The limbic system as a neuroanatomical link between obesity and depression. Neuroimaging findings

El sistema límbico como vínculo neuroanatómico entre obesidad y depresión. Hallazgos en neuroimagen

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Abstract

It has been described high comorbidity between depression, therefore, it becomes interesting to explore the activity of brain structures common to both conditions through neuroimaging studies. Objectives. First - to identify neuroimaging structures concerning to morbid obesity and mayor depression disorder. Second - to analyze the common structures to both conditions. Methodology. Articles were searched in Pubmed and Science databases with the following keywords: MRI (magnetic resonance imaging) obesity, mayor depression disorder, depression and brain activity; with publication dates from 2007 to 2021, no review articles were considered. Contribution. Obesity has a very high comorbidity with depression. In both pathologies the activation of prefrontal cortex, putamen and insula is altered. These neuroanatomical structures are part of the reward system, so the response to hedonic stimuli is mediated by them and altered in obesity and depression.

Resumen

Se ha descrito una alta comorbilidad entre obesidad y depresión, por lo que resulta interesante explorar la actividad de las estructuras cerebrales comunes a ambas afecciones a través de estudios de neuroimagen. Objetivos. Primero – Identificar las estructuras de neuroimagen relacionadas con obesidad mórbida y trastorno depresivo mayor. Segundo - Analizar estructuras comunes en ambas condiciones. Metodología. Se buscaron artículos en bases de datos Pubmed y Science con las siguientes palabras clave: MRI (resonancia magnética) obesidad, trastorno depresivo mayor, depresión y actividad cerebral, con fechas de publicación de 2007 a 2021; no se consideraron artículos de revisión. Contribución. La obesidad tiene alta comorbilidad con depresión. En ambas patologías se altera la activación de la corteza prefrontal, el putamen y la ínsula. Estas estructuras neuroanatómicas forman parte del sistema de recompensa, por lo que la respuesta a los estímulos hedónicos está mediada por ellos y alterada en la obesidad y la depresión.

Obesity, Depression, Neuroimaging   **Obesidad, Depresión, Neuroimagen**

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Introduction

Obesity has been called the epidemic of the 21st century (Barrera-Cruz, Rodríguez-González, & Molina-Ayala, 2013; Hernández Arteaga, Rosero Galindo, Coral, & Andrés, 2015). It has become one of the most challenging important aspects of public health (Contreras Landgrave et al., 2014) since it affects all dimensions of quality of life of those who suffer from it (Pimenta, Saruwatari, Corrêa, Genaro, & Aguilar-Nascimento, 2010). According to ENSANUT, 2018 in Mexico, 36.1% of the population suffered from obesity; 26.6% of men and 40.1% of women (ENSANUT, 2018). Unfortunately, from 2012 to 2018 the prevalence in Mexican women has increased by 13.5% (Shamah-Levy, 2019).

Obese patients are known to have a high prevalence of depression (Castellini et al., 2008; Scott et al., 2008); in addition to a strong relationship between somatic symptoms, waist circumference and body mass index (BMI) in girls (Aparicio, Canals, Voltas, Hernandez-Martinez, & Arija, 2013) and paranoia in women (Desai, Manley, Desai, & Potenza, 2009).

Obesity is coupled to structural and functional changes in the brain that are remarkably like those observed in depressive disorders, such as region-specific increases in cell density and compromised neural connectivity and excitability (Opel et al., 2021; Rapuano et al., 2020). The main common neurobiological substrate between obesity and depression is the limbic system and its connection with insular cortex. Neuroimaging studies demonstrate structural alterations in obesity, most consistently decreases in cortical grey matter that are strikingly comparable with those observed in individuals with mood disorders (Opel et al., 2021). Obese adults exhibit increased cellularity in the hippocampus and amygdala (Samara et al., 2019), whereas greater cell density in the nucleus accumbens, dorsal striatum, pallidum, hypothalamus, amygdala, and hippocampus correlates positively with waist circumference in adolescents (Rapuano et al., 2020).

Due to the importance and neuroanatomical link of these two public health problems, obesity and depression, it will be analyzed reports of neuroimaging findings. We will begin by describing the limbic system neuroanatomy, later the magnetic resonance imaging as a tool for studying neuroanatomy; obesity; psychopathological comorbidity; functional neuroanatomy of obesity; depression; functional neuroanatomy of depression; and we will finish explaining the neuranatomical link between obesity and depression.

Limbic system neuroanatomy

The term limbic comes from the Latin limbo, meaning edge or border (White et al., 2008). The neuroanatomical structures that conform it, are basically divided into two regions: the cortical region that includes the cingulate gyrus and parahippocampal gyrus, prefrontal and orbitofrontal cortex; and the subcortical regions that comprise the hippocampus, amygdala, septal nucleus, nucleus accumbens, striatum, mammillary bodies, hypothalamus, thalamus, ventral tegmental area, raphe nuclei and locus coeruleus (Laviolette, 2007; Maclean, Flanigan, Flynn, Kim, & Stevens, 1955).

There have been identified four tracts according to their projections and combined effects that imply different areas of the limbic system:

a) Nigrostriatal pathway: projections from the substantia nigra pars compacta (SNC) to striatum (Taylor, 2001). It has been related to the motor control (Alcaro, Huber, & Panksepp, 2007; Marsden, 2006). In general, the dorsolateral striatum regions (caudate and putamen) are innervated by ventrolateral regions of the substantia nigra; while the ventrolateral regions of the striatum (nucleus accumbens), the globus pallidus and the cerebral cortex are innervated by the dorsal ventral tegmental area (Taylor, 2001). The basal ganglia are composed by: globus pallidus (inner and outer), putamen, caudate nucleus, nucleus accumbens (core and shell), olfactory tubercle and innominate substance. These nuclei and structures adopt different names depending on how they are grouped.

b)   Mesolimbic pathway: includes projections from ventral tegmental area to the nucleus accumbens, striatum and amygdala. This tract is associated with emotions and reward processes (Alcaro et al., 2007; Marsden, 2006).

c)   Mesocortical pathway: projections from the ventral tegmental area to prefrontal cortex and cingulate gyrus. This pathway is associated with reward processes (Afifi, 2005; Alcaro et al., 2007; Marsden, 2006).

d)   Tubero - infundibular pathway: projections that originate in the arcuate nucleus and paraventricular nucleus of the hypothalamus, to the median eminence (Lechan, 1980)and pituitary gland; it is associated with neuroendocrine regulatory functions (Alcaro et al., 2007; Marsden, 2006).

Magnetic Resonance Imaging (MRI) as a tool for neuroanatomy studies

The MRI images are based on the premise that when a mental process occurs, neurons involved require a greater amount of energy obtained from circulating oxygen from the blood of the nearby capillaries (Pauling & Coryell, 1936). The change in the blood-oxygen-level dependent (BOLD) resulting from a change in hemodynamic response, occurs due to cerebral process carried out at the time (Ogawa, Lee, Kay, & Tank, 1990). According to these authors, the generation of images from these processes involves: a) the increased flow of oxygenated blood to the neurons mostly involved in the process, b) the magnetic properties of the molecule that carries oxygen (oxyhemoglobin oxygen and deoxyhemoglobin without oxygen) c) changes in the brain in the above conditions after exposure to an external magnetic field (Armony, 2012; Ogawa et al., 1990; Pauling & Coryell, 1936).

One of the tasks used to study brain activity with this technique involves viewing images. For example, to study obesity, images of food with different calorie content are used, on the understanding that this task will facilitate the activation of brain areas associated with motivation for food (Rothemund et al., 2007).

On the other hand, to determine changes in brain activity in subjects suffering from depression, is quite common use the test "Pictures of Facial Affect" (POFA), test that makes use of facial expressions representing the six basic emotions: joy, anger, fear, sadness, surprise and disgust (Ekman, 1993).

Obesity

Obesity is a condition characterized by alterations in energy balance resulting in excessive body fat accumulation (Mataix Verdú, 2009).

According to the World Health Organization, WHO, 2021, the worldwide obesity has nearly tripled since 1975; in 2016, more than 1.9 billion adults, 18 years and older, were overweight; of these over 650 million were obese; 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese; most of the world's population live in countries where overweight and obesity kills more people than underweight; 39 million children under the age of 5 were overweight or obese in 2020; over 340 million children and adolescents aged 5-19 were overweight or obese in 2016 (WHO, 2021a). Mexico ranks first worldwide overweight women and fourth in women with obesity (OMS, 2015).

Obesity is a condition characterized by alterations in energy balance. The obesity causes have been grouped on environmental and physiological. Within the first kind of causes are implied the type of diet mainly consumed, family eating behavior and physical inactivity; among the latter causes are involved changes in the factors that regulate body energy balance, intake and energy expenditure and excessive body fat accumulation (Baqai, 2015; Skelton, Irby, Grzywacz, & Miller, 2011).

Psychopathological comorbidity

Relationship between obesity and depression in different age groups, has been widely reported (Aparicio et al., 2013; Calderón, 2010; Castellini et al., 2008; Cebolla & Torró, 2011; Desai et al., 2009; Pompa Guajardo, 2011; Rosen, 2010; Scott et al., 2008).

However, regarding results about relationship between body mass index (BMI) and severity of depression are discrepant. While some authors report a positive relationship between BMI and severity of depression (Calderón, 2010; Scott et al., 2008) or BMI and the tendency to personality disorders (Desai et al., 2009); others reports not show such association (Castellini et al., 2008; Isnard, 2010). Another constant in the reviewed studies is the higher prevalence of obesity and depression in females (Desai et al., 2009; Scott et al., 2008), although it should be noted that in some studies more than 50% of the sample were women (Aparicio et al., 2013; Calderón, 2010; Castellini et al., 2008; Isnard, 2010). Among other psychopathological findings in people with obesity it has also being described the presence of low self-esteem (Brauhardt, Rudolph, & Hilbert, 2014; Cebolla & Torró, 2011), eating disorders (Calderón, 2010; Castellini et al., 2008; Isnard, 2010)and somatic symptoms (Aparicio et al., 2013).

It has even been reported relationship between race, obesity and depression (Rosen, 2010). In addition to social phobia, panic disorder and dysthymia in childhood and adolescence; all of them predictors of BMI increased in adulthood (Aparicio et al., 2013).

Functional neuroanatomy of obesity

Ahead are described, neuroimaging findings in obese subjects.

It has been reported, that when visualizing pictures of food with high calorie, obese women aged 21 to 40 years old, showed activation of areas associated with reward processes such as dorsal striatum (set of areas associated with reward anticipation and learning habits), anterior insula, and orbitofrontal cortex (areas involved in processing gustatory information), claustrum and anterior cingulate (emotionally relevant stimuli processing and memory) (Rothemund et al., 2007). These findings have supported the following hypothesis "hyperphagia compensates hypo-dopaminergic state of obesity" (Blum, Thanos, & Gold, 2014). It has been shown that obese subjects have fewer dopamine receptor 2 (D2) and less striatal response to food intake (Stice, Yokum, Burger, Epstein, & Small, 2011).

Other neuroimaging findings that support this hypo-dopaminergic hypothesis of obesity are:

a) When to performing a test to measure impulsive choice for high calorie food, obese women showed less activation of areas associated with inhibitory control (lower superior frontal gyrus, frontal gyrus, medial frontal gyrus and inferior parietal lobe); which also was proved to be a predictor factor of greater weight gain in 1.3-2.9 years (Kishinevsky et al., 2012). Consistent with the above, it has also been informed that impulsive choices are associated with lower activity superior frontal gyrus, medial frontal gyrus and inferior parietal lobe in obese women (Stoeckel, Murdaugh, Cox, Cook, & Weller, 2013).

b) Patients between 25 and 40 years of age prone to obesity, presented reduction in activity of insula and inferior prefrontal cortex; coupled with increased activity in medial prefrontal cortex when visualizing images of food after food consumption (Cornier et al., 2013).

c) Obese children between 10 and 17 years of age, demonstrated increased activity of prefrontal cortex (superior frontal gyrus, medial frontal gyrus, inferior frontal gyrus) and insula during fasting while viewing pictures of food, in addition to increased activity of orbitofrontal cortex after food intake (Bruce et al., 2010).

d) Investigating the brain activity of adolescents (age $15 + 2.9$ years) with high risk of obesity when being rewarded with palatable food in fasting conditions, it has been showed increased activity of caudate, parietal operculum and frontal operculum in response to food (Stice et al., 2011).

e)   When visualizing images of high-calorie food, obese subjects had pre-prandially increased activation of anterior prefrontal cortex; and post-prandially increase in activity insula, dorsolateral prefrontal cortex, lateral orbitofrontal cortex, superior and medial frontal gyrus, anterior and posterior cingulate, entorhinal cortex, caudate, superior frontal gyrus, temporal lobe, temporal supramarginal gyrus, medial temporal gyrus; areas associated with high gustatory cortex, motivation and reward (Dimitropoulos, Tkach, Ho, & Kennedy, 2012).

Depression

Depression is a disorder of mood characterized by the presence of anhedonia (loss of interest and ability to experience pleasure) and feelings of sadness, hopelessness or irritability; it could be accompanied by somatic symptoms (physical aches and pains) functionally preventing the person (APA, 2000).

According to WHO, 2021, depression affects 264 million people worldwide. Each year more than 800,000 people commit suicide, and suicide is the second leading cause of death in the age group 15 to 29 years affecting mainly females. An estimated 76–85% of people suffering from mental disorders in these countries lack access to the treatment they need (WHO, 2021b).

Among the causes of depression it has proposed several hypotheses involving the role of: monoamines (Krishnan & Nestler, 2008), neurotrophins, cytokines (Haase & Brown, 2015)and stress (Brouwer et al., 2005).

Functional neuroanatomy of depression

It will be described here the neuroimaging findings of depression.

Recently it was shown that challenged with a task of facial emotional identification, subjects with major depressive disorder (MDD) between 33 and 56 years had less activity in several regions of the right hemisphere, including: insula, temporal gyrus (medial and inferior) hippocampal gyrus, putamen, occipital gyrus (Brodmann area 18), fusiform gyrus and cerebellum. In addition, subjects with MDD and anxiety, had decreased activity in orbitofrontal cortex (Townsend et al., 2010).

This may imply that the mentioned areas have an important role in the visual processing of negative emotions (Townsend et al., 2010).

However, it has also been reported that when using a test of dysfunctional relationships (Operationalized Psychodynamic Diagnosis OPD) in MDD women and men between 20 and 64 years old, increased activity of the medial frontal gyrus and inferior, pre and post-central rotation, amygdala and basal ganglia was showed; this areas are associated with emotional processing. This shows that the type of task used may lead to a greater or lesser response, in this case, by using individualized statements associated with a particular situation, greater emotional involvement is generated (Kessler et al., 2011).

In women and men between 14 and 17 years old and MDD, it has being shown less cerebral blood flow (hypoperfusion) in frontal gyrus and dorsolateral prefrontal cortex; areas related to psychomotor and executive functions deficit present in patients with depression, they also showed hypoperfusion in the anterior cingulate cortex, amygdala and insula, which is explained as a reflection of reduced motivation or anhedonia. On the other side, cingulate subcallosum, right and upper right insula showed hyperperfusion; the former structure is considered as an interface between cognitive and emotional processing given its connections with frontal, limbic and paralimbic structures. Increased activity of insula was described as a reflection of experiencing negative emotions. Hyperactivity of the mentioned areas in subjects with depression may be associated with hyper-reactivity or inadequate regulation to negative stimuli. This is one of the few studies that reported hyper-perfusion putamen and explain its association with negative emotional stimuli assessment (Ho et al., 2013).

Other studies reflected that functional connectivity between amygdala and prefrontal cortex of men and women with MDD between 19 and 46 years old, during recognition of facial emotional expressions, decreased during fear emotion processing. It is proposed a minor inhibitory control from prefrontal cortex to amygdala, resulting in the delay of the extinction of the negative emotion (Kong et al., 2013).

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In addition, it has been reported that women and men between 29.5 and 54.9 years old with MMD, which do not respond to transcranial magnetic stimulation in dorsomedial prefrontal cortex have: a higher level of anhedonia; less functional connectivity between ventral tegmental area and caudate nucleus with left ventromedial prefrontal cortex; and less functional connectivity between left prefrontal cortex (ventromedial prefrontal cortex, cortex, dorsomedial, dorsolateral cortex) and inferior parietal lobe and anterior insula. Therefore, two subtypes of depression where considered: one characterized by hypo-activity of the dorsomedial prefrontal cortex and intact hedonic response; and other characterized by hyper-activity and altered hedonic response (Downar et al., 2014).

Neuranatomical link between obesity and depression

The main common neurobiological substrate between obesity and depression is the limbic system and its connection with insular cortex. The limbic system is miscellaneous in functions and diverse in areas, however, due to functional magnetic resonance imaging, a technique that allows us to study real-time changes in brain activity based on the need of blood supply, there have identified common active areas committed to both, obesity and depression. Such areas are integrated into basically three circuits: frontal area, basal ganglia and insula; the higher activity has been identified in frontal gyrus, putamen and insula; while the lower activity has being associated to prefrontal cortex, the activity of the specific areas implied in both conditions, regardless the type of study used are shown in Table 1.

Structure	Obesity		Depression	
	Brain activity			
	High	**Low**	**High**	**Low**
Frontal area	Prefrontal cortex (Bruce et al., 2010; Cornier et al., 2013; Dimitropoulos et al., 2012) Superior frontal gyrus (Dimitropoulos et al., 2012) Frontal Operculum (Stice et al., 2011)	Frontal gyrus (Stoeckel et al., 2013) Prefrontal cortex (Kishinevsky et al., 2012)	Frontal gyrus (Kessler et al., 2011)	Poorer conectivity between prefrontal cortex and insula, (Downar et al., 2014) And between Prefrontal cortex – Ventral Tegmental Area/Caudate (Downar et al., 2014)
Basal Ganglia	Putamen (Stice et al., 2011) Caudate (Dimitropoulos et al., 2012; Kishinevsky et al., 2012; Stice et al., 2011) Ventral striatum (Bruce et al., 2010)	---	Putamen, higher blood flow (Ho et al., 2013)	Putamen, lower blood flow (Townsend et al., 2010)
Ínsula	Insula (Bruce et al., 2010; Cornier et al., 2013; Rothemund et al., 2007; Stice et al., 2011)	---	Right superior insula (Ho et al., 2013)	Insula (Townsend et al., 2010) Inferior bilateral insula (Ho el., 2013)

Table 1 Neuroanatomical link between obesity and depression

In this regard, a problem that was found when analyzing the published reports, is that depending on the type of technique used is higher or lower activity of the studied area, hence reports with conflicting results were found. For example, some authors reported decreased blood flow in amygdala and others report increased activity based on the level of oxygenation of the blood (Table 1).

Besides this, the task used in each study and gender to which reference is made, may also influence the results.

Therefore, the specific results that converge both pathologies will be discussed.

Discussion

Neuroimaging studies allow us to know and correlate brain activity in different pathologies to identify symptomatology similarities and make it possible found a common origin; in this review this was attended to obesity and depression.

It has been documented that in obesity exists a hypersensitivity to reward while the opposite has been described for depression, anhedonia. However, in both pathologies it has been found less activity in frontal area, which may result in less inhibitory control of some limbic areas. In obesity, loss of inhibitory control has been associated with low frontal gyrus activation, resulting in impulsive consumption choice of high-calorie food for the immediate reward it represents (Stice et al., 2011).

In depression, lack of inhibitory control of prefrontal cortex to amygdala, favors delaying the extinction of negative emotions (Kong et al., 2013); in addition, the lower activity of frontal area may be related to lower connectivity between prefrontal cortex and ventral tegmental area/caudate and insula (Downar et al., 2014).

However, it has also been reported increased activity in certain regions of the frontal area in obesity and depression; all this in relation to hyper-reactivity of the mesolimbic circuit in obesity (Bruce et al., 2010; Dimitropoulos et al., 2012; Kishinevsky et al., 2012; Stice et al., 2011); and increased of hemodynamic activity in limbic regions and subcortical structures including amygdala in depression (Dougherty & Rauch, 1997; Kessler et al., 2011). In obesity, the orbitofrontal cortex is actively involved in processing reward signals through the association of primary reinforcers (gustatory stimuli, olfactory, somatosensory) by afferents of taste and olfactory areas, amygdala, striatum, hypothalamus and insula (Rolls, 2004). However, in depression it has been reported increase metabolism in orbitofrontal area (Dougherty & Rauch, 1997) and the presence of greater frontal gyrus activity coupled with increased activity in putamen and amygdala; which is related to verbal emotional sensitivity caused by the evocation of personal experiences (Kessler et al., 2011).

As mentioned above, in subjects suffering from depression it has being showed increased putamen activity, a situation that has also being described in obese subjects. In obesity, the increase in activity of this areas is associated with hyper-reactivity of the mesolimbic dopaminergic system (Bruce et al., 2010; Cornier et al., 2013; Dimitropoulos et al., 2012; Rothemund et al., 2007; Stice et al., 2011); however in depression, the study of this area should be studied further because it is mentioned that the increased activity of putamen is linked with the patient's sensitivity to negative emotional situations (Fitzgerald, Laird, Maller, & Daskalakis, 2008), which is important but little investigated.

Regarding to insula, the third area where correlation of activity was found in the studied pathologies, is known to be involved in the integration of autonomic functions: viscero-sensory, viscero-motor and limbic ones (Gu, Hof, Friston, & Fan, 2013), because in this structure various sensory routes converge (taste, smell, touch) and interaction with other neural networks is present in order to attend or remember (salience network) (Menon & Uddin, 2010; Rolls, 2015). In obesity, it has being reported increased general activity of the insular area, which has also been attributed to hyper-reactivity of the mesolimbic system. In depression, detailed studies based on the insula cytoarchitecture, reported greater blood supply to upper right insula (Ho et al., 2013), an area that has been linked to processing somatosensory information, cognitive control and decision making (Klein, Ullsperger, & Danielmeier, 2013); while reduced blood supply to lower bilateral insula was observed, an area that is related to emotional processing, autonomic interoception and as part of the network of salience (brain network involving anterior insula, anterior cingulate cortex and subcortical structures whose function is to identify internal and external relevant stimuli for driving behavior) (Seeley et al., 2007); which has resulted in recognition deficit of experienced emotions in depressed subjects.

However, more studies are needed to enable the identification of the common causes of greater or lesser activity of these or other shared areas in the studied conditions, either from hemodynamics or neurochemical approaches, and furthermore to determine the cytoarchitecture of the precise area active in each condition, for example to identify the specific active areas of the frontal area. All this in order to prevent development of the disease and identify targets for specific treatment.

Acknowledgements

Conclusions

- Obesity has a very high comorbidity with depression.

- In obesity and depression, the activation of prefrontal cortex, putamen and insula is altered.

- The former structures are part of the reward system, so the response to hedonic stimuli is mediated by them and altered in obesity and depression.

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