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Gastric distention activates satiety circuitry in the human brain

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Gastric distention during meal ingestion activates vagal afferents, which send signals from the stomach to the brain and result in the perception of fullness and satiety. Distention is one of the mechanisms that modulates food intake. We measured regional brain activation during dynamic gastric balloon distention in 18 health subjects using functional magnetic resonance imaging and the blood oxygenation level-dependent (BOLD) responses. The BOLD signal was significantly changed by both inflow and outflow changes in the balloon's volume. For lower balloon volumes, water inflow was associated with activation of sensorimotor cortices and right insula. The larger volume condition additionally activated left posterior amygdala, left posterior insula and the left precuneus. The response in the left amygdala and insula was negatively associated with changes in self-reports of fullness and positively with changes in plasma ghrelin concentration, whereas those in the right amygdala and insula were negatively associated with the subject's body mass index. The widespread activation induced by gastric distention corroborates the influence of vagal afferents on cortical and subcortical brain activity. These findings provide evidence that the left amygdala and insula process interoceptive signals of fullness produced by gastric distention involved in the controls of food intake.
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Introduction

Multiple internal feedback signals influence food intake including gut-secreted peptides that provide information to the brain to inhibit feeding and terminate meal consumption (Blundell and Gillett, 2001; Cummings et al., 2002). Many of these signals are conveyed to the brainstem and hypothalamus via the vagus nerve (Hellstrom et al., 2004; Schwartz and Moran, 1996). Reduced neuronal sensitivity to these signals could result in unrestrained eating and obesity (Powley, 2000).

One of the key satiation mechanisms is gastric distention during food intake. Positron emission tomography (PET) with [O-15] water (Ladabaum et al., 2001; Stephan et al., 2003; Vandenbergh et al., 2005) or functional magnetic resonance imaging (fMRI) with blood oxygenation level-dependent (BOLD) contrast (Ladabaum et al., 2007; Lu et al., 2004) method have been used to examine brain activation during gastric distention. In these studies, a balloon was orally placed in the stomach and its volume was suddenly enlarged to a feeling of fullness that elicited pain (however, during normal food intake gastric distension is gradual and not painful), activating several brain regions, including the anterior insula and somatosensory cortices, but not the amygdala.

The amygdala might have an important role in feeding behavior. Amygdala lesions in animals (Rollins and King, 2000) or humans (King, 2006) lead to hyperphagia and excessive weight gain, and neuroimaging studies have demonstrated that food-related stimuli, tastes and odors activate the amygdala (Del Parigi et al., 2002; O'Doherty et al., 2002; Gottfried et al., 2003; Small et al., 2005; Smeets et al., 2006).

Here we aimed to study the brain response during the gradual gastric distention produced by moderate food intake in order to better understand the mechanisms underlying normal and abnormal eating behavior. We used the gastric balloon distention procedure developed by Geliebter (1988), which has been used to assess changes in fullness and to test meal intake as well as to measure human gastric capacity in subjects with bulimia nervosa and binge eating disorders (Geliebter and Hashim, 2001; Geliebter et al., 1992, 2004). In this procedure, the balloon is filled with water warmed to normal body temperature (37 °C). This method

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mimics better the gastric distention during food intake more closely than methods used in prior fMRI studies (Ladabaum et al., 2007; Lu et al., 2004). Furthermore, while previous fMRI studies used sudden volume changes to assess fullness and pain sensations, we changed the balloon volume slowly to study the brain response to a slow stomach distension that mimics normal food intake. We hypothesized that the involvement of the amygdala in feelings of fullness could be demonstrated using fMRI and this gradual and not painful gastric distension paradigm that mimics normal food intake.

Materials and methods

Subjects

Three female and 15 male healthy subjects (32.0±6.6 years of age, range 22–47 years old) all with body mass index (BMI) lower than 30 (kg/m^2) participated in the study. All subjects gave written informed consent after the experimental procedure was explained and after they had read the Consent form approved by the Institutional Review Boards at Brookhaven National Laboratory and State University of New York-Stony Brook. The exclusion criteria of the study were urine positive for psychoactive drugs or pregnancy; present or past history of dependence on alcohol or other drugs of abuse (caffeine >5 cups/day or nicotine >1 pack/day); present or past history of neurological disorders of central origin or major psychiatric disorders; use of anorexic medications for weight loss in the past 6 months; history of esophageal reflux; present history of uncontrolled cardiovascular disease (e.g. hypertension); present history of diabetes or other uncontrolled endocrine disease; history of acute or chronic medical illness that may affect brain function; and head trauma with loss of consciousness >30 min. Pre-scan urine tests ensured absence of psychoactive drug use in all subjects. Subjects were asked to have their last meal at 7 PM the evening before the day of the study and were studied between 16 and 18 h after the last meal.

Balloon insertion

The gastric distention procedure was based on that by Geliebter (1988). The balloon assembly consisted of a double-lumen tube (Fr-10), covered distally with a thin Latex condom (10 cm portion of a condom, plain end, non-lubricated) tied securely with unwaxed white dental floss. Before the balloon insertion, the physician placed a small plastic mouthpiece coated with about 3 ml (less than a teaspoon, maximum lidocaine dose was 100 mg) of 2% lidocaine viscous gel in the subject's mouth. A short time later (3 min or less), the mouthpiece was removed. Subjects were given a cup of water that contains lidocaine and they were asked to rinse the back of the tongue several times with it. The lubricant-coated tube with the deflated balloon was orally placed in the stomach by advancing the tube. During this procedure, the subject was asked to swallow to facilitate placement of the tube into the stomach. The balloon was filled with 100 ml of water at body temperature (~37 °C), through one lumen, and the tube gently withdrawn until resistance was met at the gastroesophageal junction. The tube was then passed down another 2 cm to avoid obstructing esophageal flow (Fig. 1A). The exterior end of the tube was taped to the cheek and shoulder to fix the balloon's position.

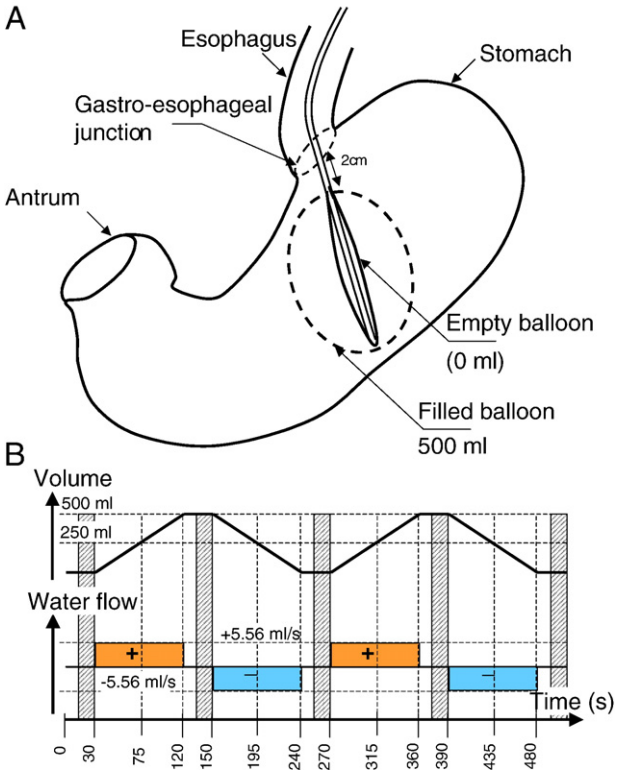

Fig. 1. (A) Schematic of the balloon placement in subjects' stomach, 2 cm below the gastro-esophageal junction. (B) Time course for the balloon inflation paradigm. Dashed periods indicate the time of questionnaire (16 s). Orange and blue blocks indicate constant (5.56 ml/s) water flow in (+) and out (−), respectively.

Gastric distention paradigm

There were two distention–contraction cycles with blocked design (Fig. 1B). After 30 s, the balloon was filled with 500 ml of water at body temperature (~37 °C) at a rate of 5.56 ml/s over 90 s, by using an electric pump (easy-load Masterflex 7518-80, Cole-Parmer Instrument Co., Vernon Hills, IL). At 500 ml, the water flow was interrupted for 30 s, and then the balloon was emptied in 90 s using the same flow rate (5.56 ml/s) in reverse. When the balloon was at null volume, there was a pause for 30 s and the filling–emptying sequence was repeated. The total time of the gastric distension protocol was 8 min 30 s.

Rating questionnaire

The last 16 s of the pauses, the subjects rated their fullness (how full are you right now?), discomfort (how comfortable are you right now?), hunger (how hungry are you right now?) and desire for food (do you desire for food right now?). MRI-compatible goggles (MRVision2000, Resonance Technology Inc., Northridge, CA) were used to project these rating questions. The subjects responded by pressing one of the four available buttons in an MRI-compatible pad (Lumila LP-400, Cedrus Corporation, San Pedro, CA). There were four possible responses for each question: "not at all" (blue button, left hand pad, rating score=1), "just a little" (yellow button, left hand pad, rating score=2), "somewhat" (green button, right hand pad, rating

score=3) and "very much" (red button, right hand pad, rating score=4). Each question and all corresponding potential answers were displayed simultaneously on the goggles for 4 s, allowing the subjects to read and respond in this time window. Each questionnaire was repeated during each of the five null-flow periods (Fig. 1B). The subjects were trained on how to use the response pad and how to respond to the questionnaire prior to balloon insertion.

Peptide measurements

Because gastric distention might activate vagal chemosensitive elements and stimulate the release of gut peptides [i.e. cholecystokinin (CCK), peptide YY (PYY)] or inhibit their release (i.e. ghrelin), blood samples were drawn twice on the day of study to quantify the plasma glucose, insulin, ghrelin, leptin and peptide YY (PYY) levels immediately before (after orogastric tube placement and pre-balloon distention) and after the fMRI scan (20 min post the last inflation/deflation cycle). Plasma hormone measurements were performed on blood samples in EDTA tubes that were centrifuged for 15 min at 4 °C after collection and stored at −80 °C until assayed. Thawed samples were not refrozen for other assay measurements. Total plasma immunoreactive ghrelin was measured by a RIA kit (Phoenix Pharmaceuticals, Belmont, CA) using ^{125}I-iodinated ghrelin tracer and a rabbit polyclonal antibody against full-length, octanoylated human ghrelin that recognizes the acylated and des-acyl forms of the hormone. The lower limit of detection for this assay was 20 pg/ml; the coefficient of variation was 8.5% within assays and 11.3% between assays. Total plasma levels of PYY were measured using a commercial enzyme-linked immunosorbent assay (ELISA; Diagnostic Systems Laboratories, Webster, TX) that measures $PYY_{(1–36)}$ and $PYY_{(3–36)}$. The lower limit of detection was 12 pg/ml, and the coefficients of variation were 10.1% within and 10.3% between assays. Leptin was measured with a human RIA kit (LINCO Research, Inc., St. Charles, MO) using a ^{125}I-iodinated human leptin tracer. Plasma insulin was measured with the Immulite Analyzer with the lower limit of detection of 2 μIU/ml.

MRI acquisition

A 4-T whole-body Varian/Siemens MRI scanner equipped with a self-shielded whole-body SONATA gradient set was used to acquire the data. A T2*-weighted single-shot gradient-echo planar (EPI) sequence (TE/TR=20/2000 ms, 4 mm slice thickness, 1 mm gap, typically 33 coronal slices covering the whole brain, 64×64 matrix size, 3.1×3.1 mm in-plane resolution, time points: 255) was used to measure the blood oxygenation level-dependent (BOLD) responses. A coronal scanning geometry and a relatively short echo time of 20 ms were used to minimize susceptibility artifacts close to the inferior part of the frontal lobe. The fMRI run was repeated as described above to increase statistical power. Head padding was used to minimize motion. A T1-weighted 3D-MDEFT sequence (Lee et al., 1995) (TE/TR=7/15 ms, 0.94×0.94×3 mm spatial resolution, axial orientation, 256 readout and 192×48 phase-encoding steps, 8 min scan time) and a modified T2-weighted Hyperecho sequence (Hennig and Scheffler, 2001) (TE/TR=42/10000 ms, echo train lengths=16, 256×256 matrix size, 30 coronal slices, 0.86×0.86 mm in-plane resolution, 5 mm thickness, 1 mm gap, 2 min scan time) were used to obtain anatomical brain images.

Image and data analyses

The first four volumes in each time series were discarded to avoid non-equilibrium effects of the MR signal. The statistical parametric mapping package SPM2 (Welcome Department of Cognitive Neurology, London UK) was used for fMRI analyses. The time series were realigned to the first volume using a six-parameter rigid body transformation; all fMRI runs had head motion less than 2-mm translations and 1° rotations. The realigned data sets were then normalized to a Talairach template using a 3×3×3 mm^3 voxel size (Ashburner et al., 1997) and smoothed using an 8-mm FWHM Gaussian kernel. The general linear model (Friston et al., 1995) and a castle design with six conditions – (1) ratings (stimuli onset: 15, 125, 255, 375 and 495 s; duration: 15 s); (2) flow in and volume <250 ml (stimuli onset: 30 and 270 s; duration: 45 s); (3) flow in and 250 ml>volume<500 ml (stimuli onset: 75 and 315 s; duration: 45 s); (4) null flow and volume=500 ml (stimuli onset: 120 and 360 s; duration: 30 s); (5) flow out and 250 ml<volume<500 ml (stimuli onset: 150 and 390 s; duration: 45 s); and (6) flow out and volume<250 ml (stimuli onset: 195 and 435 s; duration: 45 s) – were used to calculate the activation maps (Fig. 1B). Thus, conditions 1 and 4 are the static volume conditions that are comparable to previous fMRI studies (Ladabaum et al., 2007; Lu et al., 2004), while conditions 2, 3, 5 and 6 are the dynamic volume conditions, which are used for the first time in this study. The design matrix was convolved with a canonical hemodynamic response function (HRF). The BOLD signal strength was estimated without the removal of global effects (global normalization) to minimized false deactivation signals (Aguirre et al., 1998; Gavrilescu et al., 2002). The time series were band-pass filtered with HRF as low-pass filter and a high-pass filter (cut-off frequency: 1/500 Hz). BOLD responses (% signal change maps) for each trial and subject were included in a voxel-by-voxel one-way (repeated measures) analysis of variance (ANOVA) model with six conditions to identify the brain areas involved during balloon inflation and deflation. Simple regression analyses between BOLD signals and gut peptides in blood and rating scores during fMRI were conducted across subjects and tasks in SPM2 to complement the statistical analyses of brain activation. Clusters with $p<0.05$, corrected for multiple comparisons, were considered significant in group analysis of brain activation.

Region-of-interest analyses

Functional ROIs with a volume of 0.73 ml were defined at the cluster centers of brain activation to extract the average statistical

Table 1
Plasma levels of gut peptides (PYY and ghrelin), insulin, leptin and glucose immediately before and after the fMRI study

	Before (mean±SE)	After (mean±SE)
Glucose (mg/dl)	92.4±2.7	91.2±2.2
Insulin (μIU/ml)*	4.1±0.7	2.7±0.3
Ghrelin (pg/ml)	229±21	232±24
PYY (pg/ml)*	90±11	71±7
Leptin (ng/ml)	4.1±1.0	3.8±0.9

Sample: 18 healthy volunteers.
* Indicates statistically significant differences ($p<0.05$).

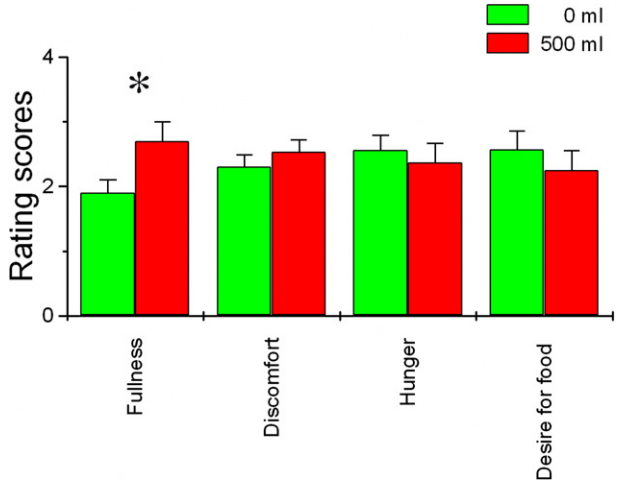

Fig. 2. Rating of subjects' sensations during the fMRI balloon inflation paradigm for the empty (0 ml) and full (500 ml) balloon conditions; sample size = 15.

significance (*t*-scores) from the SPM activation maps for each condition as well as for within group comparisons of brain activation (Table 1); for this purpose, we developed a program written in IDL (Research Systems, Boulder, CO) (Tomasi et al., 2005).

Results

Rating scores of self-report questionnaire

The range of body mass index (BMI) for these 18 subjects was 20–29 (mean: 24.4±3.0). The rating score data sets of 3 subjects were lost due to data acquisition problems. During the gastric distention paradigm (Fig. 1), we obtained self-reported ratings of fullness, discomfort, hunger and desire for food during the empty (0 ml) and full (500 ml) balloon conditions for the remaining 15 subjects. Each of the ratings was averaged across the fMRI runs. Fullness sensation was significantly higher during the 500-ml (red) condition compared to the 0-ml (green) condition ($p = 0.005$; paired *t*-test; Fig. 2). The higher discomfort and lower hunger and desire for food during the 500-ml condition, compared to the 0-ml condition, did not reach statistical significance. There was no significant correlation between the BMI and the self-report scores.

Peptide measurements

Table 1 shows the levels of plasma glucose, insulin, ghrelin, leptin and PYY before and after the fMRI scan. The insulin and PYY levels were lower after the study than prior the study ($p < 0.01$, paired *t*-test). There were no changes in plasma glucose, ghrelin and leptin.

Brain activation

For lower balloon volumes (<250 ml), water inflow was associated with activation of sensorimotor cortices and of right insula (see Table 2 and Fig. 3). For larger balloon volumes (250 ml < volume < 500 ml), water inflow was additionally associated to activation of the left posterior amygdala and left posterior insula. The largest volume condition (500 ml) additionally activated the left precuneus.

For the 250 ml < volume < 500 ml condition, water outflow activated the same clusters as water inflow; the only exception was the left precuneus that activated during outflow but not during inflow. Water outflow during the <250-ml condition activated the posterior insula.

Thus, (1) activation of the left amygdala was associated to the higher volume (>250 ml) conditions; (2) activation of the right posterior insula was associated to all 5 volumetric conditions; (3) activation of the left posterior insula was associated to the 250 ml < volume < 500 ml conditions; and (4) activation of the left precuneus was associated to volumes of 500 ml or >250 ml and water outflow. There were no significant activation differences between the high (>250 ml) and low (<250 ml) volume conditions.

Table 2
Coordinates of major activation clusters in the Talairach frame of reference and average *t*-scores in 0.73 ml isotropic ROI centered at these coordinates

Region	Side								
	X (mm)	*Y* (mm)	*Z* (mm)	In (<250 ml)	In (>250 ml)	No (500 ml)	Out (>250 ml)	Out (<250 ml)	In > out (>250 ml)
						Activation			
Amygdala/L	−24	−12	−12		2.5	2.4	2.2		4.1
STG38/L	−36	0	−15						3.0
Insula/R	39	−12	9	2.5	4.1	2.9	4.0	2.8	6.4
Insula/L	−33	−9	12		2.6		2.7		4.2
Precuneus/L	−33	−78	42			2.3	3.5		4.4
Precuneus/L	−6	−63	39	2.5	2.8	2.9	5.1		6.2
SPG7/L	−39	−63	51	3.0	3.3	2.9	4.1		6.0
PosC40/L	−51	−33	51	2.4	4.4	2.9	2.9		5.9
PreC4/L	−48	−15	36	3.7	2.7	2.3	3.6		4.9
SFG8/L	−18	39	42		3.0		4.0		5.3
MFG8/L	−51	12	42						2.8
Thalamus	0	−21	9						2.6
Cerebellum/R	30	−78	−30						3.5

Statistical significance for all clusters: $p < 0.05$ corrected for multiple comparisons.
STG: superior temporal gyrus (Brodmann area: BA 38); SPG: superior parietal gyrus (BA 7); PosC: posterior central gyrus; PreC: precentral gyrus (BA 4); SFG: superior frontal gyrus (BA 8); MFG: middle frontal gyrus (BA 8).

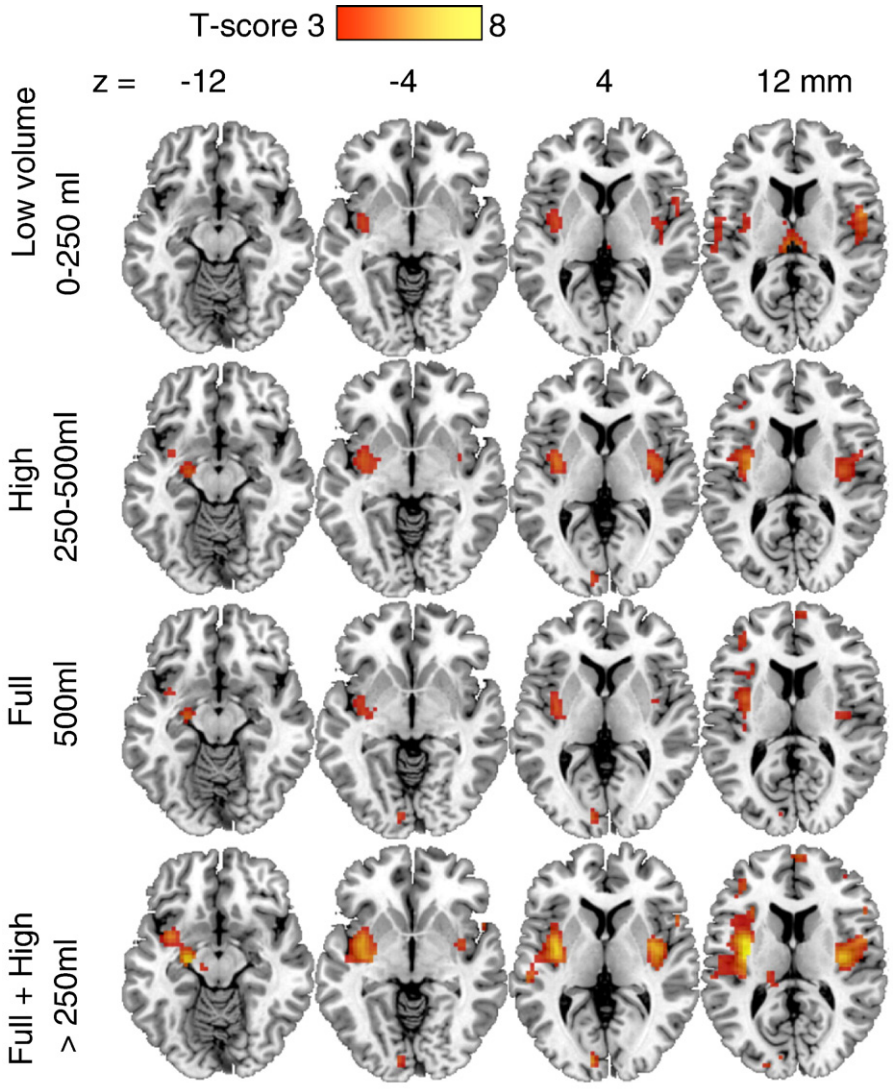

Fig. 3. Statistical maps of brain activation for different gastric distension volumes (low, high and full compared to baseline) of water in the balloon. Statistical analysis: one-way ANOVA; eighteen healthy volunteers.

Brain activation vs. BMI and rating scores of self-report questionnaires

Higher BMI was associated with decreased activation of the right amygdala/hippocampus and insula ($r=-0.7$, $p_{corr}<0.03$, corrected for multiple comparisons; Fig. 4). Increases in rating scores of fullness sensation caused by increases in balloon volume were associated to decreased activation of the left amygdala/insula ($r=-0.8$, $p_{corr}=0.01$; Fig. 5).

Brain activation vs. plasma peptide measures

There were no significant correlations between baseline plasma gut peptide measures and regional brain activation or between baseline plasma gut peptide measures and BMI. Changes in ghrelin levels (pre−post balloon inflation) were associated with activation of the left posterior amygdala ($r=+0.85$, $p_{corr}=0.04$). Correlations between brain activation and other peptide changes (PYY, leptin, insulin and glucose) were not significant.

Discussion

Here we show that non-painful proximal gastric distension activated the posterior insula, left posterior amygdala and sensorimotor cortices. The activation in these regions is compatible with those reported by studies on gastric sensation (Stephan et al., 2003) and is therefore likely to reflect the sensation of the stomach in response to the dynamic volume changes of the balloon.

Activation of left posterior amygdala during gastric distention

The main finding of this study was that gastric distention activated left posterior amygdala. The activation of the left posterior amygdala during low volume gastric distention was associated with the subjective feelings of fullness; the subjects that reported the largest changes in perception of fullness were the one that had the lowest activation of the left posterior amygdala. Also the subjects with the highest scores on self-reports of hunger had the most activation in the left posterior amygdala.

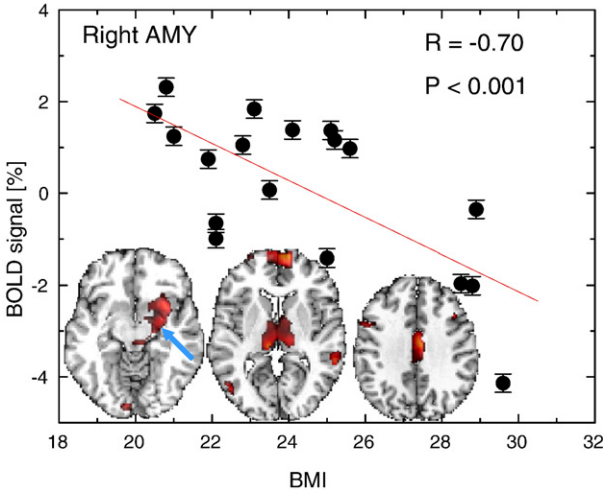

Fig. 4. BOLD signal in the right amygdala/hippocampus as a function of the BMI and three representative image slices showing the brain regions exhibiting a linear correlation between brain activation and BMI. Sample size = 18.

The amygdala plays a central role in the processing and memory of emotional reactions, which is important in the establishment of conditioned responses and in the response to novel stimuli (Ernst et al., 2006; Quirk and Gehlert, 2003). The amygdala is part of the limbic system and plays an important role in feeding behavior, which involves learning and recognition of the biological significance of the objects during procurement of food (Petrovich and Gallagher, 2003). Human subjects who received amygdala surgery for relieving epileptic seizures reported hyperphagia following the procedures (reviewed) (King, 2006). Experimental lesions in the amygdala have been reported in many animal species to induce eating food without discrimination, hyperphagia and excessive weight gain (Rollins and King, 2000). However, the amygdala lesions that induced obesity were influenced by the location of the lesion and the experimental method. For example, lesions in the medial amygdala disrupt the normal feeding pattern and result in impaired response to caloric challenge (Box and Mogenson, 1975). It has been shown from rodent studies that the most effective site to induce hyperphagia is in the posterior dorsal amygdala. Rats with lesion in the posterior dorsal amygdala are hyperinsulinemic during food restriction and prefer high carbohydrate diets (reviewed) (King, 2006). Functional neuroimaging studies using PET and fMRI have shown activation of the amygdala with food-related stimuli, tastes and odors (Del Parigi et al., 2002; Small et al., 2005; Smeets et al., 2006). Most of these studies did not distinguish among the various amygdala nuclei due to limited temporal and spatial resolutions of the imaging modalities. Recent fMRI studies did report that the posterior dorsal amygdala was involved in signaling the impending delivery of glucose and predicting food odors in an appetitive-conditioning paradigm (Gottfried et al., 2003; O'Doherty et al., 2002).

Brain activation vs. plasma peptide measures

The gastrointestinal peptide hormones insulin, ghrelin and PYY play a role in the regulation of metabolism and appetite. Ghrelin is predominantly secreted by the stomach, PYY by the intestine and insulin by the pancreas (Perez-Tilve et al., 2006). Ghrelin receptor mRNA is found in the hypothalamus, HIP and dorsal vagal complex (i.e. the nucleus tractus solitarius) (Zigman et al., 2006). Injection of ghrelin into the hypothalamus and hippocampus stimulates food intake (Carlini et al., 2004). Human and animal studies have shown that ghrelin concentration in peripheral blood decreases rapidly following food intake. However, preclinical studies showed that when glucose or water were directly delivered into the stomach, neither of them affected ghrelin concentration (Williams et al., 2003). Similarly, neither gastric distention nor chemosensitization of the stomach changed ghrelin concentration. It appears that the changes in ghrelin concentration are a function of postgastric feedback (Blom et al., 2006; Overduin et al., 2005). In our study, as would have been expected, we did not find changes in peripheral ghrelin concentration after gastric distention. However, we found that subjects who had greater increases in peripheral ghrelin levels after gastric distention also had greater activation of the left amygdala. Gastric ghrelin reaches the brain by crossing the blood–brain barrier or indirectly via the vagus. Direct injection of ghrelin to the amygdala does not affect food intake (Carlini et al., 2004), and thus peripheral ghrelin signals are most likely transmitted via vagal afferents to the nucleus tractus solitarius (Solomon et al., 2006). The nucleus tractus solitarius is a viscerosensory relay center, which receives a wide variety of inputs from visceral systems (i.e. gastrointestinal afferents) and carries signals to the forebrain (i.e. hypothalamus, amygdala and insula) by ascending projections. The extensive distribution of the vagus to the gut provides a bi-directional link with the brain that regulates appetite and physiological sensation (i.e. satiety) as well as secretion and motility functions of the gastrointestinal system (Andrews and Sanger, 2002). The correlation between changes in ghrelin concentrations and amygdalar activation may reflect ghrelin's signaling through the vagus into the nucleus tractus solitarius and from there to the amygdala.

PYY release is modulated by peptides such as CCK but the vagus may also participate in its release. In this study, we found that peripheral PYY and insulin concentration decreased after the balloon distension. It is possible that decreases in PYY and insulin after the balloon distention reflected inhibitory control through the

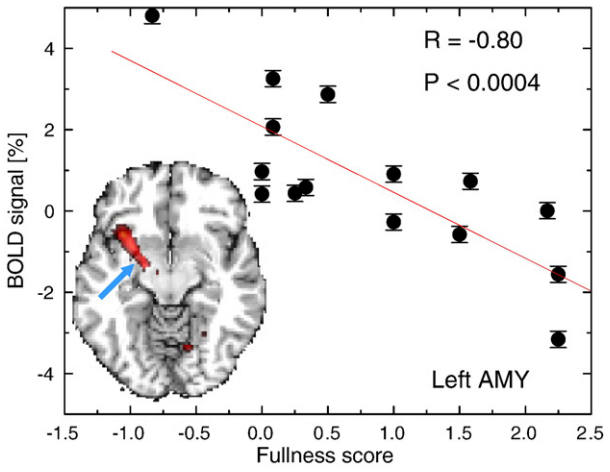

Fig. 5. BOLD signal in the left amygdala as a function of increases in the rating score of fullness sensation from the empty (0 ml) balloon condition to the full (500 ml) balloon condition. The slice shows the brain region exhibiting this linear correlation. Sample size = 15.

vagus (Owyang, 1994). Indeed truncal vagotomy has been shown to result in significant elevations of basal and food-induced release of PYY (Zhang et al., 1993).

Activation of posterior insula

The posterior insula is a neuronal structure involved in processing somatic and visceral sensations (reviewed) (Craig, 2002). It connects with the primary and secondary somatosensory cortex and receives input from the ventral posterior inferior thalamic nuclei and posterior part of ventromedial thalamic nucleus. The posterior part of the ventromedial thalamic nucleus receives vagal visceral input and projects into the insula (Craig and Zhang, 2006). A complex network of intrinsic and extrinsic sensory innervations serves the gastrointestinal tract. Stimuli (i.e. distention) are detected by vagal and spinal mechanosensitive afferents and project into the central nervous system. The smooth muscle mechanoreceptors have low thresholds of activation and reach maximal responses within physiological levels of distention. The information is transmitted via vagal afferents through the nodose ganglion into the nucleus tractus solitarius in the brain stem, medulla and forebrain regions (i.e. the ventromedial hypothalamus, amygdaloid nuclei and thalamus) for integration into autonomic responses and complex behaviors (Bailey et al., 2006). In contrast, the information transmitted via the spinal afferents is through the thoracic cord via dorsal root ganglion cells that can encode both physiological and noxious stimulation (Ozaki and Gebhart, 2001). These different stimulus responses are consistent with the involvement of vagal afferents in physiological regulation (i.e. lower volume distention) and the involvement of spinal afferents in mediating pain (Bielefeldt et al., 2005). It is possible that the activation of the posterior insula is caused by the lower volume distention in the stomach via the vagal afferents, which is different from the activation of anterior insula caused by higher volume distention (i.e. pain sensation) via the spinal afferents (nociceptive sensory pathway). The anterior insula has been implicated with integration of emotion, behavior (Jabbi et al., 2007; Stein et al., 2007) and perception of pain (reviewed) (Craig, 2002). The anterior insula receives afferent projections from the ventromedial nucleus of the thalamus and in turn connects with limbic brain regions.

Summary

This is the first study to assess the effect of dynamic gastric distention to brain. These findings provide insight into the brain circuits involved in processing the vagal signals that originate from the stomach of healthy subjects. The results suggest that the amygdala and the insula play an important role in the perception of fullness produced by gastric distention, which could influence the volumes of food consumed in a given meal. This study also provides evidence that ghrelin may modulate amygdalar reactivity in the human brain.

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