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# Pituitary Gland Functional Connectivity and BMI

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Pituitary Gland Functional Connectivity and BMI

by  
Paige Rucker

A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of  
the requirements of the Sally McDonnell Barksdale Honors College.

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## ABSTRACT

PAIGE RUCKER: Pituitary Gland Functional Connectivity and BMI  
(under the supervision of Dr. Toshikazu Ikuta)

This study examined the link between pituitary gland functional connectivity and BMI. The pituitary gland plays various roles in the body through the secretion of hormones, but its direct role in development of obesity and BMI management is unknown. Resting state functional Magnetic Resonance Imaging (rsfMRI) brain data of individuals with diverse BMIs were analyzed by voxel-wise analysis to determine the functional connectivities of the pituitary gland to other regions of the brain. A significant negative correlation was found between BMI and pituitary gland functional connectivity in eleven different brain regions. These regions include the posterior thalamus, lingual gyrus, precuneus, right superior temporal gyrus, right middle temporal gyrus, right pallidum, hippocampus, pons, orbitofrontal cortex, left temporal pole, and left inferior frontal gyrus. All regions were linked in some way to eating and weight management; six of them presented specific connections between function and a distinct pituitary hormone or hormone influenced by the pituitary. Lingual gyrus, hippocampus, and temporal pole showed connection to cortisol while precuneus, pallidum, and left inferior frontal gyrus showed connection to oxytocin. Through this evidence, brain disconnectivities in relation to the pituitary gland may contribute to or reflect obesity. This data should be further studied to provide evidence into causative factors that could be used to treat and prevent obesity.

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## **I. Introduction**

### *Obesity and BMI*

In our world today of impressive and innovative medical technologies, we still see an overwhelming prevalence of obesity. According to the Centers for Disease Control and Prevention (CDC), more than 1/3 of the United States population (36.5%) was classified as “obese” as of September 2016 (“Adult Obesity Facts | Overweight & Obesity | CDC” n.d.). The human body has evolved to require a stable balance of energy and nutrients to maintain body weight. In early times when food sources were sometimes inconsistent, the body would house fat and nutrients to maintain this critical balance. Now, thanks to an ever-available source of food (especially those high in fat) and an increase in sedentary lifestyles, obesity is becoming more and more prevalent (Jéquier and Tappy 1999). Body Mass Index (BMI) is typically used as a screening tool to indicate where one’s body weight lies in correlation to his/her height. BMI is not a direct measure of fat nor is it a definitive measure of one’s health, but it is often used as an indicator to gauge one’s weight to the normal value for his/her height. BMI is simply the measure one’s mass in kilograms divided by height in meters squared [BMI=  $\text{kg}/\text{m}^2$ ]. A BMI of 30 or greater is classified as obese.



### *Hunger and Weight Management*

The body's drive to eat and the maintenance of weight are complex balances between physiological aspects, hormones, the brain and behavior, genetic influence, and the environment. Physiological aspects are the primary drivers of hunger. These include the body's level of satiation and its assessment of energy and nutrient levels. Previous research has identified numerous hormones correlated and intertwined with the body's state of hunger, including ghrelin and leptin. There is evidence of a learned aspect of eating and hunger. Rats who were placed on a fixed meal pattern of every four hours (vs. those who were fed at random times throughout the day) were found to have increased levels of ghrelin (hormone signifying hunger) two hours preceding mealtime (Drazen et al. 2005). These levels peaked half an hour before the fixed mealtime, showing ghrelin secretion can be a response to a learned anticipation. Visual cues, smells, textures, social cues, and many other brain processing aspects play a role in processing hunger. Genetics also influences weight management. One's inclined mass of body fat and where fat is stored (periphery vs. central deposits) are both influenced by genetics (Jéquier and Tappy 1999).

### *The Pituitary Gland*

The pituitary gland is often called the "master gland" because it plays an integral role in controlling many other parts of the body. It is about the size of a pea (8 mm) and weighs only 0.5 grams. It is located at the base of the brain directly behind the bridge of the nose, where it is tucked away in a hollow of the cranial bone for protection. The gland is composed of three lobes- anterior, intermediate, and posterior. All three lobes are

distinct in function and structure. The anterior lobe is fleshy and serves as the pituitary's endocrine region. It is composed of hormone-secreting epithelial cells. The intermediate lobe is often thought of as congruent to the anterior lobe because it is not a distinct lobe in humans. Rather, it is a collection of distinct cells dispersed throughout the anterior lobe. The posterior pituitary lobe is a direct extension of the hypothalamus. This lobe is made mostly of unmyelinated secretory neurons. The posterior lobe is directly connected to the hypothalamus via the pituitary stalk, which is a collection of neuronal axons. The pituitary gland is not only anatomically connected to the hypothalamus via the pituitary stalk, but it is also functionally connected (Amar and Weiss 2003). The hypothalamus secretes hormones to the pituitary that either stimulate or inhibit the production of pituitary hormones. These hormones then travel through the body via blood to act on specific cells or tissues ("The Pituitary Gland and Hypothalamus" n.d.).

The anterior, intermediate, and posterior pituitary lobes have very distinct functions. The anterior lobe secretes hormones via five different classes of epithelial cells. The intermediate lobe secretes a hormone that stimulates melanocytes in your body and brain. The posterior lobe consists mostly of extensions from two different nuclei in the brain that are known to secrete two specific hormones made in the hypothalamus itself.

### *Pituitary Hormones*

There are nine different hormones secreted by the pituitary gland (see Table 1). Each of these plays a critical role in the maintenance of homeostasis in the body. The anterior pituitary secretes seven of these nine. Listed are the major roles these hormones

possess in the body. The anterior pituitary secretes adrenocorticotrophic hormone, thyroid-stimulating hormone, growth hormone, prolactin, follicle stimulating hormone (FSH), and luteinizing hormone. Adrenocorticotrophic hormone (ACTH) stimulates the adrenal cortex in the kidneys to produce glucocorticoids such as cortisol. Thyroid-stimulating hormone stimulates the thyroid to produce its specific hormones, which play a critical role in maintaining homeostasis. Growth hormone acts on muscle and bone to promote growth. Prolactin stimulates the mammary glands to produce milk. Follicle stimulating hormone stimulates the production of sperm in the testes and ova production and secretion of estrogen by the ovaries. Luteinizing hormone works alongside FSH to stimulate the ovaries to secrete estrogen and testes to secrete testosterone.

The intermediate lobe cells secrete melanocyte-stimulating hormones. In the body, these melanocytes secrete melanin, which controls the pigmentation of the skin; in the brain these are proposed to have neuroendocrine and detoxification functions (Brenner and Hearing 2009).

The two posterior pituitary hormones are vasopressin (anti-diuretic hormone) and oxytocin. Vasopressin stimulates the re-absorption of water in the kidneys, raising blood pressure and protecting the body from dehydration. Oxytocin is most known for stimulating uterine contractions during labor and aiding with milk ejection during breast-feeding (“The Pituitary Gland and Hypothalamus” n.d.) (Caballero et al. 2016).

<b>Hormone</b>	<b>Origin of Hormone</b>	<b>Most common effect on body</b>
<b>Adrenocorticotrophic Hormone (ACTH)</b>	Anterior Pituitary	Stimulates glucocorticoid production from adrenal glands
<b>Thyroid-Stimulating Hormone</b>	Anterior Pituitary	Stimulates thyroid hormones
<b>Growth Hormone</b>	Anterior Pituitary	Promotes growth in muscle and bone
<b>Prolactin</b>	Anterior Pituitary	Stimulates mammary glands to produce milk
<b>Follicle-Stimulating Hormone</b>	Anterior Pituitary	Stimulates testes to produce sperm Ova production and secretion of estrogen in ovaries
<b>Luteinizing Hormone</b>	Anterior Pituitary	Stimulates testes to secrete testosterone and ovaries to secrete estrogen
<b>Melanocyte-Stimulating Hormone</b>	Intermediate Pituitary	Stimulates melanocytes to produce melanin for skin pigmentation; neuroendocrine and detoxification purposes in brain
<b>Anti-Diuretic Hormone (Vasopressin)</b>	Posterior Pituitary	Re-absorption of water in the kidneys
<b>Oxytocin</b>	Posterior Pituitary	Uterine contractions during labor and milk ejection during breast-feeding

**Table 1:** Pituitary hormones and their primary actions in the human body.

*Pituitary Gland, Weight Regulation, and Obesity*

The pituitary gland and BMI are typically not studied directly together in scientific literature; however, there are data linking BMI to the pituitary gland via the effect of different hormones and neuropeptides.

The hypothalamic-pituitary-adrenal axis (HPA axis) shows altered function in response to obesity. Obesity is shown to cause abnormal release levels of specific

hormones, states of hyper-responsiveness to other neuropeptides in the body, and many other effects (Chalew et al. 1995).

The most obvious connection seen between the pituitary gland and obesity is visible in the physical manifestations of Cushing's syndrome. In Cushing's syndrome, the body is subjected to abnormally high levels of circulating glucocorticoids. Most often this high exposure is induced endogenously by pituitary tumors leading to a drastic alteration of pituitary function. Increased levels of ACTH induce the adrenal glands to produce excessive cortisol, which results in serious obesity concentrated in the abdominal region. Shown by this syndrome, there is a direct result between pituitary function and BMI (Pivonello et al. 2008).

The pituitary gland is also seen to be involved in the regulation of body weight through its interactions with leptin. Leptin is a neuropeptide produced only by adipocytes (Smith 1996). It is encoded by the Ob gene (short for obese gene) (Jéquier and Tappy 1999). Research shows mice homozygous for mutations in the ob gene (ceasing all leptin production in the body) develop an obese phenotype. When these mice were administered leptin, they lost weight and were able to maintain that weight loss when the injection was continually administered. Leptin's known function in both animals and humans is to decrease food intake and increase energy expenditure by increasing the level of fat oxidation (Jéquier and Tappy 1999). In the experiment linking leptin with the pituitary gland, which is a densely concentrated area of leptin receptors (Sone et al. 2001), researchers found leptin receptors are critical for normal growth and sexual development via pituitary hormones. Those homozygous for a mutation in leptin receptors did not naturally begin puberty or develop the normal secondary sexual characteristics. Levels of

luteinizing, follicle stimulating, and growth hormone were significantly low. This data showed functional leptin receptors (and leptin itself) are not only important for normalized regulation of body weight, but also critical in contributing to other developmental processes throughout the body. These findings not only link leptin with the functioning of the HPA axis, but also associate the pituitary gland with a role in regulating body weight (Clement et al. 1998).

### *Pituitary Hormones, Weight Regulation, and Obesity*

#### I. Oxytocin

The pituitary gland is also thought to interact with BMI through specific hormones. These hormones include oxytocin, ACTH, and prolactin.

Oxytocin is called “the great facilitator of life” (Lee et al. 2009) because of its widespread influence and involvement in the physiological processes throughout the human body. In regards to eating behavior, oxytocin has been implicated to inhibit food intake. After central injections of oxytocin in rats, reduced food intake was seen due to an inhibitory effect of oxytocin on eating behavior. The inhibitory effect was seen to dissipate by afternoon meal time leading to an overall net effect of zero in weight gain (B. R. Olson et al. 1991). A net weight gain was seen when the injections were sustained over a longer period of time (Björkstrand and Uvnäs-Moberg 1996). The importance of oxytocin in food intake inhibition is somewhat conflicting. A short-term effect of inhibiting food intake has been consistently suggested. Oxytocin also may play a role in carbohydrate-specific satiety after meals. Oxytocin knock out mice over-consumed

carbohydrates and carbohydrate solutions compared to other sources of caloric intake such as lipids and proteins (Sclafani et al. 2007). These mice were also very inclined to over-consume the very sweet and highly palatable saccharin solution. It is implicated that oxytocin could play a role in inhibiting post-carbohydrate consumption (specifically those that are sweet) after satiety is achieved.

Oxytocin is also said to possess protective effects against stress. It plays a role in relaxation and lowers stress levels when it is released as a result of positive social encounters and interactions (Riem et al. 2011). In addition, people who carry the more affinitive binding form of the oxytocinergic receptor have been found to show decreased stress levels (Rodrigues et al. 2009). This connection with stress brings us to our discussion of ACTH's role in weight regulation.

## II. ACTH

Obese subjects, especially women, are seen to have HPA axes that are hyper-sensitive to the hypothalamic cortico-releasing hormone (Pasquali et al. 1999). In women who possessed abdominal obesity vs. peripheral, an increased response to both ACTH and cortisol was seen in their HPA axis (Vicennati and Pasquali 2000). Here we see there is a connection between ACTH and obesity, but how?

Cortisol is a glucocorticoid released in response to the ACTH. When cortisol is released, it serves in a negative feedback response to control ACTH release. ACTH is produced in the body's stress response, but long-term exposure to ACTH is detrimental to the human body. In an effort to reduce the autonomic and HPA axis response to stress, cortisol activates the drive to ingest "comfort food" to stimulate the reward network in

the brain. This reward system activates “pleasing” signals and helps push the body away from the stress response (Adam and Epel 2007; Dallman et al. 2003, 2005). This altered eating behavior towards sweet and savory “comfort food” can lead to an increase in weight, specifically around the visceral, abdominal area where cortisol tends to deposit fat (Smith 1996). This increase in weight consequently leads to an increase in BMI.

Glucocorticoid excess is also seen to create an insensitivity to leptin levels in the body, leading to a decreased inhibition of eating (Björntorp 2001).

In summary, ACTH leads to production of glucocorticoids like cortisol. Cortisol, in turn, induces the body to consume “comfort foods” which activate the reward system. This eating behavior, if habitually practiced, will lead to an increase in weight, especially around the abdominal area. The body also forms insensitivity to leptin, further urging the body to participate in eating.

### III. Prolactin

Prolactin is involved in energy homeostasis via adipocyte formation (Auffret et al. 2012) and lipolysis. It is released both by the pituitary gland and adipocytes, and seems to be regulated by insulin (Chirico et al. 2013).

Correlation between prolactin levels and BMI has not been shown to be consistent throughout ages. In obese children, prolactin levels were found to be lower than normal-weight children. Prolactin levels were deemed statistically significant as a marker to identify the propensity of obesity to develop into severe metabolic syndrome. In this child study, prolactin level and BMI were found to be highly inversely correlated (Chirico et al. 2013). In a study with an adult population possessing prolactin secreting pituitary



adenomas, prolactin levels were positively correlated with BMI and weight gain. When prolactin-lowering treatments were administered, weight loss was seen (Greenman et al. 1998).

Prolactin also may play a role in the circadian rhythm release of leptin, as seen by the spike throughout the night when sleeping and decrease in the morning (Mastronardi et al. 2000).

The direct role of prolactin in weight management and BMI is not known, but it is shown to be correlated with weight through its function in adipocyte formation.

Given these roles of the pituitary gland in regulating food intake and body weight through hormonal secretion, we hypothesized there are brain regions that are closely associated with the activity of the pituitary gland. The goal in this study was to find the regions whose connectivity to the pituitary gland is associated with BMI.

## II. Methods

### *Data Acquisition*

The MRI images, the clinical data, and the demographic data of the enhanced Nathan Kline Institute-Rockland Sample (Nooner et al. 2012) were obtained from Collaborative Informatics and Neuroimaging Suite (Biswal et al. 2010). This data subset consisted of 495 individuals ( $43.53 \pm 20.75$ ) years old, 310 females and 185 males for whom resting state and structural data were both available.

Resting state echo planner image (EPI) volumes had 64 slices of 2mm 112x112 matrix with 2mm thickness (voxel size = 2x2x2mm), FOV=224mm, with repetition time (TR) of 1400ms and echo time (TE) of 30ms. A total of 404 volumes (~10 minutes) were used in the analysis. High-resolution structural T1 volume was acquired as 176 sagittal slices of with 1mm thickness (voxel size = 1x1x1mm, TR=1900ms and TE=2.52ms, FOV=256).

### *Data Processing*

Script libraries ([file://localhost/fcon/ http://www.nitrc.org/projects/fcon\\_1000](http://www.nitrc.org/projects/fcon_1000)) from the 1000 Functional Connectomes Project (Biswal et al. 2010) were used for preprocessing and analysis of the Region of the Interest (ROI). Resting state images were first motion corrected and then spatially smoothed to 6mm full width at half-maximum Gaussian kernel. The structural T1 images were individually registered to the MNI152 2mm brain. Through this registration, 12 affine parameters were created between rs-fMRI volume and MNI152 2mm space, so that a seed ROI can later be registered to each individual rs-fMRI space. The rs-fMRI time series were band-pass filtered (between

0.005 Hz and 0.1 Hz). Each of the resting state volumes was regressed by white matter and cerebrospinal fluid signal fluctuations as well as the six motion parameters.

The pituitary gland ROI was manually defined in the MNI 2mm space centered approximately at [MNI: 0, 2, -32] (Figure 1). Voxel-wise connectivity analysis was conducted by the *singlesubjectRSFC* fcon script with this ROI, whereby the time course is spatially averaged within the ROI registered to the EPI space so that correlations from the ROI to each individual voxels across the brain. The *Z*-scores representing the correlations between the ROI and a voxel were used for group level analysis after registration to the MNI 2mm brain space.

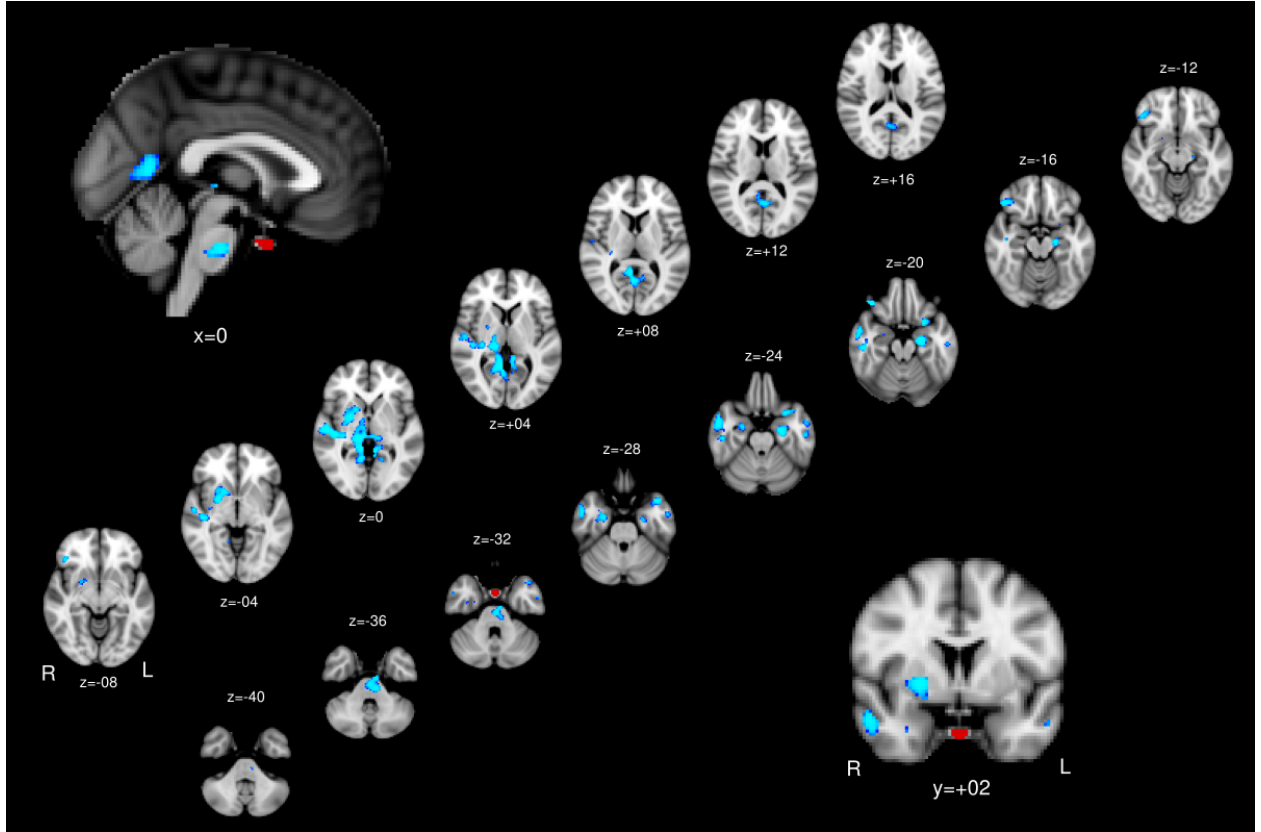
The association between BMI and whole brain functional connectivity to the pituitary gland was tested in a voxel-wise fashion using *randomise* script in FSL. *Z*-statistic images were estimated where clusters were determined by the cluster number of  $K > 100$  and statistical threshold of  $Z > 3.72$  with a family-wise error-corrected cluster significance threshold, assuming a Gaussian random field for the *Z*-statistics. The peak voxels within a cluster were calculated by using voxelwise family-wise error corrected images.

### III. Results

Voxel-wise statistical analysis of functional connectivity with the pituitary gland showed regions that have negative associations with BMI (Table 2 and Figure 1). No regions showed functional connectivity with the pituitary gland that is positively associated with BMI.

Voxels	MNI coordinates			Region
	x	y	z	
1136	10	-28	-2	Posterior Thalamus, Lingual Gyrus, Precuneus
423	44	-22	-4	Right Superior Temporal Gyrus
369	24	-2	-4	Right Pallidum
359	56	-4	-26	Right Middle Temporal Gyrus
235	-24	-14	-24	Left Hippocampus
221	0	-22	-34	Pons
176	42	32	-20	Right Orbitofrontal Cortex
168	-40	14	-28	Left Orbitofrontal Cortex, Left Temporal Pole
122	26	-6	-28	Right Hippocampus
106	-54	-16	-24	Left Inferior Frontal Gyrus

**Table 2:** Clusters whose functional connectivity to the pituitary gland showed negative association with BMI.



**Figure 1.** Red: the pituitary gland; Light Blue: clusters whose functional connectivity to the pituitary gland showed negative association to BMI.

### **III. Discussion**

There were eleven regions [posterior thalamus, lingual gyrus, precuneus, right superior temporal gyrus, right middle temporal gyrus, right pallidum, hippocampus, pons, right and left orbitofrontal cortex, left temporal pole, and the left inferior frontal gyrus] implicated by our brain imaging scans that are functionally connected to the pituitary gland in a negative fashion with BMI. The functional connectivity examined in this study is a correlation, not causation. The data would not provide evidence into whether the lower level of functional connectivity causes heightened BMI or if heightened BMI causes a decreased functional connectivity. The connectivities between the pituitary gland and these regions are negatively associated with obesity. In other words, the more disconnected the brain regions are, the higher BMI is.

#### *Posterior Thalamus*

The posterior thalamus is one of the thalamic sub-regions. The thalamus as a whole is generally known as the central relay station that sends information from the peripheral sensory modalities and sensory regions of the brain to the cerebral cortex. It is also thought to play important roles in communicating information between cortical areas, not just from the peripheral sensory regions to the cortex (Sherman 2007, p. 200).

The most well known role of the posterior thalamus specifically is its connections to the amygdala and temporal cortex (Doron and Ledoux 2000). These connections show

the posterior thalamus integrates and sends information regarding auditory cues from the temporal cortex to the amygdala (related to emotional learning). This area is said to be involved with aversive learning, which is equating a negative behavior with a negative or loud auditory signal. The posterior thalamus not only showed function in processing the level of reward of a stimuli, but it showed function in creating the anticipation of the reward itself (Komura et al. 2001). These data show the posterior thalamus is connected to many different aspects of the body including discrimination of rewarding behavior, processing auditory cues, and even possibly linking stimuli to the areas of the brain linked with motivation and reward (Stellar 1994).

The posterior thalamus doesn't have any known connections to specific pituitary hormones, but because the thalamus plays such an enormous role in the brain's central processing, there are countless ways in which the thalamus/posterior thalamus is involved in weight regulation. Most sensory relays go through the thalamus to be processed; therefore visual, taste, etc. (all aspects of eating motivation) are involved with the thalamus. It is most likely the thalamus's activation in our data was due to the activation of other brain regions that use it to send information to the cortex.

### *Lingual Gyrus*

The human lingual gyrus is located within the primary occipital lobe in the posterior region of the brain. It is most known for its role in the visual system. The lingual gyrus is thought to be responsible for encoding complex images and is activated during the recall of memorized images (Machielsen et al. 2000). It allows the brain to

process different aspects of an image, like textures, faces, shapes, letters, etc., to ultimately form one complex image of the visual stimulus (Puce et al. 1996).

The lingual gyrus is predominately involved in the visual system, but it does show associations with BMI. In an experiment conducted with women 50 years and older, both healthy and overweight, the gray matter of the lingual gyrus was seen to be lower in women with higher BMIs. Whether this relationship shows correlation or causation is unknown (Walther et al. 2010).

Looking into more indirect linkages between the lingual gyrus and BMI, the visual capacities of this brain region serve to play a role in eating behavior by processing the visual stimuli of food itself. In an experiment of healthy and binge-eating overweight individuals, the lingual gyrus was disproportionately activated in the binge-eating overweight group when viewing binge-food images vs. non-binge food images. Rather, in the healthy weight group the non-binge food images promoted a higher activation than when viewing binge-food items (Geliebter et al. 2006). These levels of activation could be due to the fact that the overweight group ate the binge-food items more often than the healthy group, so the visual system of the overweight individuals was already primed to respond to these stimuli. It could also indicate with repeated stimulus, the lingual gyrus could become primed to respond greater to certain objects, which could potentially signal other areas of the brain to respond as well (i.e. motor cortex, motivation, reward, etc.) (Catani et al. 2003). Even in healthy, satiated individuals (removing weight variable from previous experiment) there was a higher activation seen when viewing food images vs. non-food images (Uher et al. 2006).



The lingual gyrus also seems to be affected by hormones. In an experiment testing the visual recall of memorized objects from men and women (both under influence of significant testosterone and estrogen levels), men showed higher activation in the lingual gyrus than did women. The level of significance was such that the testosterone was a significant variable in this result (Konrad et al. 2008).

Not only does the lingual gyrus show association with hormones, there is evidence its activity is affected by cortisol. Activation in the lingual gyrus was positively correlated with plasma cortisol levels in monkeys after induced stressful situations (Rilling et al. 2001). This data suggest the lingual gyrus is highly linked with levels of stress. Higher levels of stress lead to increased activation of the lingual gyrus, which could produce a higher propensity to visualize/visually process food images. This could indirectly lead to increased eating motivation and eventually a higher BMI. This positive correlation doesn't explain the negative correlation found in our data between the functional connectivity of the pituitary/lingual gyrus and BMI, but it does show a potential linkage between pituitary hormone and brain region activation.

### *Precuneus*

The precuneus is a designated region within the parietal lobe and is located anterior to the occipital lobe (Cavanna and Trimble 2006). It plays an integral role in the state of self-awareness and ultimately, consciousness. Specifically, a huge increase of brain activity was seen in the precuneus when participants in an experiment were asked to describe their own personal characteristics. This area was not significantly activated when asked to describe their outer features (Kjaer et al. 2002). The precuneus, along with

other prefrontal structures, is also responsible for episodic memory (Fletcher et al. 1995). Episodic memory is the ability to recall past events and situations, often paired with visualizations of the past memory and recollection of certain emotions associated with that time and place (Lundstrom et al. 2005). The precuneus shows involvement in visuospatial processing, like detecting location of certain objects (Pennick and Kana 2012).

There is interesting new research linking oxytocin with the function of the precuneus. Because of data on possible linkages of oxytocin and social disorders (i.e. Autism) (Green et al. 2011), research was performed investigating how oxytocin would affect the precuneus due to its known participation in the “social brain” or state of self-awareness (Kjaer et al. 2002). Researchers found even a small dosage of oxytocin not only decreased the functional connectivity between the precuneus and the amygdala, it also decreased the activity of the precuneus itself. The amygdala plays a major role in the processing of emotions and in associational learning- both are functions that interact with “self-awareness” to integrate into a state of consciousness (Kumar et al. 2015).

To attempt to understand why there is a negative correlation between the functional connectivity of pituitary/precuneus and BMI, it could be possible when the functional connectivity changes between these two regions, oxytocin levels are becoming skewed from their normal release levels seen in a certain individual. These skewed oxytocin levels could then lead to both differential activation of the precuneus and an affected connectivity between the precuneus and amygdala. This could in turn change perceptions of self-meaning, self- consciousness, or emotional ties between object and

self. All of these stand a significant chance to affect eating behaviors since eating and weight do contribute to the formation of an idea of “self” (Heatherton et al. 1993).

Episodic memory could also play a role in the behaviors of eating because it is associated with the remembrance of past events, including the emotions felt during that event. If that event were centered on eating or even eating itself, the precuneus’s role in episodic memory formation could contribute to decisions regarding food.

### *Right Superior and Middle Temporal Gyrus*

Present in the temporal lobe are three distinct gyri- superior, middle, and inferior. In our findings, both the right superior and middle temporal gyri were found to present a negative correlation with functional connectivity to the pituitary gland and BMI. Both regions are involved in auditory processing, especially language. In a study investigating the brain behavior when hearing infant crying, both the right superior and middle temporal gyri showed increased activation when hearing infant crying compared to normal auditory cues (Riem et al. 2011). This study exemplified the roles these gyri play in auditory processing, but it also showed they possess functions that contribute to social perception and cognition. Deficits in these gyri are thought to contribute partly to the characteristics of autism (Bigler et al. 2007).

The middle temporal gyrus alone is also said to be involved in the process of “grounding perception.” This is the mode by which the brain equates conceptual meaning of objects with aspects like shape, specific use (function), and even the typical motion with which an object is associated. This function presents the middle temporal gyrus as being involved with the sensory/motor system (Beauchamp and Martin 2007).

The right superior temporal gyrus showed connections to eating behavior during an experiment testing brain activation when processing visual images of low calorie vs. high calorie foods. Right superior temporal gyrus was significantly activated when participants viewed images of low calorie foods, but showed no significant activation when viewing images of high calorie foods (Killgore et al. 2003). This finding could be a result of the possible connection of the superior temporal gyrus's association with the gustatory complex- an area of brain regions involved in taste perception (Kobayakawa et al. 1999). The higher activation when viewing low calorie foods could be due to the need for increased brain processing of this region to determine both the caloric and reward properties of the image. High calorie foods tend to excite areas of the brain associated with reward/motivation and normally are paired with a learned emotional response. These low calorie foods do not seem to initiate a strong learned, emotional response in the reward/motivational circuit, so this area associated with taste could become more involved with determining the intrinsic value of ingesting the food.

As for how the right superior and middle temporal gyrus are involved in the correlation between pituitary functional connectivity and BMI, there was no direct evidence found. There is, however, evidence presenting at least one of these regions as being involved in the taste perception circuit- a connection that directly relates it to the behaviors of eating.

### *Right Pallidum*

The pallidum is a region of the globus pallidus, a structure associated with the basal ganglia. The globus pallidus serves as an intermediary connector between the

nucleus accumbens and numerous other basal ganglia motor circuits, assisting with somatic motor control by integrating many motor signals for different parts of the brain (Kelley 2004). The globus pallidus also plays an inhibitory role by assisting in controlling excitatory nerve signals regarding motor movements coming from the cerebrum (Kita 2001).

In regards to food and food behavior, there is evidence linking the globus pallidus to weight regulation. In one experiment investigating the brain's metabolic differences between the "wanting" urge vs. the sensation of "liking", it was shown that the globus pallidus was specifically activated (along with other parts of the striatum) with the "wanting" urge and not with the "liking" urge. This suggests the globus pallidus is more involved in the pleasurable reward value processing that urges one to eat vs. the actual sensory perception of food (Born et al. 2011). It is also thought that the globus pallidus participates in the pleasurable response to high sugar or high fat foods (Kelley et al. 2005). These data coincide with the activation of the "wanting" urge, as mentioned above, because both are involved in the hedonic, pleasure response to ingesting or even seeing food. In another experiment, there was a marked increase of activation in globus pallidus when viewing visual images of food in 2 females with chronic leptin-deficiency (Farooqi et al. 2007). Same results were seen in persons who were leptin deficient due to recent weight loss (Rosenbaum et al. 2008). These results show 1. Leptin plays a critically important role in maintaining the sensation of satiation and 2. The globus pallidus is activated by the visual processing of food images- solidifying its role in reward processing of food cues. Weight gain was seen after medial-pallidum removal in 35% of patients who underwent surgery. Because these patients were all Parkinson's

patients, these results are not the most accurate because some gained weight from direct results of improvement of Parkinsonian symptoms like greater ease of chewing/eating and less involuntary muscle movement. Of the 35% who gained weight after removal, 50% cited an increased appetite or the introduction of a new foraging behavioral tendency that led to increased food intake (Lang et al. 1997). This indicates the globus pallidus may play a role in balancing appetite and inhibiting tendencies to eat.

There are interesting data linking the globus pallidum with oxytocin. In a study investigating the attachment effects oxytocin has on men when viewing the faces of their partners, researchers found an enhanced activation in the right GP after intranasal inhalation of oxytocin (Scheele et al. 2013). Oxytocin is known for its role in bonding and attachment, both in parental and partnership relationships. This role of attachment could be stretched to include food too- an item that often elicits a very strong emotional response.

There is no direct evidence as to what causes the negative correlation between the functional connectivity of the pituitary gland and right pallidum and BMI, but there are data linking the pallidum with food-related actions. The inhibitory motor movement action of the globus pallidus could be weakened when the functional connectivity decreases between it and the pituitary, causing a higher tendency to eat. The pallidum, during its process of hedonic value in food, could influence the pituitary. Oxytocin could influence the emotional attachment processing towards food. The answer is not known, but we do know the globus pallidus is involved in the complex process of eating and weight management.

### *Left and Right Hippocampus*

The hippocampus is a widely studied brain region that is primarily associated with memory storage. It is responsible for encoding both declarative memories (facts and events) and spatial memories (cognitive interactive maps of physical locations) (Kelley et al. 2005). It has also been identified as a brain region that interacts with the HPA axis and regulates behavioral responses to hunger cues.

The hippocampus inhibits most functions of the HPA axis (Jacobson and Sapolsky 1991). The HPA axis of the human body is activated by stress; once activated, the HPA axis stimulates the adrenal glands to produce glucocorticoids (mainly cortisol in humans). These glucocorticoids can pass the blood-brain barrier, where they bind to the glucocorticoid receptors (GCR) in the hippocampus (along with other regions of the brain). Once these GCRs are bound, the hippocampus exerts a negative feedback inhibition on the HPA axis to protect the body from excess cortisol production (Joëls 2008). Research has shown the HPA axis response to stress is influenced/formed in the early stages on development in rats. Rats that were licked by mothers more frequently (synonymous to human babies being held and touched) showed a decrease in the HPA axis response to stress versus those rats who were not licked by mothers. This so called “handling effect” leads to a higher number of glucocorticoid receptors in the hippocampus, resulting in a higher feedback inhibition of corticotrophin releasing hormone, decreasing the amount of ACTH released by the pituitary gland (Koehl et al. 1999; Liu et al. 1997). Here the hippocampus is connected to a specific pituitary gland hormone ACTH.

The hippocampus is believed to play an integral role in the brain's processing of hunger cues. It was shown by fMRI data to be the most activated brain region after stomach stimulation in obese people (Davidson et al. 2007).

Also, the hippocampus plays a direct role in connecting food or hunger cues with memory. The hippocampus is populated with both insulin and leptin receptors. Administering both leptin and insulin increases both spatial memory and long-term memory formation in the hippocampus. It is also shown the structural integrity of the hippocampus is needed to form memories of prior food intake to inhibit a subsequent meal. In one experiment, a highly amnesiac patient ate a full second meal only minutes after the first full meal was administered. The structural integrity of his/her hippocampus was compromised, leading to the inability to form the crucial memory inhibiting further food intake (Davidson et al. 2007).

Lastly, the hippocampus is shown to possess an anatomic connection to the hypothalamus. The CA1 field (a distinct region of the hippocampus) is directly linked to widespread areas of hypothalamic cell groups. It also has inputs into other regions on the brain known to regulate energy balance in the body (Cenquizca and Swanson 2006). Because the hypothalamus and pituitary gland work in such an intertwined fashion, this anatomical connection is substantial in our understanding of how the hippocampus and pituitary are connected.

There are many ways in which the hippocampus participates in the body's search for balance between hunger and satiety. The most direct connection between the hippocampus and the pituitary gland is through the pituitary hormone ACTH. A hypothesis can be made that as the functional connectivity between the pituitary gland



and hippocampus decreases, BMI increases because of the lessened negative feedback inhibition response in the hippocampus. If the hippocampus is responding less to the body's level of ACTH and cortisol, more is being produced by the adrenal glands than is needed. As previously stated in the intro, large levels of free-floating cortisol are said to increase the accumulation of fat, especially around the mid-section, thus ultimately leading to an increase in BMI (Björntorp 2001).

### *Pons*

The pons is one of three structures making up the primitive human brainstem. It is involved with many involuntary actions, such as respiration and consciousness. It also serves as the intermediary, transferring region for signals between the cerebellum and the cerebrum ("Pons | anatomy" 2002).

The brainstem is involved in simple physiological aspects of hunger and weight-regulation, such as interpreting signals from ghrelin and other hormones derived from the digestive organs. It has previously been known to influence simple aspects like the size of a meal, but its involvement with the rest of the body to maintain weight long term is unknown (Purnell et al. 2014).

In a medical study of a 30-year-old female with a lesion in her pons, significant consequences were seen after surgical removal. Just weeks after her recovery, she was experiencing huge increases in weight gain and was unable to become satiated after meals. Her excess eating led her to developing a BMI of 53.7 just 21 months after surgery. In an analysis of an MRI at 21 months after surgery, a severe loss of white matter was found between the hypothalamus and pons. These connecting fibers were

thought to be damaged during surgery. With all other factors considered, it was shown these myelinated nerve fibers were sufficient for disrupting the normal maintenance of body weight. This was the first time the brainstem was shown to play a role in long-term weight regulation (Purnell et al. 2014).

Due to our lack of scientific evidence elucidating the interactions between the pituitary and the pons directly, we cannot explain why there was a negative correlation between the functional connectivity between these two regions and BMI. This medical study shows, however, the brainstem is more involved with weight management long-term than previously thought. Also, knowing the pons directly communicates to the hypothalamus via both afferent and efferent myelinated nerve tracts hints at possible indirect interactions with the pituitary gland.

#### *Right and Left Orbitofrontal Cortices*

The orbitofrontal cortex (OFC) is most known for its role in reward processing of reinforcers and subsequent motivation. It responds to both primary and secondary reinforcers. Its main primary reinforcers are things such as taste, texture, and facial expressions. Secondary reinforcers include related stimuli from the visual and auditory systems along with other motivational cues from outside stimuli (Edmund T. Rolls and Grabenhorst 2008). Many visual, olfactory, and taste neuronal inputs from other regions of the brain are known to converge in the orbitofrontal cortex. All of these are thought to participate in the stimulation of food intake. The sensory pathways are highly coded and are very discriminatory in their responses to stimuli. These so called “sensory-specific satiety areas” respond to different sensory stimuli of food (DeParigi et al. 2005), such as

the textures of fat in food in the mouth (Edmund T. Rolls et al. 1999) or temperature of food (E. T. Rolls 2011). The OFC is also shown to have different efferent neuronal connections with the hypothalamus. Inputs from the OFC may influence the selective responses of the hypothalamus to food stimuli. (Thorpe et al.1983).

This role of processing and adapting to reward stimuli is important to consider when studying the motivations behind eating. In many experiments of the brain's activation in response to food stimuli, the orbitofrontal cortex was shown to play a major role (DelParigi et al. 2005; Killgore et al. 2003; van der Laan et al. 2011; Wang et al. 2004). In an experiment done by (Wang et al. 2004), distinctions were made between the activations to food stimuli in the right and left orbitofrontal cortices. The left OFC was shown to become more activated in response to taste and smell of food (primary reinforcers), suggesting the left OFC may be more related to the sensory processing of food. The right OFC was shown to become more activated in response to visual cues of food (secondary reinforcers), suggesting the right side is more involved in the determination of reward value of food (Wang et al. 2004).

Because the OFC is activated by visual cues of food, constant activation of this area due to highly visible food advertisements, strategic placement of vending machines, fast food restaurants, etc. could be a factor in overeating and obesity. Long-term activation of this area would motivate the body to eat due to the reward value associated with food images and stimuli (Wang et al. 2004).

Although there are no specific interactions with BMI-influencing pituitary hormones known as of now, there are significant relationships between the orbitofrontal cortex and eating behaviors. The anatomical connection between the efferent neurons of

the OFC and hypothalamus provides a promising piece of evidence that the reward motivation signals produced in the OFC directly affect the hypothalamus in some way. As said before, the hypothalamus both directly and indirectly interacts with the pituitary gland, so this direct connection between the OFC and hypothalamus would most likely subsequently affect the pituitary gland. As for explaining the negative correlation between the functional connectivity of the OFC and pituitary and BMI, more research would need to be done to hypothesize what is causing this.

### *Left Temporal Pole*

The temporal pole is located on the anterior end (towards the eyes) of the temporal lobe (Mesulam 2000). It is positioned between the orbitofrontal cortex and amygdala and is highly connected with both. Because of both its location and connectivity with these two regions, the temporal pole is often considered a paralimbic brain region (Olson et al. 2007).

The paralimbic cortex includes the temporal pole, insula, posterior orbitofrontal cortex, parahippocampal cortices, cingulate gyrus, and others. The main role of these areas is to link instinctive and physiological cues with cognition and emotional tags. They participate in emotion, memory, learning, linking of endocrine/visceral states with cognition, and the perception of some senses such as smell, taste, and auditory cues (Mesulam 2000).

The temporal pole has just recently been investigated for its potential roles in complicated processes of the human body. From a general stance, its involvement in higher order mental processing involving memory and emotion is known because of its

connections to the hippocampus (memory storage), the frontal lobe (higher order processing) and other paralimbic regions (Willeumier et al. 2012). Specifically it is most known for its role in semantic memory, which is the memory of facts and words. Brain damage to this area in patients leads to different levels of atypical word retrieval and word association when they are presented with pictures of well-known faces or objects (Damasio et al. 1996; Mummery et al. 2000).

The left temporal pole is shown to be connected to eating behavior and weight regulation in more ways than one. Kluver-Bucy syndrome occurs in humans and monkeys when there is damage to the temporal pole. This neurological disorder leads to many altered behavioral reactions, but the alteration most relevant to our study is the induced state of hyperorality. Patients show increased urges to place things in their mouths, often leading to abnormal eating patterns. Weight gain is often a result of this hyperorality (Lilly et al. 1983).

In obese men, the emotional and cognitive processing in the temporal pole in response to visceral cues from the body was found to be skewed. There was a decreased neuronal response in the left temporal pole to satiation after eating in obese men vs. normal weight men. This reduced response of satiation was not identified as a causation or correlation in this study, but it does hint the left temporal pole plays some role in processing satiation cues from the visceral organs (Gautier et al. 2000).

Weight gain was also shown to affect the metabolism of the left temporal pole in former overweight NFL athletes. There was decreased metabolic activity found in the temporal poles of these overweight former NFL athletes compared to healthy men their

age. This reason for this is unknown, but there is a connection shown between weight gain and temporal pole (Willeumier et al. 2012).

The temporal pole was also linked with cortisol during stress stimulation in soldiers experiencing PTSD. Levels of plasma cortisol and blood flow to the temporal poles were shown in co-variation in these men, meaning the two were interacting with each other during the cognition process of auditory cues that stimulated the stress response. Shown from this experiment, cortisol could be involved in “priming” the temporal pole for an emotional response to an auditory cue (Israel Liberzon et al. 2007).

As shown from the discussion above, there is no concrete evidence as to why the functional connectivity of the pituitary gland and temporal pole would be negatively associated with BMI. The temporal pole and pituitary gland show comparable functions in processing visceral cues, and the temporal pole is shown to be involved in a co-variation with plasma cortisol levels. Semantic memory could also be involved with the identification and emotional tagging to different food objects. Further research needs to be conducted, but these connections show the temporal pole does indeed play a role in weight regulation and eating behaviors.

### *Left Inferior Frontal Gyrus*

The left inferior frontal gyrus (LIFG) is located in the human frontal lobe, an area associated with higher order executive processing, planning skills, and emotion. The left inferior frontal gyrus is involved in processes related to physiological states of hunger, inhibition, selection, language, and emotions. In this study of weight regulation and BMI, the most direct association between BMI and the LIFG comes from its role in processing

stimuli (especially gastric distention of the stomach) from the gut (Stephan et al. 2003). The LIFG's role in inhibition has to do with inhibiting some automatic responses from the motor system in response to a "go/no go" stimulus that may not be appropriate in certain contexts. This context could be motor, semantic, linguistic, or others (Swick et al. 2008). This function of the LIFG could indirectly play a role in weight regulation and BMI by inhibiting automatic motor responses to eat when presented with food or a food stimulus. It also plays a part in the broad selection process, not just the semantic retrieval selection process as recently thought (Zhang et al. 2004). This could indicate the LIFG aids in the selection of which foods to eat and which not. The LIFG is also implicated as aiding in the simulation of other's emotions (empathy) (Riem et al. 2011). This connection with emotional function could be tied to weight maintenance and BMI.

In regards to pituitary hormones (or hormones closely related to it), the left inferior frontal gyrus is influenced by both oxytocin and leptin. In an experiment performed with subjects possessing lower levels of circulating leptin due to weight loss (less adipose tissue producing leptin), seeing visual cues of food increased activation of the LIFG. When leptin was replenished by injection, these results were reversed (Rosenbaum et al. 2008). As mentioned earlier, this brain region is involved in the executive decision making process of whether to eat or not to eat in response to a number of signals, one being cues from the gut. In the ghrelin experiment explained in the introduction in (Drazen et al. 2005, p. 20), it seems the brain can influence the secretion of the hunger-stimulating hormone ghrelin. Because the LIFG is activated when processing visual cues of food, it could potentially influence the stomach to create

hunger-stimulating hormones, in turn leading to intake of food. Excessive intake of food in response to visual cues would lead to increased BMI long-term.

Activation of the LIFG increased when oxytocin was administered (Riem et al. 2011). As mentioned earlier, oxytocin interaction with the LIFG helps aid in the feeling of empathy. This shows oxytocin interaction with the LIFG affects an aspect of emotion; emotion could in turn influence eating behaviors or even affect the inhibition functioning of the LIFG in some way.

As seen by our MRI data, as the functional connectivity between the left inferior frontal gyrus and the pituitary gland decreases, BMI increases (or vice versa). Why was this result seen? Although there is no direct evidence found to support this correlation, this relationship could be due to a possibility of things- fewer inhibitory messages being received by brain regions that impact pituitary gland, the pituitary (or other brain regions influencing it) are not as informed about the state of stomach distention and hunger cues, or even oxytocin induced emotional states are interrupted in some fashion, causing a cascade of events that could possibly influence BMI. We do not have direct evidence connecting these two regions, but the LIFG is seen to play a role in the urge toward food intake and executive decision-making processes.



<b>Brain Region</b>	<b>Known Hormonal Influence?</b>	<b>Role in Eating/Hunger</b>
Posterior Thalamus	No	Sensory relay station (visual, taste, auditory); linking stimuli to reward centers in brain
Lingual Gyrus	Cortisol	Processes visual aspects of food
Precuneus	Oxytocin	Perceptions of self and identity; episodic memory
R. Superior Temporal Gyrus	No	Gustatory complex (taste perception)
R. Middle Temporal Gyrus	No	Sensory/motor system through object grounding
R. Pallidum	Oxytocin	Inhibits motor movement; reward value processing; visual processing of food
L/R Hippocampus	Cortisol	Activated by stomach stimulation; memory formation of food and hunger
Pons	No	Interprets signals from hunger hormones
L/R Orbitofrontal Cortices	No	Sensory neuronal inputs converge here; sensory and reward processing of food
L. Temporal Pole	Cortisol	Kluver-Bucy syndrome; satiation cues from visceral organs
L. Inferior Frontal Gyrus	Oxytocin and Leptin	Processes stimuli from the gut; inhibits automatic responses of motor system in “go/no go” situation; selection process; emotional function, specifically empathy

**Table 3:** Summary of research conclusions for each associated brain region.

#### **IV. Conclusion**

Functional connectivity analyses of resting state fMRI data showed that the connectivities between the pituitary gland and eleven cortical and subcortical regions show negative association with BMI. We hypothesized these brain regions were functionally connected to the pituitary gland through specific pituitary hormones that are connected to BMI. Through some known specific influences of hormonal associations and data associating these cortical and subcortical regions with the drive to eat, our study suggested that decreased pituitary gland functional connectivities might be associated with obesity (see Table 3).

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