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Oxytocin Reduces the Functional Connectivity Between Brain Regions Involved in Eating Behavior in Men with Overweight and Obesity.

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Abstract

Background: Oxytocin (OXT), shown to decrease food intake in animal models and men, is a promising novel treatment for obesity. We have shown that in men with overweight and obesity, intranasal (IN) OXT reduced the functional magnetic resonance imaging (fMRI) blood oxygenation level-dependent signal in the ventral tegmental area (VTA), the origin of the mesolimbic dopaminergic reward system, in response to high-calorie food vs. non-food images. Here, we employed functional connectivity fMRI analysis, which measures the synchrony in activation between neural systems in a context-dependent manner. We hypothesized that OXT would attenuate the functional connectivity of the VTA with key food motivation brain areas only when participants viewed high-calorie food stimuli.

Methods: This randomized, double-blind, placebo-controlled crossover study of 24 IU IN OXT included 10 men with overweight or obesity (mean±SEM BMI: 28.9±0.8 kg/m^2). Following drug administration, subjects completed an fMRI food motivation paradigm including images of high and low-calorie foods, non-food objects, and fixation stimuli. A psychophysiological interaction analysis was performed with the VTA as seed region.

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Results: Following OXT administration, compared with placebo, participants exhibited significantly attenuated functional connectivity between the VTA and the insula, oral somatosensory cortex, amygdala, hippocampus, operculum, and middle temporal gyrus in response to viewing high-calorie foods ($Z \geq 3.1$, cluster-corrected, $p < 0.05$). There was no difference in functional connectivity between VTA and these brain areas when comparing OXT and placebo for low-calorie food, non-food, and fixation images.

Conclusion: In men with overweight and obesity, OXT attenuates the functional connectivity between the VTA and food motivation brain regions in response to high-calorie visual food images. These findings could partially explain the observed anorexigenic effect of OXT, providing insight into the mechanism through which OXT ameliorates food cue-induced reward anticipation in patients with obesity. Additional studies are ongoing to further delineate the anorexigenic effect of OXT in obesity.

Introduction

Despite increasing awareness of obesity as a chronic disease associated with significant comorbidities, the worldwide prevalence of obesity continues to increase, and it has nearly tripled in the last 40 years (1). The most commonly adopted treatment for obesity, lifestyle intervention, is only partially effective, and most individuals who successfully lose weight fail to maintain their weight in the healthy range (2, 3). Chronic overeating, and specifically overconsumption of high-calorie foods, is a key determinant of obesity. Functional magnetic resonance imaging (fMRI) studies in individuals with obesity have demonstrated increased activation of reward-related brain regions (e.g., insula, amygdala, orbitofrontal cortex and striatum) that drive overconsumption of foods in the absence of a homeostatic need for caloric intake, when participants view pictures of highly palatable foods (4-11). In an obesogenic environment in which palatable foods are highly accessible, hyper-responsivity of reward brain regions may contribute to the development and maintenance of obesity (12), and therefore reward pathways represent a potential therapeutic target.

The hypothalamic neurohormone oxytocin has been shown to decrease food intake and body weight in animal models and, recently, in clinical studies with men with overweight and obesity and is actively being researched as a novel and promising pharmacological treatment for obesity (13, 14). Oxytocin is a nine-amino acid neuropeptide hormone that is predominantly produced in the paraventricular and supraoptic nuclei of the hypothalamus. It is dispersed across the brain via distal axonal projections from parvocellular paraventricular nucleus oxytocin neurons as well as local dendritic release into the extracellular space (15, 16). In addition to a central release within the brain, oxytocin is also released into the peripheral circulation following activation of magnocellular supraoptic nucleus oxytocin neurons that project to the posterior pituitary (17). The G-protein coupled oxytocin receptor can be found in a wide range of brain areas, including those related to reward processing such as the ventral tegmental area (VTA), insula, amygdala, and nucleus accumbens (18, 19). Using virus-based and cell type-specific monosynaptic tracing techniques (20) as well as optogenetic and electrophysiological approaches (21), studies have shown direct projections of the paraventricular nucleus synthesizing neurons to the VTA, which is known to be critically involved in motivational food processing (22).

Animal studies support the role of oxytocin as a potent regulator of caloric intake, body weight and energy metabolism (23). Administration of oxytocin to diet-induced rats (24) and mice (25) resulted in a decrease in body weight gain with a preferential reduction in fat mass in rats (26) as well as increased adipose tissue lipolysis, reduced glucose intolerance and insulin resistance in rats (27) and mice (28). Similarly, ob-/ob- mice treated with oxytocin also displayed a dose-dependent reduction in food consumption and body weight gain (29), and obese diabetic db/db mice showed significant reduction in body fat accumulation and improved glucose and fat metabolism under oxytocin treatment (30). Consistent with a specific effect on reward-related eating behavior, administration of oxytocin directly into the VTA in rats significantly suppressed intake of a 10% sucrose solution while administration of oxytocin receptor antagonists into the VTA resulted in a significant increase of sucrose intake, suggesting that endogenous oxytocin action within the VTA suppresses palatable food intake (31).

More recently, oxytocin has also been shown to have anorexigenic effects in humans, including a specific modulation of hedonic appetite regulation. Two randomized, placebo-controlled crossover studies of a single intranasal (IN) dose of 24 IU of oxytocin in healthy men showed that oxytocin significantly reduced hunger-driven caloric intake. The effect was seen across the weight spectrum (normal weight to overweight) in one study (32), while another study concluded that oxytocin reduces food intake in those with obesity but not normal-weight participants (33). In addition, oxytocin has been shown to significantly attenuate post-prandial palatable snack consumption, representing hedonic eating in men across the weight spectrum (33, 34). Prolonged daily administration of IN oxytocin for eight weeks in a pilot study of nine men and women with obesity was well-tolerated and resulted in an overall mean body mass index (BMI) reduction of 3.2 ± 1.9 kg/m^2 (35). In patients with Prader–Willi syndrome, a complex genetic disorder characterized by severe hyperphagia, reduction in oxytocin-producing neurons and obesity, oxytocin-based therapeutics are currently under investigation with initial findings showing an improvement in hyperphagia and a reassuring safety profile (36, 37).

Functional MRI studies have provided insight into the neurobiological mechanisms by which oxytocin reduces caloric consumption, demonstrating effects of oxytocin on reward (as well as homeostatic and cognitive control) brain regions (for more details, see 38, 39). We showed that in men with overweight and obesity, oxytocin reduced the blood oxygenation level-dependent (BOLD) signal to high-calorie food versus non-food visual stimuli in the VTA (40). An exploratory whole-brain analysis revealed hypoactivation in additional hedonic food motivation brain areas (orbitofrontal cortex, insula, globus pallidus, putamen, hippocampus, and amygdala). While activity changes in singular regions linked to hedonic food motivation following oxytocin administration are a promising first indicator for the hypothesis that oxytocin might positively affect food intake and weight in part through impacting reward food motivation brain regions, dietary choices and food intake emerge from a network of synergistically acting brain regions.

Accordingly, the study of network dynamics (i.e., coordinated activation between interconnected brain regions) represents a key step in further elucidating the role of oxytocin in regulating food intake and weight, and to our knowledge, no studies have pursued this line

of research to date. Using the same data set as Plessow et al. (40), we analyzed the functional connectivity between the VTA (as a key brain region involved in food motivation and altered by oxytocin in both animal and human studies) and the rest of the brain. We used a specific method called psychophysiological Interaction (PPI) analysis to examine connectivity during our visual food cue task. First described by Friston (41), this analytic method determines which brain voxels increase their activity in synchrony with a seed region of interest in a given context or task (42). PPI differs from resting-state functional connectivity, which measures task-independent, intrinsic low-frequency BOLD signals that are assumed to reflect intrinsic functional interactions between brain regions. The PPI analysis identifies task-specific changes in the interaction between brain areas, with increased synchrony in brain activation being suggestive of task-specific increase in exchange of information.

Within the randomized, double-blind, placebo-controlled crossover pilot study of a single dose of 24 IU intranasal oxytocin, fMRI was recorded for 10 men with overweight or obesity during viewing of high-calorie food images, low-calorie images, non-food images (household objects), and fixation stimuli. We hypothesized that oxytocin (vs. placebo) would reduce the functional connectivity between the VTA and key brain areas involved in food sensory and cognitive processing when participants viewed high-calorie foods images, while this effect would not be observed in response to low-calorie food images, non-food objects, or fixation stimuli.

Subjects and Methods

Subjects

The study included ten subjects with a mean age (±SEM) of 31.4±1.8 years (range: 23-43 years) and a BMI of 28.9±0.8 kg/m^2 (range: 25.3-33.7 kg/m^2). Exclusion criteria included a history of a psychiatric disorder, history of an eating disorder, excessive exercise routine (running >25 miles or exercising >10 h in any 1 week), substance abuse, smoking, history of cardiovascular disease, diabetes mellitus, gastrointestinal tract surgery, or untreated thyroid disease, anemia, and contraindications to MRI. As outlined in the Introduction section, this analysis was based on a previously reported data set. More detailed participant characteristics and a primary BOLD analysis have been published previously (40), while the functional connectivity analyses to test the outlined hypothesis is completely novel and has not been reported before.

Procedure

This study (clinicaltrials.gov: NCT02276677) was approved by the Partners HealthCare Institutional Review Board and conducted in accordance with the Declaration of Helsinki. All participants provided their written informed consent prior to participation. Participants were admitted to the Massachusetts General Hospital Clinical Research Center for an outpatient screening visit to determine eligibility and two main study visits. They were instructed to maintain the same diet during the 72 hours prior to the main visits and to arrive after a 10-hour overnight fast. Intranasal oxytocin (24 IU, Syntocinon, Novartis, Switzerland, provided by Victoria Pharmacy Zürich, Switzerland) or placebo (same inactive

ingredients and packaging, Victoria Pharmacy) nasal spray was self-administered. For this randomized, double-blind, placebo-controlled crossover study, the research pharmacy randomized the participants 1:1 to one of two drug orders (i.e., oxytocin—placebo or placebo—oxytocin). Sixty minutes after oxytocin or placebo administration, participants underwent fMRI (For further details see 40).

Functional MRI Paradigm

Functional MRI scanning was performed during a well-established food motivation paradigm that has been reported in detail elsewhere (40, 43), in which subjects viewed 100 high-calorie food stimuli, 100 low-calorie food stimuli, 100 non-food-related household objects, and 100 fixation stimuli in a block design. Each stimulus was presented once for 3 s using Presentation® software (Neurobehavioral Systems, Albany, CA, USA). Participants were instructed to press a button when pictures changed to insure their attention to stimuli. A total of five 4-min runs with five images in each block and 16 blocks in each run were completed.

MRI Acquisition Parameters

MRI data were acquired using a Siemens 3T Trio scanner (Siemens, Erlangen, Germany) at the Athinoula A. Martinos Center for Biomedical Imaging. Head movements were restricted with foam cushions. Whole-brain functional imaging was performed using a gradient-echo EPI pulse sequence (33 contiguous oblique-axial slices, 4-mm thick, TR/TE = 2000/30 ms, flip angle = 90°, FOV = 200 × 200 mm, 120 total images per run).

Functional MRI data preprocessing and processing was carried out using FSL 6.0. Data were motion-corrected using MCFLIRT, and the motion parameters were added as confound variable in the model. Each run was analyzed separately for each condition using a custom EV file with a gamma sigma = 3 and gamma delay = 4 and then combined for each subject, using fixed effect analysis. Functional images were registered to high-resolution structural images using FLIRT, and then registered to the MNI standard space with non-linear transformation FNIRT.

fMRI and Psychophysiological Interaction (PPI) Analysis

A PPI analysis was conducted to examine the effects of oxytocin on the functional connectivity between the VTA and the rest of the brain, in response to the visual images. The bilateral VTA was chosen as the seed region based on our previous findings of oxytocin-modulated activity in the VTA (40). Seed regions were defined in the left and right VTA by creating a 2×2×2 mm space around the peak activation found in these structures in our previous paper (40). Time courses of mean activity were extracted in each seed for each subject using fslmeants. Task-specific changes (i.e., functional connectivity activation seen during each condition) were examined for each subject using the mean-centered task time course and the demeaned seed ROI time course as described by O'Reilly et al. (42). Then, within-subject fixed-effect comparison was done for each condition before and after treatment. Higher-level statistics were conducted using mixed effect GLM analysis, with FLAME 1+2 and automatic outlier detection. Functional MRI data processing was carried out using FEAT version 6.00, part of FSL FMRIB’s software library (www.fmri.ox.ac.uk/

fsl). Z-statistic images were thresholded using clusters determined by Z>3.1 and a corrected cluster significance threshold of p=0.05 (44).

Results

Following administration of oxytocin, compared with placebo, participants exhibited significantly attenuated functional connectivity between the VTA and the insula, oral somatosensory cortex, amygdala, hippocampus, operculum, middle temporal gyrus and primary visual cortex in response to viewing high-calorie foods (see Table 1, Figures 1-2). In contrast, there was no difference in the functional connectivity between the VTA and these brain areas when comparing oxytocin and placebo for each one of the other conditions (low-calorie food items, objects, or fixation stimuli). Moreover, there were no significant increases in functional connectivity between the VTA and any brain regions following oxytocin versus placebo.

Discussion

In this pilot study of men with overweight and obesity, we have shown that when subjects were processing high-calorie food images, a single dose of 24 IU oxytocin reduced the functional connectivity between the VTA, a key hedonic brain region that drives efforts to obtain desired foods, and multiple brain areas involved in the sensory, cognitive, and emotional processing of food cues. Importantly, this effect was not found when subjects viewed low-calorie food items, household objects, or fixation stimuli and thus it is specific to the context of pictures of palatable food. To our knowledge, our study is the first analysis of task-dependent functional-connectivity using an fMRI paradigm in individuals with overweight and obesity receiving oxytocin. Our findings are particularly relevant to individuals with obesity, since previous neuroimaging studies have shown hyperactivation of brain reward areas in response to palatable food images in these subjects (8, 45-47), and it has been proposed that this hyperactivity of the dopaminergic reward circuit may exacerbate overeating behavior in individuals with obesity (22).

In our study, administration of oxytocin resulted in attenuation of the functional connectivity of the VTA with the insula, somatosensory cortex, operculum, amygdala and hippocampus, all of which have been shown to have structural neuronal connections with the VTA (20, 48, 49). Our analysis supports a task-dependent synchrony between the VTA and a group of food motivation brain areas that was attenuated by oxytocin and only in the setting of viewing high-calorie food items. The insular cortex has been shown to function as a gustatory center, integrating input from both external cues (sight and taste of food) and internal signals such as interoceptive attention, energy bioavailability (e.g., peripheral glucose levels) and visceral signals such as gastric distention (50-54). It is closely interconnected with the orbitofrontal cortex, which represents reward value and functions as a hub involved in the neural processing of external sensory information tightly linked to reward processing (55). The anterior insula has a core role in supporting subjective feeling. In more detail, it has been proposed that objective interoceptive signals arriving to the posterior insula are further processed and re-represented in the anterior insula. This posterior-to-anterior remapping of interoceptive signals allows for conscious perception of

the interoceptive information and occurs due to integration with emotional, cognitive, and motivational signals collected from other cortical and subcortical regions, such as the amygdala, anterior cingulate cortex, and striatum (56, 57). Our findings show that oxytocin significantly attenuates the connectivity between the VTA and the insula only in response to high-calorie images, suggesting it specifically affects the process of subjectively representing palatable food images. Interestingly, neuroimaging studies show that individuals with obesity demonstrate fMRI hyperactivation of the insular cortex in response to visual food cues in comparison to lean individuals (7) with a positive correlation between the degree of hyperactivation and BMI (58). Furthermore, an fMRI *resting-state* functional connectivity study showed that while normal-weight subjects exhibited a significant decrease in pre- to post-meal resting-state functional connectivity between the mid-insula and ventral-striatal reward areas, subjects with obesity demonstrated an opposing pattern with significant increase in connectivity between these areas pre- and post-meal (59). Importantly, this effect varied in proportion to how pleasant the subjects rated the intervening meal, postulating that in the state of obesity, reward-seeking brain activity rather than homeostatically relevant interoceptive information is guiding eating behavior.

We identified that the operculum, which is also involved in gustatory processing (60-62), had decreased connectivity with the VTA under oxytocin administration. Similarly, we found that the somatosensory cortex had attenuated connectivity with the VTA under oxytocin. Importantly, this brain area has been shown to have altered fMRI reward processing of food stimuli in obesity (63, 64). Subjects prone to obesity instructed to consume a low-calorie diet for 3 days exhibited significant hyperactivation of the somatosensory cortex together with the insula and the visual cortex in response to palatable food stimuli. Interestingly, this pattern of activation was not seen in subjects “resistant” to obesity (65). Notably, the region demonstrating the highest peak activation within the somatosensory cortex in our analysis mapped to a region responsible for orosensory processing (66, 67), the same region shown to be hyperactive in response to food commercials in youth with obesity (63). Together, these findings suggest that in the state of obesity, there is over-recruitment of somatosensory and gustatory areas in response to visual food signals and that oxytocin may alter the hyperactivation of these areas. The amygdala, a brain region involved in salience and stimulus-reward learning (68) was also found in our study to have attenuated functional connectivity with the VTA following the administration of oxytocin. The amygdala has been shown in fMRI studies to respond specifically to visual food cues (69, 70) with increased activity in obesity (71) predictive of future weight change (72). In our analysis we also found decreased connectivity between the VTA and hippocampus under oxytocin treatment and in response to the high-calorie visual food images. Increased fMRI activation of the hippocampus in the state of obesity is a consistent finding in neuroimaging studies (73, 74). Activation of this area may indicate memory formation or retrieval, and it has been suggested that in obesity there is enhancement of memory processes in response to visual palatable food stimuli (43, 75). In light of these findings, our analysis showing attenuated VTA-hippocampal connectivity under oxytocin, specifically in response to high-calorie stimuli, suggests a potential mechanism by which oxytocin acts as an anorexigenic agent in the state of obesity.

Several studies have characterized the differences between appetite regulation in subjects with obesity and those with normal-weight using fMRI *resting-state* functional connectivity. These studies show that compared with normal-weight controls, subjects with obesity demonstrate increased resting-state functional connectivity in reward-related areas and those that comprise the salience network, including the insula, anterior cingulate cortex, striatum, amygdala, and orbitofrontal cortex (76-78). Since hyperactivation of reward areas in response to visual images of palatable foods seen in obesity versus normal-weight is highly established as discussed above, describing the task-dependent functional connectivity is critical to closely mimic the day-to-day neural response that an individual with obesity experiences when seeing visual food cues. The high-calorie food items presented in our fMRI task have the potential to trigger the strong urge to eat, one that can potentially override homeostatic intrinsic signals reflecting the nutritional status thus leading to overeating and obesity. Several studies have also shown altered task-dependent functional connectivity in the state of obesity, including generalized augmented response to high- vs. low-calorie foods in the salience network compared with lean individuals (79) and altered connectivity between the amygdala, orbitofrontal cortex, and nucleus accumbens compared with lean individuals (80).

There is strong evidence that oxytocin acts as an anorexigenic agent in both animal models and humans (14, 23, 81), and the neurophysiological action of oxytocin in the VTA has been well depicted and established (18, 19, 31). We have previously shown that following a single dose of oxytocin compared with placebo, subjects with obesity viewing high-calorie food stimuli versus non-food stimuli demonstrated bilateral VTA hypoactivation to high-calorie food stimuli. A secondary exploratory whole-brain analysis revealed hypoactivation in additional hedonic areas including the insula, hippocampus and amygdala (40). Our functional connectivity analysis extends these findings, providing a more accurate representation of the dynamic, task-dependent neuronal *circuitry* on which oxytocin acts. It is noteworthy that structural connections are important for task- and time-dependent functional connectivity. However, they do not provide constraints for functional connectivity, and synchronized brain activation between two brain areas does not necessary imply anatomical connections, since it may be mediated by a third brain area (41).

While food intake was not assessed in our study, a single dose of intranasal oxytocin (the same dose as used in this study) compared with placebo, has been found to reduce total caloric intake at breakfast (32), and to reduce consumption of palatable chocolate cookies (34) as well as chocolate biscuits and salty crackers (82) in previous studies. We speculate that the significantly attenuated functional connectivity between the VTA and the brain regions important for motivation processing of food stimuli presented in our study, could explain the clinically observed anorexigenic effect of oxytocin.

Although our sample size was relatively small, this first evidence of oxytocin-induced effects on functional connectivity between the VTA and key brain regions processing sensory, cognitive, and emotional aspects of the visual food cues is important and suggests that oxytocin may cause a decrease in exchange of information between key food motivation brain areas in response to palatable food images. Only men were included in this pilot study due to the variations in oxytocin levels seen in females related to menstrual cycle, functional

hypothalamic amenorrhea, hormonal contraceptive agents and menopause (83-85). Future research examining the effects of oxytocin on post-prandial fMRI functional connectivity in response to high-calorie food stimuli (vs. non-food stimuli) after consumption of calorie-dense foods would be useful in understanding the mechanisms underlying oxytocin effects on appetite regulation. Further, whether oxytocin effects on caloric intake and fMRI functional connectivity are sustained with long-term administration will be important to determine. Additional studies are currently taking place to further delineate the neural connections underlying the clinically observed anorexigenic effect of prolonged administration of oxytocin in males and females with overweight and obesity.

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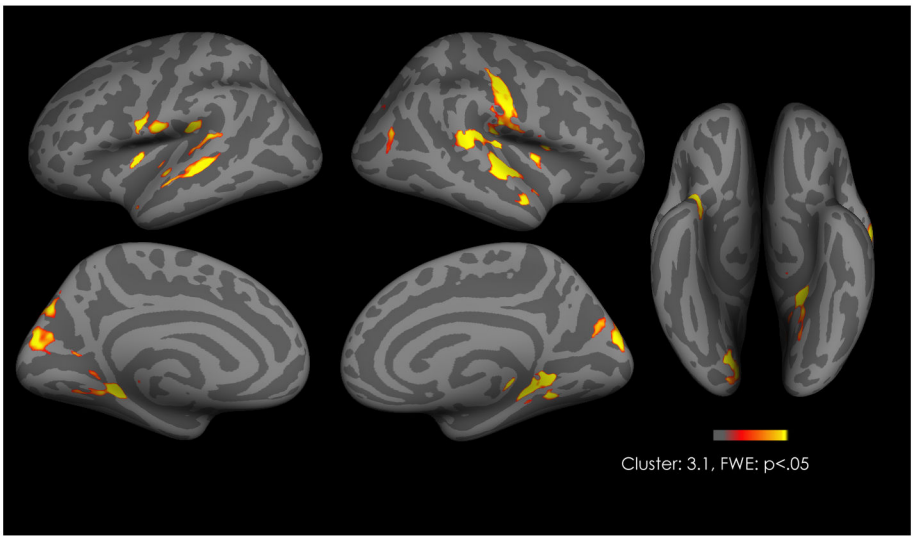

Figure 1:
Inflated brain image, functional connectivity with the left VTA analyzed for the high calorie condition, Placebo>Oxytocin.

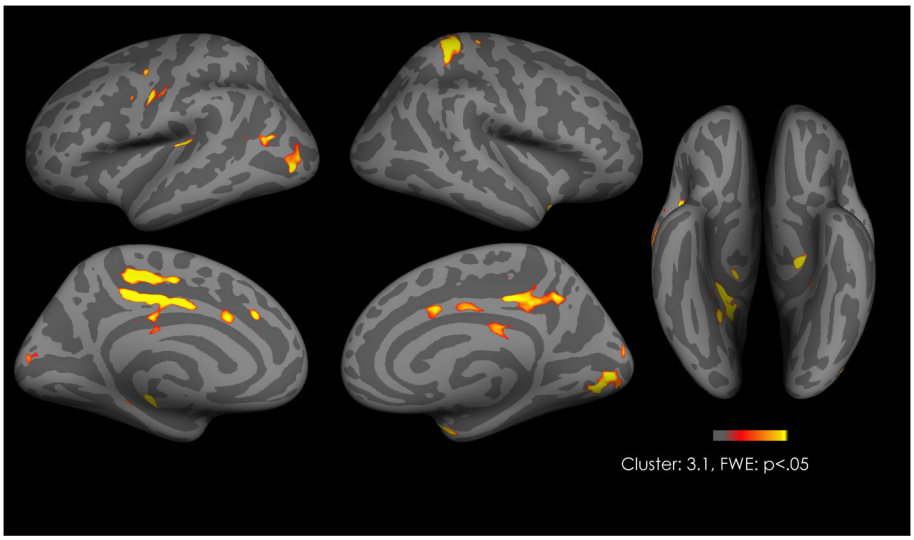

Figure 2:
Inflated brain image, functional connectivity with the right VTA analyzed for the high calorie condition, Placebo>Oxytocin.

Table 1:

Functional connectivity of the left and right ventral tegmental areas during high-calorie food condition for the contrast Placebo>Oxytocin

Seed	Brain regions	L/R	MNI (x, y, z)	Z
L Ventral tegmental area	**Cluster 1 (Cluster size: 3,770)**			
	Temporal pole	L	−48, 14, −24	**5.07**
	Middle temporal gyrus anterior	L	−58, 2, −18	**4.98**
	Insula	L	−36, −4, 6	**4.93**
	Temporal pole	L	−46, 18, −24	**4.87**
	Superior temporal gyrus posterior	L	−54, −32, −2	**4.84**
	Superior temporal gyrus anterior	L	−62, 0, −8	**4.82**
	Parahippocampal gyrus	L	−18, −38, −10	**4.69**
	Precentral gyrus	L	−60, 2, 18	**4.5**
	Parietal operculum (S2)	L	−48, −26, 18	**4.29**
	Postcentral gyrus	L	−64, −14, 12	**4.2**
	Supramarginal gyrus	L	−66, −40, 20	**4.15**
	Frontal operculum/insula	L	−40, 10, 4	**4.02**
	Temporal pole	L	−52, 0, 24	**3.93**
	Lingual gyrus	L	−24, −52, −4	**3.81**
	Insula	L	−42, −6, −2	**3.57**
	Left hippocampus	L	−32, −34, −6	**3.49**
	Central operculum	L	−38, 8, 10	**3.47**
	Cluster 2 (cluster size: 3,763)			
	Planum temporale	R	58, −8, 0	**5.15**
	Parietal operculum (S2)	R	58, −26, 20	**4.99**
	Superior temporal gyrus anterior	R	64, 4, −12	**4.71**
	Postcentral gyrus	R	50, −14, 42	**4.6**
	Supramarginal gyrus	R	62, −26, 24	**4.56**
	Postcentral gyrus	R	58, −10, 32	**4.31**
	Middle temporal gyrus posterior	R	52, −8, −22	**4.3**
	Insula	R	38, 0, 6	**4.21**
	Central operculum	R	40, 6, 12	**4.02**
	Cluster 3 (cluster size: 1,641)			
	Cuneal cortex	R	8, −84, 22	**4.13**
	Cuneal cortex	L	−4, −86, 26	**4.11**
	Precuneus	L	−14, −74, 38	**3.91**
	Primary visual cortex	L	−6, −74, 14	**3.79**
	Lateral occipital cortex	R	42, −72, 18	**3.73**
	Occipital pole	R	4, −94, 32	**3.51**
	Lateral occipital cortex	R	32, −72, 22	**3.45**
	Cluster 4 (cluster size: 618)			
	Lingual gyrus	R	22, −52, −4	**4.53**

Seed	Brain regions	L/R	MNI (x, y, z)	Z
	Right hippocampus	R	22, −34, −6	**4.44**
	Posterior cingulate	R	18, −44, −2	**4.34**
	Parahippocampal gyrus	R	28, −24, −18	**3.86**
	Temporal fusiform cortex	R	26, −34, −22	**3.7**
R Ventral tegmental area	**Cluster 1 (cluster size: 2,469)**			
	Posterior cingulate	L	−8, −24, 36	**4.84**
	Precentral gyrus	L	−12, −28, 44	**4.71**
	Paracingulate gyrus	L	−12, 28, 32	**4.2**
	Anterior cingulate	L	−4, −10, 40	**4.17**
	Anterior cingulate	R	2, 8, 38	**3.98**
	Posterior cingulate	R	6, −30, 24	**3.93**
	Precuneus	R	12, −50, 36	**3.79**
	Postcentral gyrus	L	−6, −42, 58	**3.58**
	Cluster 2 (cluster size: 1,196)			
	Lingual gyrus	R	12, −80, −6	**4.61**
	Occipital fusiform	R	16, −76, −12	**4.53**
	Primary visual cortex	L	−6, −86, 6	**4.08**
	Occipital pole	R	4, −88, 16	**3.85**
	Primary visual cortex	L	−8, −74, 16	**3.43**
	Primary visual cortex	R	12, −74, 4	**3.42**
	Cluster 3 (cluster size: 633)			
	Middle temporal gyrus	L	−44, −54, 6	**4.15**
	Lateral occipital cortex	L	−40, −66, 14	**3.97**
	Parietal operculum (S2)	L	−44, −32, 16	**3.95**
	Planum temporale	L	−38, −34, 10	**3.9**
	Cluster 4 (cluster size: 461)			
	Left hippocampus	L	−26, −28, −6	**4.9**
	Cluster 5 (cluster size: 455)			
	Superior parietal lobule	R	28, −42, 62	**4.2**
	Postcentral gyrus	R	24, −38, 62	**4.06**
	Cluster 6 (cluster size: 392)			
	Temporal pole	R	36, 6, −20	**4.75**
	Right amygdala	R	20, −2, −26	**4.11**
	Parahippocampal gyrus, anterior	R	28, 4, −32	**3.75**
	Right hippocampus	R	24, −12, −26	**3.49**
	Temporal pole	R	20, 10, −30	**3.43**
	Cluster 7 (cluster size: 351)			
	Precentral gyrus	L	−46, −6, 34	**4.14**
	Postcentral gyrus	L	−44, −22, 36	**3.45**