

Neural Correlates of Weight Gain With Olanzapine

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Context: Iatrogenic obesity caused by atypical antipsychotics increases the rate of death from all causes. Olanzapine is a commonly prescribed atypical antipsychotic medication that frequently causes weight gain. To our knowledge, the neural correlates of this weight gain have not been adequately studied in humans.

Objective: To test the hypothesis that olanzapine treatment disrupts the neural activity associated with the anticipation and receipt (consumption) of food rewards (chocolate milk and tomato juice).

Design: Event-related functional magnetic resonance imaging study, before and after a 1-week treatment with olanzapine.

Setting: A university neuroimaging center.

Participants: Twenty-five healthy individuals.

Main Outcome Measures: Changes in blood oxygen level–dependent activations to the anticipation and receipt of food rewards after olanzapine treatment.

Results: One week of olanzapine treatment caused significant increases in weight, food consumption, and disinhibited eating. Our imaging data showed enhanced activations in the inferior frontal cortex, striatum, and anterior cingulate cortex to the anticipation of a food reward. Activation in the caudate and putamen were enhanced to the receipt of the rewarding food. We also found a decrease in reward responsivity to receipt of the rewarding food in the lateral orbital frontal cortex, an area of the brain thought to exercise inhibitory control on feeding.

Conclusions: Olanzapine treatment enhanced both the anticipatory and consummatory reward responses to food rewards in the brain reward circuitry that is known to respond to food rewards in healthy individuals. We also noted a decrease in responsivity to food consumption in a brain area thought to inhibit feeding behavior.

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INDIVIDUALS WITH PSYCHIATRIC DISORDERS have significantly higher mortality rates than the general population, with an average of 22 lost potential years of life.¹ Heart disease is the leading cause of death in the mentally ill population,¹ and obesity is a key modifiable risk factor for heart disease and other co-occurring conditions such as diabetes mellitus.² Iatrogenic obesity caused by antipsychotic medications, especially the commonly prescribed atypical antipsychotics, negatively impacts medication compliance^{3,4}; predisposes patients to cardiovascular illness, type 2 diabetes, and metabolic dysregulations; and increases the rate of death from all causes.⁵⁻¹⁰

Weight gain and obesity are thought to reflect a complex interplay between homeostatic food intake mechanisms and brain reward circuitry.¹¹⁻¹³ Such homeostatic food intake mechanisms involve the hypothalamus and neuroregulatory peptides and hormones, both central (eg, neuropeptide Y and orexin) and peripheral (eg, ghrelin, leptin, and insulin), that dynamically regulate caloric intake through their modulation of the

brain reward circuitry.^{3,13-17} Recent advances in functional neuroimaging techniques have started to elucidate the brain reward circuitry that is involved in the pleasurable or hedonic response to taste in healthy humans and the neural substrates of taste reward expectancy and taste experience in obesity.^{18,19} The main components of this taste reward processing circuit involve the highly interconnected striatum (dorsal and ventral), amygdala, cingulate cortex, insula, and orbitofrontal and medial prefrontal cortex (**Figure 1**).²⁰⁻²⁶

This reward circuitry has significant dopaminergic components, in addition to the involvement of other neurotransmitter systems such as opioids, serotonin, and cannabinoids.^{17,27-29} For example, a positron emission tomography (PET) study in healthy, nonobese humans showed that dopamine release increased in the striatum after consumption of a favorite meal and that this increase correlated with ratings of meal pleasantness.²⁸ Another series of PET studies showed significant increases of dopamine in the dorsal striatum in response to food cues³⁰ and increased food cue–related me-

tabolism in the orbitofrontal cortex.³¹ Both of these increases in nonobese, healthy humans correlated with perception of hunger and desire for food. Additionally, PET studies in obese individuals have also demonstrated the role of dopamine signaling in food reward and the inhibitory control of behavior, disruptions of which could lead to disinhibited eating.³²⁻³⁴

Functional magnetic resonance imaging (fMRI) studies similarly have found abnormalities in dopaminergic taste reward-related areas in obese individuals. These studies have found enhanced striatal activation to food-related cues^{25,35-37} while there is less activation in these regions to the actual consumption of food.^{25,36} This pattern was correlated with significant weight gain in adolescents over a 1-year period.³⁶ Based on these findings, it is reasonable to posit that dopaminergic disruptions may cause a mismatch between enhanced reward expectation and diminished reward experience in obese individuals. This disequilibrium may cause overeating as a compensatory mechanism to obtain the anticipated reward.

Among the atypical antipsychotic medications, olanzapine has been shown conclusively to cause significant weight gain in both patients³⁸⁻⁴⁰ and healthy individuals.⁴¹⁻⁴³ This predictability and relative safety^{38,40} have made olanzapine the prototypical antipsychotic agent used in studies investigating antipsychotic-induced weight gain. A number of rodent experiments point toward disruptions in the hunger-satiety balance and resultant hyperphagia as putative mechanisms for the increased adiposity associated with olanzapine.⁴⁴⁻⁴⁷ Similarly, metabolic studies in healthy humans have also shown that increased appetite and increased food consumption were key contributors to olanzapine-induced weight gain.^{41,48}

However, the exact mechanisms for the weight gain remain unclear. Several studies converge on serotonin, histamine, dopamine, and catecholamine neurotransmitter systems that are dynamically impacted by olanzapine.^{16,49} H₁ receptor binding affinity is closely associated with weight gain liability.^{16,49-51} Serotonin 2A receptor antagonism, the inverse agonist effects at serotonin 2C receptors, and the muscarinic M₃ receptor antagonism also play a prominent role⁵²⁻⁵⁷ as do D₁ and D₂ dopamine receptor antagonism, especially through their impact on the reward system.^{30,31} Additionally, these receptor mechanisms may have synergistic effects that disrupt satiety signaling^{58,59} and alter taste reward processing,^{60,61} effects that are especially relevant to this study. This multifactorial interplay between the pharmacological effects of olanzapine, homeostatic food intake mechanisms (central and peripheral), and the taste reward system likely results in weight gain.

At present, there is a lack of human studies that have examined the neural mechanisms associated with olanzapine-induced weight gain. As such, the goal of the current study was to test the hypothesis that olanzapine treatment disrupts the neural circuitry associated with the anticipation and receipt of food rewards. To do so, we used a taste reward paradigm that is biologically salient and that would allow us to explore the anticipatory response to a food cue and the response to the actual taste (receipt) of the cued food. We expected to find that olanzapine treatment would cause weight gain, increased food consumption, and disinhibition in eating behavior in the

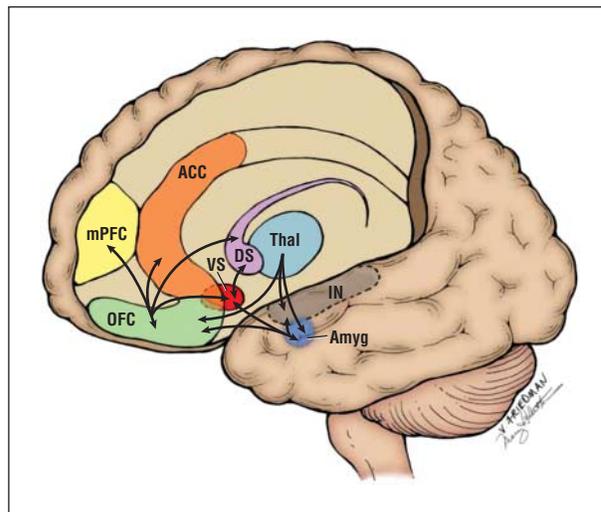


Figure 1. A schematic depiction of the approximate anatomical locations and connections of the taste reward pathways. Information from taste receptors project to the thalamus (Thal) via the nucleus tractus solitaries. This taste information along with information from other sensory modalities (eg, smell and appearance of food) then converge on the insula (IN), amygdala (Amyg), and orbitofrontal cortex (OFC). From here they access the other major components of the reward processing circuit including the highly interconnected striatum (ventral striatum [VS] and dorsal striatum [DS]), anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC).

healthy participants. We hypothesized that there would be increases in the food cue-related responses in the reward circuitry (eg, dorsal striatum and inferior frontal cortex) that could signify an enhanced food reward expectancy. We also hypothesized that the neural response to the actual receipt of taste reward would be enhanced and that we may find alterations in the activity of regions involved in inhibitory mechanisms that control feeding, such as the lateral orbital frontal cortex.

METHODS

PARTICIPANTS

This study was approved by the Washington University institutional review board. The participants were 25 right-handed healthy adults with a mean body mass index (calculated as weight in kilograms divided by height in meters squared) of 25.78 (range, 19.29-35.41; the only individuals with body mass index >30 were 4 muscular male football players) recruited through flyers in St Louis, Missouri. One subject withdrew consent on the second day of the study because of intolerable somnolence and fatigue. Another subject withdrew consent on the fourth day because of intolerable headache. Four subjects were excluded because their imaging data showed excessive movement in the scanner at 1 or both sessions. The final data set included 19 subjects (see **Table 1** for demographics).

All of the participants were initially interviewed to determine their eligibility via a screening telephone interview (see **Table 2** for criteria). Subjects who met the entrance criteria were invited for an interview with a psychologist. Subjects were evaluated using the Structured Clinical Interview for DSM-IV-TR⁶² to ascertain that they did not have any current or past mental disorders. The principal investigator (J.M.) then conducted a medical history and a physical examination. Subjects who qualified for the study and consented were then assessed with 2 fMRI scans, each after an overnight fast.

The first fMRI scan was done when subjects were drug naive and the second scan was obtained after 7 consecutive days of olanzapine treatment, both using the identical taste experiment described later. Subjects were contacted by telephone on the evening prior to their first fMRI scan and reminded not to eat or drink any fluids except for water after dinner. All subjects then spent 7 consecutive nights after the first scan at the Clinical Research Unit at Washington University to ensure safety and compliance. They continued their regular routines during the day. Subjects once again fasted, except for drinking water, after dinner on the night prior to their second fMRI scan. All participants confirmed that they complied with the instructions. Subjects took 5 mg of olanzapine on the first night and 10 mg on the subsequent 6 nights.

Each day subjects completed the Patient Rated Inventory of Side Effects^{63,64} to assess any adverse effects. Subjects also filled out the Three-Factor Eating Questionnaire,⁶⁵ a self-report scale that assesses cognitive and behavioral components of eating and a 5-point hunger rating scale ranging from 0 (not hungry) to 4 (very hungry), before and after the fMRI scans.

EXPERIMENTAL PARADIGM

A biologically relevant visual cue (a picture of a glass of tomato juice, chocolate milk, or water) was presented for 2 seconds while subjects were in the magnetic resonance imaging scanner. Subjects identified each cue with a corresponding unique button press. At a varying interval of between 2 and 6 seconds, the cued taste (tomato juice, chocolate milk, or tasteless water) was delivered to the participant in small quantities (0.5 mL) via 3 small tubes (1/8-in diameter) that were held in their mouth and lay on the anterior one-third of their tongue. These tubes were each connected to a 60-mL syringe that held

the fluids and was attached to a syringe pump. The syringe pumps were triggered by PsyScope software.⁶⁶

At a variable interval between 2 and 6 seconds after the delivery of the taste stimulus to the mouth, another cue (an asterisk) signaled swallowing. This cued swallowing was used to allow for a sufficient taste experience. This was immediately followed by delivery of 0.5 mL of tasteless water to rinse out the earlier taste stimulus. Subjects were instructed to immediately swallow the tasteless water rinse and the asterisk cue remained on the screen for 2 seconds after the rinse was triggered (eFigure 1, <http://www.archgenpsychiatry.com>).

In 75% of the trials, the cue for tomato juice and chocolate milk resulted in the delivery of the cued taste stimulus. In 25% of the trials, it resulted in the delivery of the tasteless solution, thus introducing a small element of uncertainty to aid anticipation.^{23,67,68} However, the relative contribution of uncertainty cannot be estimated from this design. All the cues for the tasteless solution resulted in the delivery of the tasteless solution. There was a variable intertrial interval of 2 or 4 seconds. There were a total of 24 trials in each blood oxygen level-dependent (BOLD) run, and each BOLD run lasted 7.4 minutes. The subjects rated the pleasantness of the taste stimuli on a 5-point Likert scale by pressing a button after each BOLD run. An example of the exact phrase that was used is "How will you rate the chocolate milk?" Subjects could choose between very pleasant, pleasant, neutral, unpleasant, and very unpleasant (eFigure 2).

The visual cue was projected onto a screen behind the subject's head within the imaging chamber and was viewed by a mirror attached to the head coil. Stimuli were presented through the program PsyScope, and a fiber-optic key press interfaced with the PsyScope button box to record subjects' button press to the task. Each subject had a brief practice session in the scanner to establish the cue-button-taste association prior to the acquisition of fMRI data.

After completing 5 BOLD runs, subjects were taken out of the scanner for a liquid breakfast session. Subjects were given either the savory drink of tomato juice or the sweet drink of chocolate milk for breakfast in a pseudorandom, counterbalanced manner. Subjects knew their breakfast selection prior to each of the 2 scans. They were instructed to drink as much of the tomato juice or chocolate milk so that they were no longer hungry. The amount consumed was recorded. Subjects were then instructed to use the bathroom and were rescanned for 5 more BOLD runs. This exact protocol, with the same breakfast selection, was repeated after 7 days of treatment with olanzapine.

Subjects found both chocolate milk and tomato juice significantly more pleasant than the tasteless liquid (eFigure 3) but had a significantly stronger preference for chocolate milk over juice. We had counterbalanced which liquid was satiated (offered for breakfast), but this stronger preference for chocolate milk over tomato juice was a significant confound in assessing postfeeding satiety effects. Thus, postfeeding satiety effects will not be dis-

Table 1. Demographic Characteristics

Characteristics	No. (%)
Age, y, mean (SD)	27.5 (5.9)
Education, y, mean (SD)	16.1 (2.0)
Sex	
M	10 (52.6)
F	9 (47.4)
Race	
White	14 (73.7)
African American	2 (10.5)
Hispanic	2 (10.5)
>1 Race	1 (5.3)
Marital status	
Single	14 (73.7)
Divorced	5 (26.3)

Table 2. Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age 18-50 y. Male or female. Any race or ethnicity.	Any magnetic resonance imaging contraindication.
Does not meet <i>DSM-IV</i> criteria for any mental illness.	Any current medical disorder or any impairment in taste or smell sensation.
Capacity to give informed consent and follow study procedures.	Subjects taking any prescribed medications or over-the-counter herbal remedies.
Ability to read, speak, and understand English.	Any female subject who is currently pregnant, nursing, or planning to become pregnant during the course of the study.
Right handed as judged by the Edinburgh Inventory.	Smoking cigarettes.
Liking for tomato juice and chocolate milk.	
Willingness to spend 7 consecutive nights at the Clinical Research Unit.	

cussed further and this article will focus on the anticipatory and experiential responses to rewarding taste (collapsing across juice and chocolate milk) prior to the satiation phase.

fMRI ACQUISITION AND PROCESSING

Imaging was done on a 3-T Siemens TRIO scanner. High-resolution structural images were acquired using a 3-dimensional sagittal T1-weighted magnetization-prepared rapid-acquisition gradient-echo acquisition optimized for contrast to noise ratio and resolution. A 2-dimensional multislice spin density/T2-weighted fast spin-echo structural image was also acquired, and both of these images were used in the fMRI atlas registration procedure. The functional images were collected in runs using an asymmetric spin-echo sequence sensitive to BOLD contrast (T2* weighting). The imaging parameters were echo time = 27 milliseconds, field of view = 25.6 cm, and flip angle = 90°. Thirty-two contiguous, 4-mm-thick slices were acquired parallel to the anterior-posterior commissure plane (4-mm approximately isotropic voxels) providing complete brain coverage. Each fMRI run included 235 volumes continuously acquired at a repetition time of 2 seconds.

The fMRI data were reconstructed into images and normalized across runs by following standard preprocessing methods using in-house software. The preprocessing steps involved correction for asynchronous slice acquisition, normalizing whole-brain signal intensity to a fixed value within each scanning run; and using a rigid-body rotation and translation protocol to correct for motion. These anatomical images were then registered with a standardized atlas space⁶⁹ using a 12-parameter affine transformation. The fMRI volumes were then coregistered with the subject's anatomical images, transformed into common atlas space, and spatially smoothed using a 6-mm full-width-half-maximum gaussian filter.

fMRI ANALYSIS

The fMRI analysis was done using in-house software (Functional Interactive Data language)⁷⁰⁻⁷² and the behavioral data were analyzed using SPSS version 20 (IBM SPSS). Within each subject, a general linear model approach was used to estimate magnitudes of task-related activity in each voxel using an event-related design. The general linear model was computed without assuming a predefined hemodynamic response function. Task-related activity was computed for time points within a hemodynamic response period that lasted for 18 seconds (9 frames) following an event. There were 2 regressors for the different types of cues (rewarding taste and tasteless liquid) and 2 regressors for the receipt of the liquid following the cue. Separate regressors coded for the receipt of taste that was mislabeled (tasteless liquid delivery following a cue for rewarding liquid).

A region of interest (ROI)-based approach was used to identify regions that showed cue-related anticipatory effects and receipt-related experiential effects to the taste stimuli within the ROI mask. This identical ROI mask was used in prior published studies exploring reward response⁷³ and included the amygdala, nucleus accumbens, putamen, caudate nucleus, substantia nigra, ventromedial prefrontal cortex, insula, and orbitofrontal cortex.

At the group level, we used the parameter estimates from the subject's general linear model to conduct 2 repeated-measures analyses of variance treating subjects as a random effect. The first examined reward anticipation-related effects (ie, cue-related effects). Olanzapine treatment was used as a between-subject factor, and cue type (rewarding or neutral) and time point within trial (time points 1-9) were within-subject factors. The second analysis of variance examined reward receipt-

Table 3. Paired *t* Tests Comparing Vital Signs and TFEQ Scores Prior to and Following 7 Days' Administration of Olanzapine

Variable	Olanzapine, \bar{x} (SD)		t_{18}	<i>P</i> Value
	Before	After		
Weight, kg	77.18 (21.66)	78.27 (21.58)	2.67	.02
BMI	25.78 (4.82)	26.17 (4.84)	2.88	.01
Range	19.29-35.41	19.59-35.58		
Blood pressure, mm Hg				
Systolic	125.95 (17.29)	128.37 (15.01)	1.03	.32
Diastolic	69.53 (12.77)	71.32 (9.06)	0.685	.50
Pulse, beats/min	74.89 (12.79)	82.37 (20.48)	1.78	.09
Respiration, breaths/min	16.11 (2.05)	17.37 (1.17)	2.88	.01
Temperature, °C	36.41 (0.348)	36.46 (0.293)	0.638	.53
TFEQ				
Total score	35.55 (7.07)	37.89 (6.85)	2.95	.009
Disinhibited eating factor score	16.50 (3.97)	17.94 (4.98)	2.36	.03

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); TFEQ, Three-Factor Eating Questionnaire.

related effects (ie, liquid receipt effects). Olanzapine treatment was used as a between-subject factor, and fluid type (rewarding or neutral) and time point (1-9) were within-subject factors. For each of these analyses, we computed voxel \times voxel repeated-measures analyses of variance with the ROI mask described earlier. This constrained our analysis to areas that are strongly associated with reward processing and we used a *z* value of more than 2.58 and a minimum cluster size of 10 to identify significant task-related brain activations (to obtain a within-mask overall *P* value of $<.05$ based on AlphaSim from Analysis of Functional NeuroImages). The interaction with stimuli type (cue or fluid receipt) reflects a statistically significant difference between the reward and neutral conditions.

RESULTS

BEHAVIORAL RESULTS

Adverse Effects From Olanzapine

All except the 2 subjects described earlier tolerated the course of olanzapine without experiencing any severe adverse effects. The adverse effects that were reported by more than 2 subjects were excess sleep, fatigue, decreased energy, dry mouth, difficulty sleeping, headache, dizziness, and poor concentration (eTable).

Weight and Vital Signs

Subjects gained on average 1.1 kg over 1 week of taking olanzapine, which is a significant increase (**Table 3**). Subjects did not experience any significant changes in their blood pressure, temperature, or heart rate. They had a significant increase in their respiratory rate (Table 3).

Eating Behavior

Subjects had a significant increase in their overall Three-Factor Eating Questionnaire score ($t_{17}=2.946$; $P=.009$) and in the disinhibited eating factor subscale score ($t_{17}=2.362$; $P=.03$) after treatment with olanzapine (Table 3).

Hunger Rating, Salience of Reward, and Breakfast Amount

Subjects rated their hunger before the fMRI scan and after the first half of the experiment, but before they had their liquid breakfast. Subjects' perception of hunger was close to 3 (hungry) before the scan and this did not change significantly before breakfast or with olanzapine treatment (eFigure 4). During the scan, subjects rated their experience of the rewarding taste and the tasteless solution after each BOLD run. As described in the "Methods" section, they rated both chocolate milk and tomato

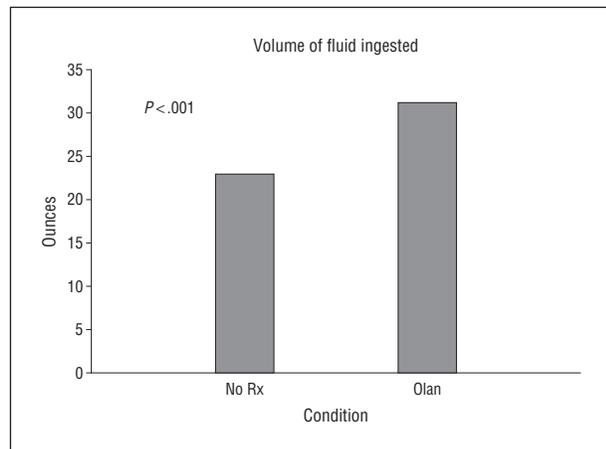


Figure 2. Increased consumption of liquid breakfast after a 7-day treatment with olanzapine (Olan). The P value reflects the results of a t test. Rx indicates prescription.

juice as significantly more pleasurable than the tasteless solution. Their ratings of these liquids did not differ significantly after treatment with olanzapine (eFigure 1). There was a significant increase in the amount of liquid breakfast consumed during the out-of-scanner satiety phase after treatment with olanzapine ($P<.001$) (**Figure 2**).

IMAGING RESULTS

Anticipation of Reward

We first examined BOLD responses to cues predicting reward vs tasteless solution, irrespective of treatment with olanzapine (eg, cue type \times time point interaction). This analysis revealed a number of expected regions in the inferior frontal gyrus, claustrum, insula, and caudate (**Figure 3** and **Table 4**) that showed greater response to cues predicting reward as compared with cues predicting tasteless liquid (see **Figure 4** for time course examples). Importantly, there were additional brain areas that showed further interactions with olanzapine treatment (eg, treatment \times cue type \times time point interactions) (Figure 3 and Table 4). The time courses of the activations in these regions showed a consistent pattern of increased responses to the anticipation of reward and a decreased response to the tasteless solution cue after treatment with olanzapine (Figure 4).

Experience of Reward

We next examined BOLD responses to the receipt of rewarding fluids in comparison with the tasteless liquid, collapsed across the treatment condition (eg, liquid type \times time point interaction). This analysis again revealed a number of expected regions in the insula, caudate, putamen, amygdala, inferior frontal gyrus, middle frontal gyrus, and medial prefrontal cortex

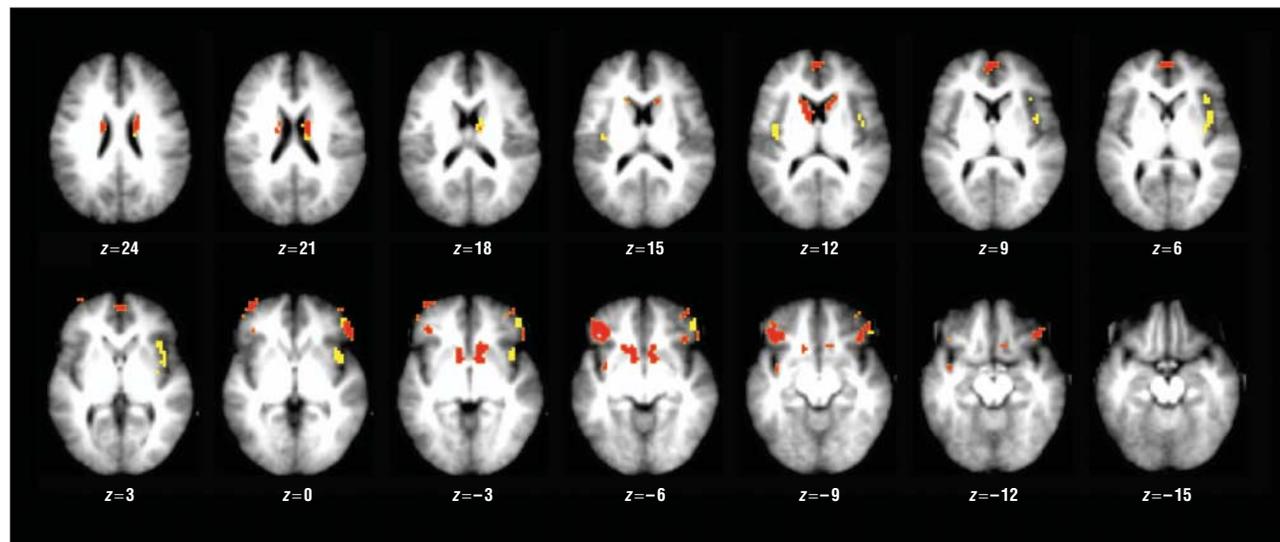


Figure 3. Activation maps of cue-related anticipatory response. Right is on the right and left is on the left. Regions displaying a cue type (reward vs tasteless) \times time point interaction are in yellow and regions displaying a further interaction with treatment (treatment \times cue type \times time point) are in red. All the significant task-related brain activations depicted here have a P value of $<.05$ at the mask level, which corresponds to a z value of more than 2.58 ($P<.005$) per voxel and a minimum cluster size of 10 voxels.

Table 4. Brain Regions Identified in Analysis of Reward Anticipation (Cue-Related Activity)

Region	Brodman Area	Cluster Size, Voxels	x	y	z	z Score	Effect Size, ω^2
Cue × Time Point							
Inferior frontal cortex	47	29	46	33	-3	4.75	0.20
Clastrum		57	38	4	3	3.67	0.14
Insula	13	12	-38	-12	12	3.28	0.12
Caudate		22	11	-10	20	3.71	0.14
Cue × Session × Time Point							
Inferior frontal cortex	47	28	40	25	-9	4.51	0.19
Inferior frontal cortex	47	69	-39	28	-6	4.75	0.21
Caudate		41	9	8	-5	5.30	0.24
Clastrum		10	-37	-4	-8	3.40	0.11
Inferior frontal cortex	10	13	38	45	-4	3.87	0.15
Lentiform nucleus		34	-10	7	-5	4.99	0.22
Inferior frontal cortex	47	20	49	27	-1	3.97	0.15
Middle frontal gyrus	10	17	-37	52	0	3.86	0.15
Anterior cingulate	32	36	0	49	7	4.62	0.19
Caudate		12	11	14	12	3.24	0.11
Caudate		19	-11	8	12	3.32	0.11
Caudate		19	13	-6	22	3.37	0.13
Caudate		11	-15	-7	22	3.28	0.11

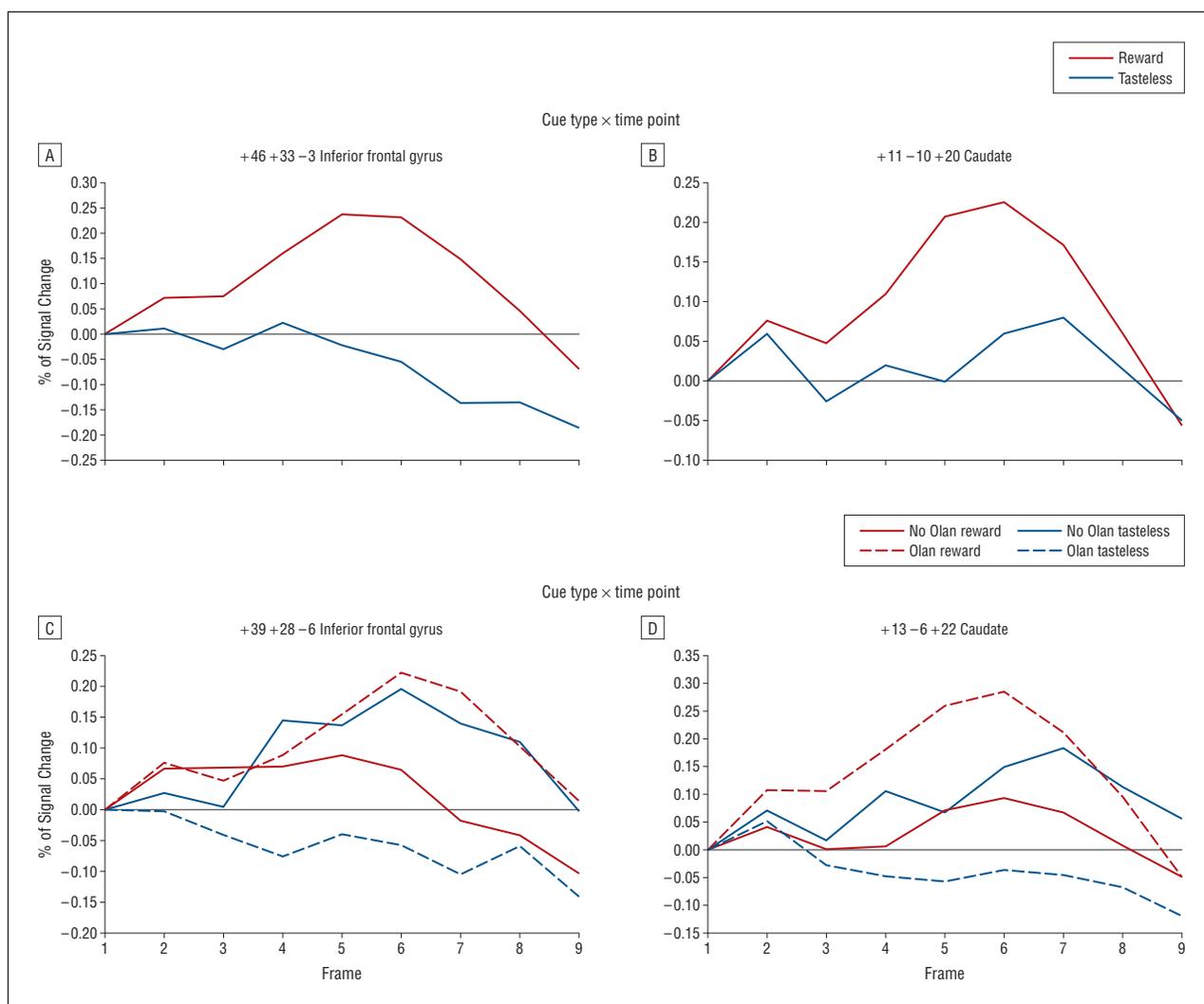


Figure 4. Examples of graphs plotting the time courses of the hemodynamic response curve to cue-related activity. Each time point on the x-axis represents 1 frame (2 seconds). A and B, Examples of the cue type × time point analysis, irrespective of treatment with olanzapine (Olan). C and D, Examples of further interaction with treatment (treatment × cue type × time point), where the red dotted line represents responses after olanzapine treatment for the rewarding taste while the blue dotted line represents the responses to the tasteless liquid after olanzapine treatment. All the significant task-related brain activations depicted here have a *P* value of <.05 at the mask level, which corresponds to a *z* value of more than 2.58 (*P* < .005) per voxel and a minimum cluster size of 10 voxels.

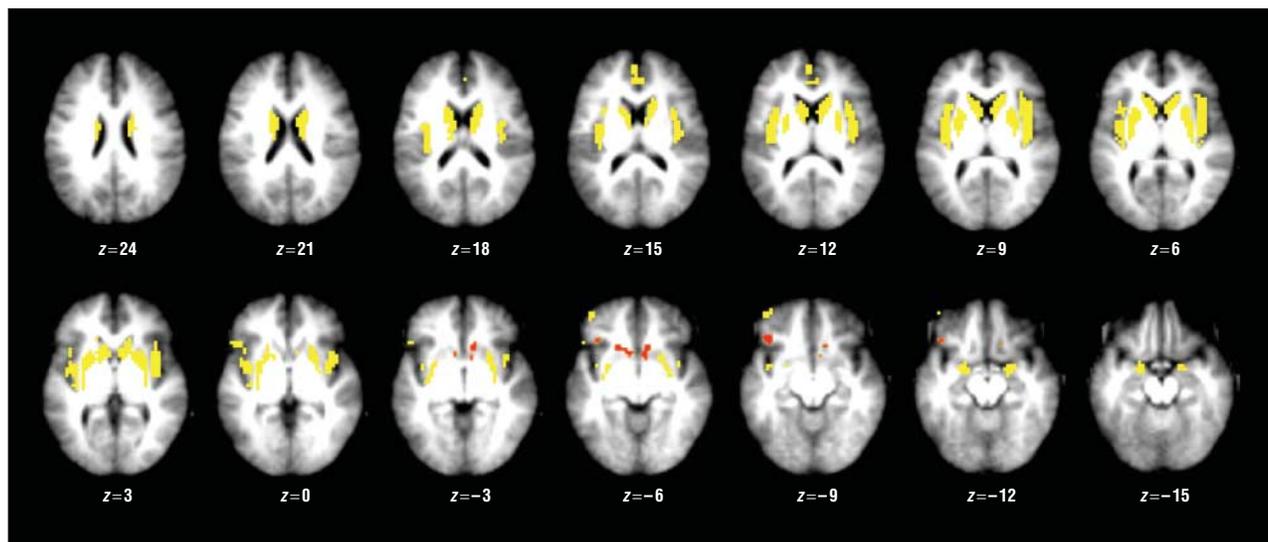


Figure 5. Activation maps of liquid receipt-related response. Right is on the right and left is on the left. Regions displaying a liquid type (reward vs tasteless) \times time point interaction are in yellow and regions displaying a further interaction with treatment (treatment \times liquid type \times time point) are in red. All the significant task-related brain activations depicted here have a P value of $<.05$ at the mask level, which corresponds to a z value of more than 2.58 ($P < .005$) per voxel and a minimum cluster size of 10 voxels.

Table 5. Brain Regions Identified in Analysis of Reward Receipt (Liquid Receipt-Related Activity)

Region	Brodmann Area	Cluster Size, Voxels	x	y	z	z Score	Effect Size, ω^2
Receipt \times Time Point							
Insula	13	87	-36	-18	13	5.68	0.26
Lentiform nucleus		18	30	-14	7	5.11	0.23
Caudate		51	13	-7	21	6.30	0.31
Amygdala		46	22	-5	-12	5.55	0.26
Caudate		27	-14	-15	21	5.97	0.29
Caudate		103	-12	0	12	5.12	0.24
Putamen		92	-30	-13	-2	4.67	0.20
Caudate		150	13	7	9	4.73	0.20
Insula	13	115	36	12	6	3.97	0.15
Inferior frontal gyrus		17	-47	16	0	4.13	0.16
Insula	13	89	-33	6	12	4.05	0.17
Caudate		37	-16	19	8	3.67	0.14
Middle frontal gyrus	11	12	-42	44	-8	4.31	0.17
Amygdala		31	-20	-6	-15	4.47	0.18
Medial frontal gyrus	10	27	-3	45	13	3.22	0.11
Receipt \times Session \times Time Point							
Inferior frontal gyrus	47	14	-39	20	-8	4.23	0.17
Caudate		20	8	11	-5	4.69	0.20
Putamen		12	-11	10	-5	3.96	0.15

(**Figure 5** and **Table 5**). As shown in **Figure 6**, the time courses in these regions showed a greater response to the receipt of rewarding liquids as compared with the tasteless solution. There were 3 additional brain areas that showed a further interaction with treatment (eg, treatment \times liquid type \times time point interactions), which included the inferior frontal gyrus, caudate, and putamen (Table 5). The time course of activations in these regions showed that in the inferior frontal gyrus, there was a decrease in activation to the rewarding taste after olanzapine treatment, while the response to the tasteless solution increased. In the caudate and putamen, the response to rewarding taste increased after olanzapine treatment

while the response to the tasteless solution decreased (Figure 6).

COMMENT

To our knowledge, this is the first human study to look at the neural correlates of weight gain after a 1-week trial of an antipsychotic medication. We were interested in characterizing the taste reward response underlying olanzapine-induced weight gain. Our study design allowed us to evaluate the impact of olanzapine on both the anticipatory and experiential aspects of a taste reward. We found that our subjects gained weight, in-

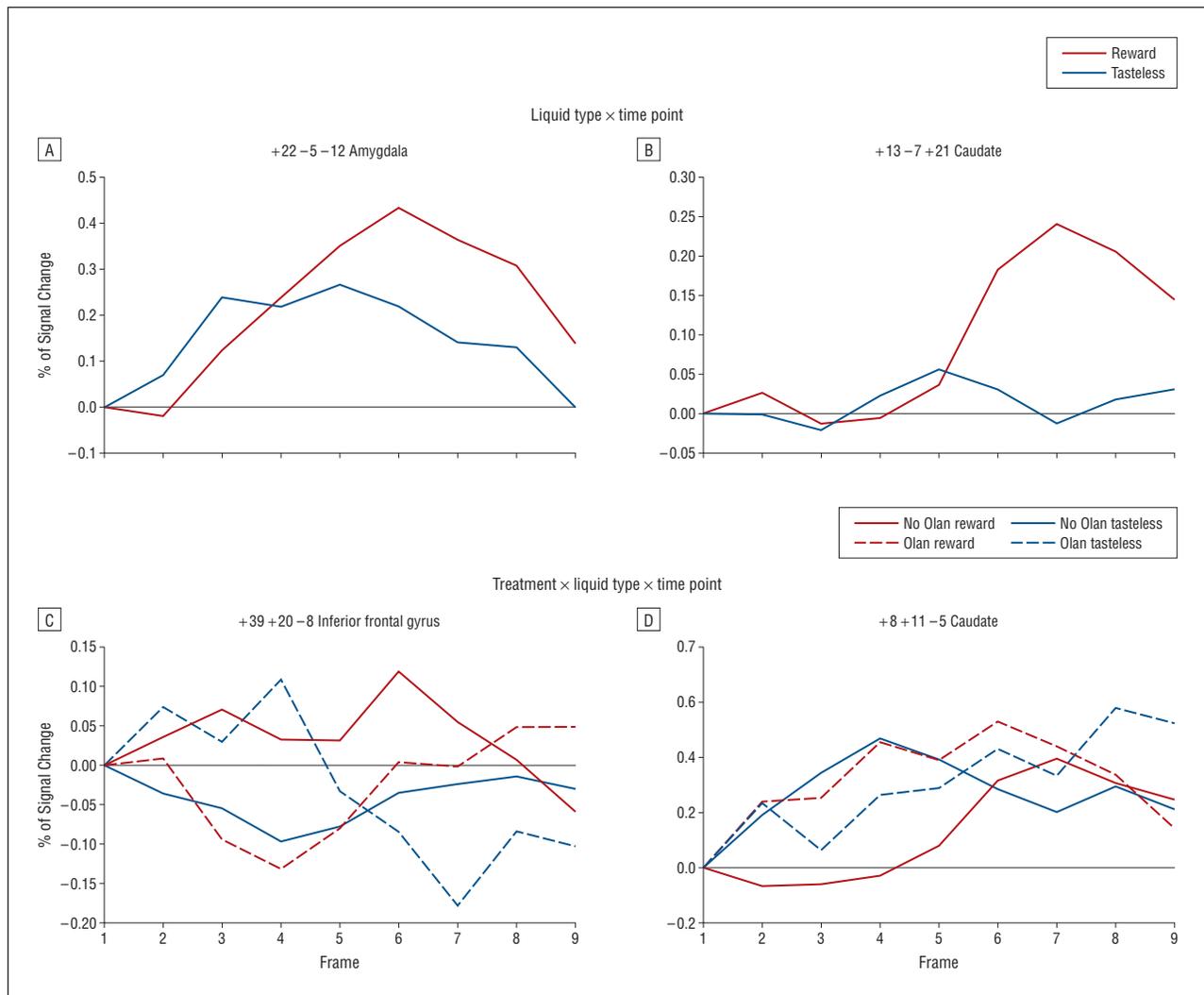


Figure 6. Examples of graphs plotting the time courses of the hemodynamic response curve to receipt-related activity. Each time point on the x-axis represents 1 frame (2 seconds). A and B, Examples of the liquid type \times time point analysis, irrespective of treatment with olanzapine (Olan). C and D, Further interaction with treatment (treatment \times liquid type \times time point). In the inferior frontal gyrus (C), the response to rewarding taste receipt goes down after olanzapine treatment (solid red line compared with the dashed red line) while the converse is noted in the caudate (D). All the significant task-related brain activations depicted here have a P value of $<.05$ at the mask level, which corresponds to a z value of more than 2.58 ($P < .005$) per voxel and a minimum cluster size of 10 voxels.

creased their food intake, and demonstrated an increase in their self-reported disinhibited eating behavior. Further, our imaging data showed an increase in the anticipatory reward responsivity toward food reward in the inferior frontal cortex, striatum, and anterior cingulate cortex. We also found an increase in reward receipt responsivity in the caudate and putamen but a decrease in reward receipt responsivity in the lateral orbital frontal cortex, an area of the brain regarded as exercising inhibitory control on feeding.^{28,29,74,75}

The adverse effects experienced by subjects in this study were consistent with other studies that administered olanzapine to healthy participants⁴¹⁻⁴³ and with the Food and Drug Administration–approved prescribing information for olanzapine.⁷⁶ Subjects gained on average 1.1 kg after 1 week of olanzapine treatment, thus lending ecological validity to the experiment. A significant degree of weight gain has been reported in several studies investigating olanzapine-induced weight gain in healthy subjects^{41-43,48} and in people with schizophrenia.³⁸⁻⁴⁰ One small study that explored in-

sulin resistance after 8 days of olanzapine treatment did not find statistically significant weight gain. However, this study detected insulin resistance and other metabolic changes that presage weight gain and there was a trend toward weight gain.⁷⁷

Subjects also had a significant increase in the amount of liquid breakfast they consumed after olanzapine treatment. A recent study investigated changes in food intake and energy expenditure in healthy, nonobese male subjects who took olanzapine for 15 days.⁴⁸ This study found a 23% average increase in food consumption, which is consistent with the 35% increase in the breakfast consumption that we noted after a week of olanzapine treatment. Another study that investigated olanzapine-induced weight gain in healthy subjects over a 2-week period found significant weight gain but not a significant increase in caloric consumption, although the means slightly increased.⁴¹

Participants also had significant increases in the Three-Factor Eating Questionnaire total score and the disinhib-

ited eating factor subscale score. The other 2 factor scores—eating restraint and hunger—were not significantly different. An elevated disinhibited eating score has been shown to predict weight gain in healthy adult subjects^{78,79} and was related to obesity in otherwise healthy adolescents.⁸⁰ In a study that used the Three-Factor Eating Questionnaire to assess patients with schizophrenia, the disinhibited eating scores were found to be higher in patients taking atypical antipsychotic medications, those who were obese, and those with elevated waist circumference.⁸¹

Interestingly, subjects' perception of hunger did not change significantly after olanzapine treatment nor did their perception of the pleasantness of chocolate milk or V8 tomato juice (Campbell Soup Company). These findings contrast to the actual behavior of the subjects described earlier, as they consumed significantly more breakfast and gained weight after treatment with olanzapine. The neuroimaging data discussed later may shed some light into this dissociation between hunger perception and eating behavior. In sum, we found that 7 days of olanzapine treatment in our healthy, nonobese participants caused significant increases in their weight, self-reported disinhibited eating behavior, and amount of liquid breakfast they consumed, all while their hunger score and perceived pleasantness of the taste reward remained stable.

Recent neuroimaging literature provides good evidence for reward processing networks that encode the anticipatory "wanting" aspect of a taste reward and the experiential "liking" aspect of that taste.^{24,82} There are dissociable differences in the neural response to these 2 aspects of reward processing^{24,82} (Table 4 and Table 5). Consistent with prior research, we found that regions in the anterior insula, caudate, and inferior frontal cortex all showed increased BOLD responses to cues that predicted upcoming rewarding liquids, suggesting that our paradigm was successful in eliciting anticipatory reward-related responses.^{23,24,82,83} When we looked at the regions that further interacted with olanzapine treatment, we found regions in the inferior frontal cortex, striatum, and anterior cingulate. All these regions showed enhanced responses to cues predicting rewarding liquids after olanzapine, while there was a decrease in activations elicited by the picture of the tasteless liquid. Increased anticipatory responses in these reward regions to the anticipation of a pleasant taste have been associated with obesity in a number of studies.³⁵⁻³⁷ Furthermore, a recent study found that elevated activations in the anterior cingulate cortex and orbital frontal cortex to the anticipation of palatable food correlated with higher scores of a validated food addiction scale: the Yale Food Addiction Scale.⁷⁵ The increase in food cue-related reward response we found after olanzapine treatment in our nonobese participants, taken together with studies showing similar increases in obese individuals and those with disinhibited eating, is consistent with the hypothesis that enhanced responses to food cues may contribute to the increased food intake and weight gain we observed with olanzapine treatment.

The experience of rewarding taste showed activations in the insula, amygdala, caudate, putamen, medial frontal cortex, and inferior frontal cortex. All of these re-

gions have been shown to respond to the experience of a taste reward in previous studies^{24,36,82,84} and indicated that our paradigm was successful in eliciting taste receipt-related responses. The regions that further interacted with olanzapine treatment were in the lateral orbital frontal cortex, caudate, and putamen. In the caudate and putamen, activation to the experience of rewarding taste was enhanced after treatment with olanzapine. This enhanced activation in the striatum in our nonobese participants is in contrast to studies in obese individuals where either striatal hypoactivity^{25,36} or no change in striatal activity was noted.⁸⁵ However, these studies compared obese and lean healthy individuals who were not taking any medication.

In the lateral orbital frontal cortex, the response to the actual experience of chocolate milk and tomato juice was diminished after treatment with olanzapine. This region is hypothesized to play a role in suppressing response to taste stimuli that were previously rewarding^{28,74} and may play a role in satiety.⁷⁵ The increase in the anticipation responses or "wanting" of food reward along with an increased consummatory "liking" response to food, in the context of a decreased response in a lateral orbital frontal region thought to inhibit responses to food taste, could dynamically interact to contribute to the increased food intake, disinhibited food attitudes, and resultant weight gain that we observed after treatment with olanzapine.

This imbalance between the reward circuitry and circuits that inhibit prepotent responses to rewarding food^{75,84,86,87} could extend our understanding of the mechanism of weight gain with atypical antipsychotic medications. Further, these findings in our nonobese subjects are in general agreement with models of obesity,^{17,25} albeit with an important difference: We found an increased response to food consumption in the dorsal striatum, while the literature in obese individuals points to a reduced response. As such, it is possible that this pattern is present in the initial stages of rapid weight gain and that we would find evidence for a decreased response to food in the striatum if we studied individuals taking olanzapine for longer periods. Such reduction in striatal responsivity to the taste of milkshake was recently reported in healthy women after they had gained weight over a 6-month period.⁸⁸

Our results contrast with a small pilot study with 8 subjects investigating monetary reward-related brain activation after a single dose of 5 mg of olanzapine.⁸⁹ This study found reduced activations in the ventral striatum, anterior cingulate, and inferior frontal cortex while taking olanzapine compared with placebo. However, this study used a monetary reward paradigm that did not distinguish reward anticipation from reward experience and focused on the acute 1-dose effect of olanzapine. Our study showed a more complex relationship of olanzapine treatment to an ecologically valid food reward after a steady-state dosing duration.

There were several limitations of this study. First, we did not have a placebo control group and this limits our ability to conclusively demonstrate that the changes we observed were due to olanzapine treatment. Second, because our unmedicated scan always preceded the scan

with olanzapine, it is possible that habituation effects could be confounded with the olanzapine effects. However, the majority of the olanzapine-related anticipatory and receipt effects were in the direction of increased responses to rewarding food cues or to the receipt of food (eg, in the caudate), which is in the opposite direction of the effects predicted by habituation over time. Further, we also saw reduction of response in regions of the lateral orbital cortex that may play a role in inhibition. Thus, this interpretable pattern of both increased and decreased activation is not consistent with a general change in activity as a function of time.

Third, although participants had significant increases in their breakfast consumption, a food record and a measure of their physical activity would have yielded a more detailed picture. Fourth, we used an ROI approach to analyze the data in view of our sample size and our a priori hypothesis that focused on the reward regions. Future research with a larger sample size may indicate changes in a wider array of brain regions.

Finally, although subjects preferred both chocolate milk and tomato juice over the tasteless liquid, subjects had a stronger preference for chocolate milk over tomato juice. This presented a significant confound in assessing postfeeding satiety effects; hence, this aspect of the data could not be examined and differences in homeostatic regions such as the hypothalamus that differ as a function of satiety could not be explored.⁹⁰⁻⁹²

CONCLUSIONS

With these limitations in mind, our study was the first, to our knowledge, to assess the neural mechanism underlying olanzapine-induced weight gain using an ecologically valid food-related reward paradigm. Our participants experienced significant weight gain, increased food intake, and disinhibition in their eating behavior. These changes in food-related cognition and behavior were accompanied by enhanced fMRI responses to food cues and the taste of food in a number of reward-related brain regions, including the inferior frontal cortex, striatum, and anterior cingulate. Further, the use of olanzapine was associated with a decrease in activity to food receipt in the lateral orbital frontal cortex, a region thought to play a role in satiety responses. These fMRI changes suggested an enhanced anticipatory desire for food, an enhanced reward experience of consuming the anticipated food, and a compromised satiety-related mechanism. This pattern of change after treatment with olanzapine provides a plausible set of mechanisms that may contribute to the weight gain commonly associated with this medication.

Our understanding of this common and unfortunate adverse effect of treatment with atypical antipsychotics would be enhanced by larger placebo-controlled studies that use comparator antipsychotic agents with low weight gain liability in patient populations; use continuous records of food intake and physical activity; use body composition assessments; explore prediction error-related effects, sex differences, and neural activity that correlates with the degree of weight gain; use appropriate satiety stimuli; and

examine interactions with other malfunctions of the reward system such as substance abuse. This could pave the way for targeted treatments that may help dial down the enhanced reward value of food while strengthening the inhibitory circuits that control food intake.

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