subjects as overweight (BMI = 27.0 ± 1.4), and 75 subjects as obese (BMI = 32.8 ± 2.9). Demographic profiles for each group are shown in **Table 1**.
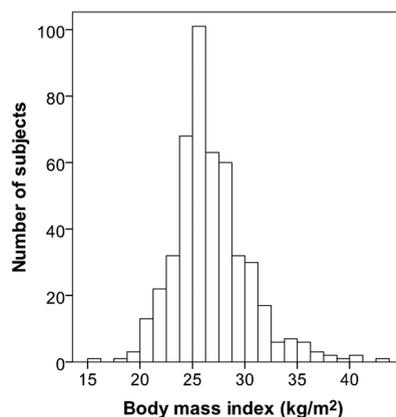
Figure 1. BMI distribution for all subjects.

Table 1. Demographics and group characteristics

Variable	Normal-weight	Overweight	Obese	P value		
	($n = 140$)	($n = 256$)	($n = 75$)	Normal-weight vs. overweight	Overweight vs. obese	Normal-weight vs. obese
Male sex [n (%)][†]	82 (59)	152 (59)	29 (39)	0.961	0.002*	0.008*
Age (y)	74.8 ± 3.3	74.3 ± 3.1	73.8 ± 3.0	0.277	0.469	0.071
Weight (kg)	67.7 ± 8.4	78.7 ± 8.2	92.6 ± 11.5	0.000*	0.000*	0.000*
Height (cm)	170.7 ± 7.9	170.5 ± 8.4	167.9 ± 9.3	0.978	0.062	0.068
BMI (kg/m^2)	23.2 ± 1.6	27.0 ± 1.4	32.8 ± 2.9	0.000*	0.000*	0.000*
MMSE score (points)	28.4 ± 1.3	28.4 ± 1.4	28.1 ± 1.6	0.993	0.288	0.397
History of vascular disease [n (%)][†]	60 (43)	109 (43)	29 (39)	0.958	0.637	0.653
History of MI [n (%)][†]	7 (5)	34 (13)	13 (17)	0.083	0.486	0.079
History of stroke/TIA [n (%)][†]	30 (21)	30 (12)	13 (17)	0.121	0.281	0.592
Current smokers [n (%)][†]	37 (26)	47 (18)	10 (13)	0.080	0.401	0.042*
Hypertension [n (%)][†]	77 (55)	159 (62)	58 (77)	0.203	0.021*	0.002*
DM [n (%)][†]	14 (10)	50 (20)	17 (23)	0.047*	0.666	0.020*
Insulin use [n (%)][‡]	1 (1)	6 (2)	3 (4)	0.429	0.428	0.123
Fasting glucose (mmol/L)	5.4 ± 1.1	5.9 ± 1.7	6.0 ± 1.8	0.003*	0.883	0.013*
Systolic BP (mmHg)	155.6 ± 21.9	158.8 ± 21.9	158.2 ± 18.2	0.375	0.982	0.694
Diastolic BP (mmHg)	84.7 ± 10.6	86.3 ± 10.7	87.7 ± 10.9	0.327	0.634	0.143
Total cholesterol (mmol/L)	5.8 ± 0.9	5.7 ± 0.8	5.7 ± 0.8	0.832	0.968	0.793
LDL cholesterol (mmol/L)	3.9 ± 0.7	3.9 ± 0.7	3.9 ± 0.7	0.880	0.997	0.957
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	0.000*	0.509	0.000*
Triglycerides (mmol/L)	1.3 ± 0.5	1.6 ± 0.7	1.6 ± 0.6	0.000*	0.845	0.003*

MMSE = Mini-Mental State Examination, MI = myocardial infarction, TIA = transient ischemic attack, DM = diabetes mellitus, BP = blood pressure. Data were compared by one-factor ANOVA with Scheffe's post hoc analysis. *$P < 0.05$.
[†] Chi-square test.
[‡] Fisher's exact test.

Obese subjects had larger left ($P = 0.013$) and right ($P = 0.003$) amygdalar volumes and a larger left hippocampal volume ($P = 0.040$) than did normal-weight subjects. None of the other basal ganglia or the thalamus differed significantly in size between groups (**Table 2**).

Multiple linear regression analysis examined the association between BMI and the basal ganglia, thalamus, and hippocampus, the left and right sides of which were assessed separately. After correction for age, sex, smoking, hypertension, and pravastatin use, a significant association was observed between BMI and normalized left ($\beta = 0.175$, $P = 0.001$) and right ($\beta = 0.157$, $P = 0.001$) amygdalar volumes, and normalized left hippocampal volume ($\beta = 0.121$, $P = 0.016$) (**Figure 2**). This indicates that a high BMI is associated with large volumes

Table 2. Magnetic resonance imaging characteristics of normal-weight, overweight, and obese subjects

	Normal-weight		Overweight		Obese		P value		
	n	Volume cm^3	n	Volume cm^3	n	Volume cm^3	Normal-weight vs. overweight	Overweight vs. obese	Normal-weight vs. obese
L nuc acc	86	0.58 ± 0.16	156	0.60 ± 0.16	45	0.61 ± 0.18	0.728	0.879	0.577
R nuc acc	68	0.54 ± 0.16	164	0.54 ± 0.16	38	0.51 ± 0.16	1.000	0.779	0.814
L glob pal	117	1.96 ± 0.46	214	1.95 ± 0.40	65	1.97 ± 0.43	0.978	0.939	0.986
R glob pal	119	1.97 ± 0.45	213	1.95 ± 0.34	64	1.99 ± 0.41	0.864	0.733	0.948
L amyg	126	1.95 ± 0.36	226	2.02 ± 0.33	66	2.10 ± 0.33	0.144	0.253	0.013*
R amyg	130	1.93 ± 0.32	224	2.01 ± 0.33	68	2.10 ± 0.35	0.151	0.097	0.003*
L putam	120	5.16 ± 0.61	226	5.18 ± 0.61	69	5.17 ± 0.75	0.952	0.996	0.988
R putam	123	5.34 ± 0.61	220	5.33 ± 0.61	67	5.18 ± 0.61	1.000	0.184	0.235
L caud nuc	126	3.57 ± 0.50	222	3.58 ± 0.51	69	3.51 ± 0.53	0.966	0.611	0.772
R caud nuc	127	4.05 ± 0.57	225	3.98 ± 0.63	68	3.84 ± 0.63	0.560	0.277	0.077
L thal	129	8.01 ± 0.65	224	8.09 ± 0.64	69	8.09 ± 0.74	0.481	0.998	0.707
R thal	128	8.04 ± 0.66	224	8.13 ± 0.68	69	8.13 ± 0.74	0.506	0.998	0.656
L hipp	124	4.52 ± 0.68	223	4.63 ± 0.58	64	4.77 ± 0.70	0.309	0.301	0.040*
R hipp	124	4.60 ± 0.63	219	4.66 ± 0.59	64	4.77 ± 0.57	0.600	0.476	0.177
Gray matter	143	$5.93 \pm 0.50 \times 10^2$	252	$5.91 \pm 0.41 \times 10^2$	76	$5.93 \pm 0.44 \times 10^2$	0.953	0.923	0.990
White matter	143	$7.71 \pm 0.41 \times 10^2$	252	$7.66 \pm 0.36 \times 10^2$	76	$7.66 \pm 0.41 \times 10^2$	0.495	0.999	0.665
Gray + white	143	$13.64 \pm 0.71 \times 10^2$	252	$13.57 \pm 0.62 \times 10^2$	76	$13.60 \pm 0.69 \times 10^2$	0.667	0.970	0.911

Values are means ± SDs unless otherwise indicated. L = left, R = right, nuc acc = nucleus accumbens, glob pal = globus pallidus, amyg = amygdala, putam = putamen, caud nuc = caudate nucleus, thal = thalamus, hipp = hippocampus, Gray matter = volume of normalized gray matter, White matter = volume of normalized white matter, Gray + white = total volume of white and gray matter. Data were compared by one-factor ANOVA with Scheffe's post hoc analysis.

* $P < 0.05$.

of amygdala and left hippocampus. BMI showed no association with other basal ganglia or thalamus volumes (**Table 3**).

The subjects included in this study might have had one or more risk factors for vascular disease, namely current smoking, hypertension, current drug treatment, known diabetes mellitus, or fasting blood glucose > 7 mmol/L. We found no association between volumes of basal ganglia and any of these cardiovascular disease risk factors.
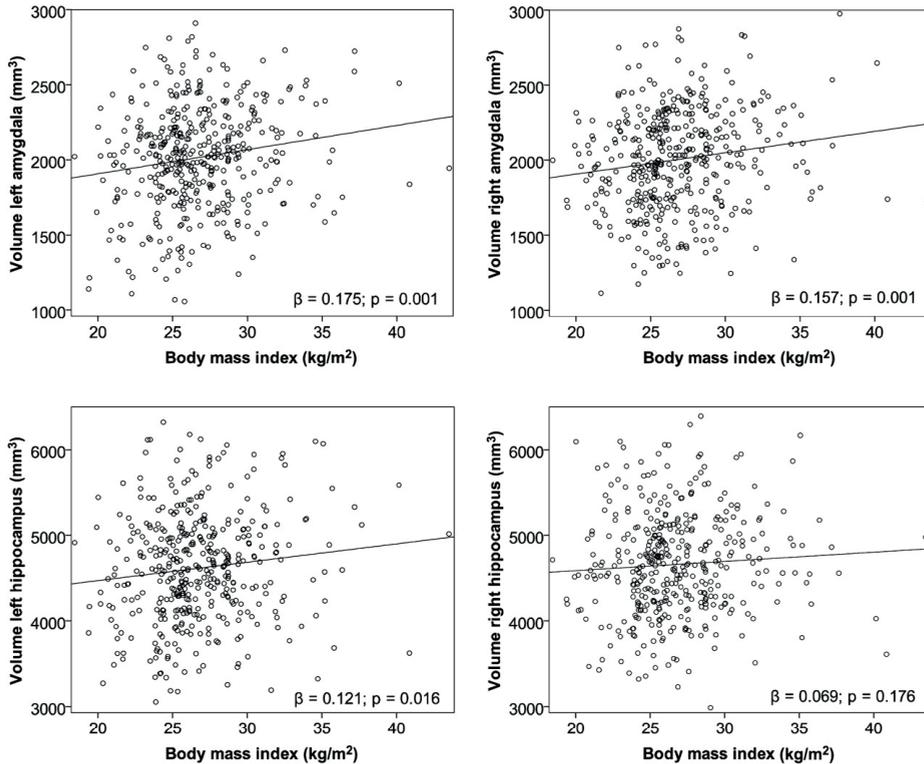
Figure 2. Bivariate relations between amygdalar and hippocampal volumes and BMI. Reported β and *P* values were obtained by multiple linear regression analysis with correction for age, sex, smoking, hypertension, and pravastatin use.

DISCUSSION

The main findings of this study were enlargements of the amygdala and hippocampus in the obese subjects. In addition, an association of amygdalar and hippocampal enlargement with BMI corrected for age, sex, smoking, hypertension, and pravastatin use was observed. Both brain structures play a crucial role in the process of feeding behavior. Interestingly, none of the other investigated brain structures showed a significant association with BMI.

Table 3. Association between BMI and volumes of subcortical structures

	Crude		Adjusted	
	β	*P* value	β	*P* value
L nuc acc	0.036	0.543	0.044	0.455
R nuc acc	-0.012	0.843	0.002	0.968
L glob pal	0.023	0.650	0.021	0.683
R glob pal	0.021	0.679	0.020	0.707
L amyg	0.164	0.001*	0.175	0.001*
R amyg	0.151	0.002*	0.157	0.001*
L putam	-0.011	0.818	0.020	0.667
R putam	-0.068	0.171	-0.050	0.300
L caud nuc	-0.050	0.308	-0.027	0.577
R caud nuc	-0.079	0.109	-0.045	0.353
L thal	0.022	0.658	0.056	0.229
R thal	0.037	0.446	0.064	0.180
L hipp	0.118	0.016*	0.121	0.016*
R hipp	0.063	0.202	0.069	0.176
Gray matter	0.005	0.921	-0.054	0.202
White matter	-0.060	0.190	-0.057	0.226
Gray + white	-0.032	0.485	-0.070	0.119

Results are from a multiple linear regression analysis. L = left, R = right, nuc acc = nucleus accumbens, glob pal = globus pallidus, amyg = amygdala, putam = putamen, caud nuc = caudate nucleus, thal = thalamus, hipp = hippocampus, Gray matter = volume of normalized gray matter, White matter = volume of normalized white matter, Gray + white = total volume of white and gray matter.
* Significant β values before and after adjustment for age, sex, smoking, hypertension, and pravastatin use.

The amygdala plays an important role in the coordination of appetitive behavior. It is part of a complex neural system that is responsible for the evaluation of food. The electrophysiological responses on taste and picture-odor contingencies in the amygdala suggest a sensory function[22, 23]. Furthermore, rat studies suggest that the amygdala is critical to learning representations of specific experiences with food and using them to guide appetitive behavior[24]. Enlargement of the amygdala with respect to BMI has not been described before. It is known that enlargement can occur in patients with depression[25, 26], psychosis[27], autism[28], and bipolar disorder[29, 30]. A slight enlargement of the hippocampus has also been reported in bipolar disorder[30].

Although we found that volume changes were more pronounced in the right hemisphere of the amygdala and in the left hemisphere of the hippocampus, we believe that these differences are statistically not convincing enough to speculate on lateralization.

A possible explanation for amygdalar enlargement is higher glucose metabolism and cerebral blood flow[31]. However, a direct relation with amygdalar enlargement remains unclear, because cerebral blood flow and metabolism might be affected by multiple physi-

ologic events, e.g., dynamic changes in neurotransmitter-neuroreceptor function[26]. Other proposed mechanisms of amygdalar enlargement are an increase in size or number of neurons or glial cells, increased connective tissue, and increased intercellular fluid[31]. Rat studies have shown that chronic stress induces dendritic remodeling of the hippocampus and amygdala, which leads to atrophy and hypertrophy, respectively[32]. Hypermetabolism of the amygdala may also result from an increased afferent glutamatergic transmission between and within amygdala nuclei[33]. Glutamatergic transmission is part of the endocannabinoid system, which is related to obesity when dysregulated[34]. On the basis of this principle, pharmacologic agents, particularly cannabinoid receptor antagonists, are currently used as antiobesity drugs[35].

The amygdala and hippocampus relate memory to pleasure, respectively, by establishing the reward value of food and food-related stimuli or situations and by consolidating pleasure memories. On the basis of the previously described mechanisms, we assume that our findings are in part explained by an increased activity and possibly an elevated metabolism in the amygdala and hippocampus. Statements about the order of events (excessive feeding leading to or resulting from enlargement) are limited because this study was cross-sectional. However, it is just as likely that the described changes are the effect of enjoying food on hedonic centers, rather than hedonic center changes leading to eating more food.

Studies have shown that smoking history is associated with brain atrophy[36-39]. Therefore, we adjusted for smoking in the linear regression analysis. Hypertension has also been recognized as a risk factor for brain atrophy[40, 41], and moreover, hippocampal atrophy[42]. Hence, we used hypertension as a covariate in the linear regression analysis.

We realize that in an explorative study, significant results may occur by coincidence. In the current study, we performed a one-factor analysis of variance with subsequent Scheffe's post hoc analysis, correcting for multiple comparisons between groups (Table 2). We did not correct a priori for the number of structures (Tables 2 and 3). Because the amygdala is associated with BMI (Tables 2 and 3) in both hemispheres, we believe that our data are not driven by coincidence. Still, it must be emphasized that significant findings that are just below the threshold value ($P = 0.05$) should, in general, be treated with care.

No association was found between volumes of basal ganglia and cardiovascular disease risk factors. Because only cross-sectional data were available, no statements can be made about the influence of the duration of cardiovascular disease risk factors. For the same reason, cause and effect cannot be distinguished.

The obese group consisted of more women than men. Estrogen use has been shown to increase hippocampal volume relative to estrogen nonuse and findings in males[43]. Estrogen therapy was not investigated in this study. Therefore, sex or estrogen therapy could have been confounders in the relation between BMI and hippocampal volume.

We used the algorithm FIRST to estimate volumes. Existing and upcoming evidence indicate that different segmentation tools show structural differences between them. Com-

parison of data assessed with different segmentation techniques is therefore discouraged. A final limitation of this study was that it was performed in elderly individuals. Therefore, our results cannot be generalized to the population aged < 70 y.

In conclusion, this explorative study showed that the amygdala and hippocampus, which are very important structures in regulating feeding behavior, are enlarged in obesity. Furthermore, an association between BMI and enlargement was seen. The finding that these anatomic changes only occurred in the amygdala and hippocampus, and not in other brain structures that play a role in feeding behavior, suggests that cognitive aspects may be a major issue in the regulation of feeding. To our knowledge, this is the first study to have explored the relation between obesity and the basal ganglia specifically. Additional studies are required to examine the mechanisms behind enlargement of the amygdala and hippocampus in obesity.

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