

# The Right Brain Hypothesis for Obesity

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**T**HE PREVALENCE OF OBESITY CONTINUES TO INCREASE exponentially worldwide. In the United States, where the majority of the adult population is at least overweight, this condition accounts for an economic burden in billions of dollars per year. Despite increased awareness and determined efforts, the epidemic remains uncontrolled and constitutes a global public health problem. Moreover, the current state of knowledge may not include critical aspects of the etiology of obesity.

## Role of the Brain in the Control of Body Weight

Research during the past decades has drawn attention to the role of the brain in the regulation of food intake and the pathogenesis of obesity. The current paradigm, derived from carefully studied animal models, emphasizes neuroendocrine circuits involved in the control of appetite, with the hypothalamus as the main orchestrator. Peripheral information from the gastrointestinal tract, the pancreas, and adipose tissue is provided to the hypothalamus and brainstem via the vagus nerve and hormonal mediators, such as ghrelin, insulin, and leptin (FIGURE). As a result, adjustments in feeding and energy expenditure take place to ensure an adequate balance that matches bodily needs. Aside from satiating appetite, eating provides feelings of gratification, and palatable foods stimulate brain circuits of reward and motivation, engaging limbic and paralimbic areas under the modulatory influence of neurotransmitters and releasing neuropeptides, such as dopamine and endorphins. Beyond genetic predispositions and metabolic needs, hedonic aspects of food intake are important to understand body weight regulation and the genesis of obesity.

However, humans are unique in the way that food is viewed. For humans, food intake has evolved from subsistence to a highly elaborated behavior that carries social and cultural messages.<sup>1</sup> This dimension, which pertains to food, eating, and body image, can override driving forces elicited by metabolic needs or palatability. People share food with others to build a sense of community, avoid certain food products because of religious beliefs, and judge what is appropriate to eat according to future predictions and cultural norms (eg,

long-term effects on health or body shape). This essentially human, cognitive dimension of eating may play a critical and insufficiently emphasized role in obesity.

Several lines of evidence from the study of patients with brain diseases converge on the prefrontal cortex (PFC), especially in the right hemisphere, as a critical area involved in the cognitive control of food intake. The PFC is the part of the brain that has undergone the biggest expansion during evolution, accounting for approximately one third of the surface of the human brain (Figure). Many complex aspects of behavior that distinguish humans from other species originate here, through the confluence of sensory, limbic, and autonomic information. Current theories on the PFC posit a crucial role for this region in the top-down control of behavior, especially under conflicting situations, when inappropriate responses need to be inhibited.

Diverse findings suggest a crucial role of the PFC in obesity. In the mid-1900s, overeating and weight gain were a common side effect in patients who underwent frontal leu- kotomy, a psychosurgical procedure that disconnects the frontal lobe from the rest of the brain.<sup>2</sup> Damage to the right frontal lobe can cause a passion for eating and a specific preference for fine food, the so-called gourmand syndrome.<sup>3</sup> In patients with degenerative dementia, the presence of hyperphagia correlates positively with right frontal atrophy and negatively with left frontal atrophy.<sup>4</sup> Hypoperfusion of the right frontal lobe has been identified by using single-photon emission computed tomography in overeating conditions, such as Kleine-Levin syndrome.<sup>5</sup> Conversely, hyperactivity of the right PFC can lead to anorexia-like symptoms, for example, in patients with right prefrontal focal epilepsy, in which the eating disorder can cease after initiation of anticonvulsant therapy.<sup>6</sup>

Additional data support a link between the right PFC and spontaneous physical activity. The PFC is densely connected with neighboring areas involved in motor planning and execution, enabling accurate coupling between cognition and action. Increased activation of the PFC facilitates motor activity and can cause prominent motor manifestations, as occurs during seizures arising from this area.

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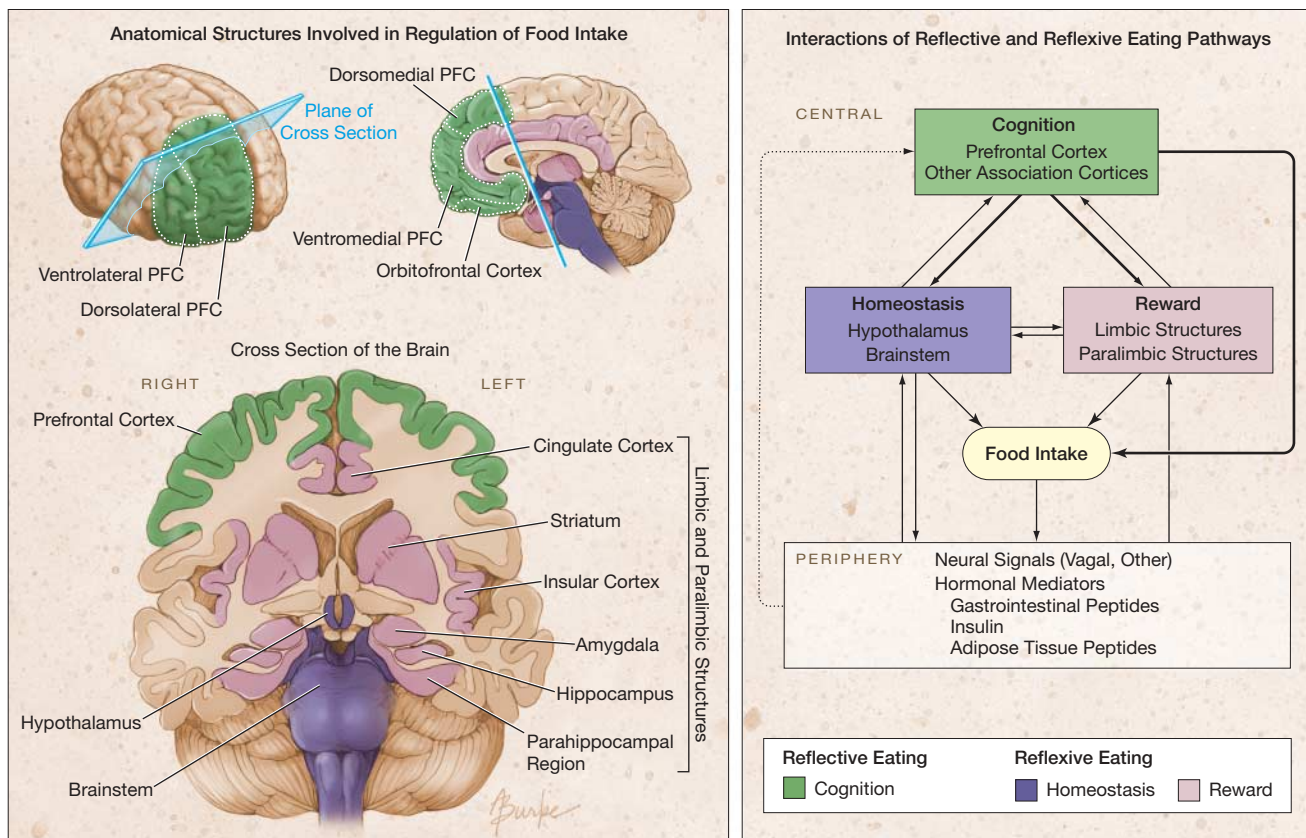
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On the other hand, decreased function of the PFC may lessen physical activity through effects on motor areas, as well as on the drive to move, underlying sedentarism, apathy, and central fatigue. Reciprocally, physical activity can also shape the function and structure of the PFC. Exercise training improves performance in PFC-related cognitive tasks over time and increases right frontal lobe volume.<sup>7</sup> In line with this finding, compared with untrained controls, professional athletes show an enhanced right-hemispheric preference in motor and cognitive tasks that assess hemispheric preference.<sup>8</sup> An opposite pattern can be seen in obese individuals, and body mass index (BMI) correlates positively with left-hemispheric preference in these types of tasks.<sup>9</sup> Studies suggest that reduced function or loss of function of the right PFC may lead to overeating and inactivity, whereas an excess activation of the right PFC can reduce eating drive and promote mobilization.

The right PFC is preferentially involved in guiding decision making according to social conduct and comprehen-

sion of bodily information at a higher level.<sup>10</sup> Recent studies in normal volunteers using repetitive transcranial magnetic stimulation, a technique that allows transient and noninvasive interference with cortical activity, provide further support for an asymmetric control of decision making in the PFC. Disrupting the activity of the right but not the left dorsolateral PFC induces a disregard for the long-term adverse consequences of choices, favoring risk-taking when subjects perform a gambling task.<sup>11</sup> Some evidence suggests a decision-making impairment in obese patients. For example, very obese individuals score worse than substance abusers in the Iowa Gambling Test, a paradigm that also relies on the integrity of the right PFC for execution.<sup>12</sup> These deficits in decision making may contribute to the inability of obese patients to commit to weight loss interventions long term and thus may help explain the usual refractoriness associated with this condition in clinical settings. Obesity has been found to be a marker of relapse and low treatment adherence in many

**Figure.** Brain Areas Involved in the Regulation of Food Intake and Schematic Representation of Their Interactions in the Proposed Model



The regulation of food intake in humans involves 3 hierarchical levels of control: cognition, homeostasis, and reward. Information on nutritional status is transmitted from the periphery to lower brain centers by neural and humoral signals. Indirect evidence suggests that peripheral mediators may also act on the cerebral cortex (dotted line). Extensive interconnectivity between these regulatory pathways allows precise and integrated control of food intake according to internal and external factors. These interactions are complex and may be inhibitory or facilitatory. Homeostatic and reward circuits (reflexive eating mode) tend to favor food intake. Brain areas involved in cognition (reflective eating mode), especially the right prefrontal cortex (PFC), tend to decrease food intake. Under normal circumstances, reflective areas can override and suppress reflexive areas (thick arrows). When activity of the right PFC is diminished, however, cognitive control of food intake decreases, favoring obesogenic habits.

epidemiologic studies. For instance, higher BMI has been associated with poor compliance with breast cancer screening programs, despite the fact that obese women have the highest risk for this disease.<sup>13</sup>

The right PFC is also emerging as a critical area in moral cognition. Inhibition of the right dorsolateral PFC with repetitive transcranial magnetic stimulation decreases rejection rates of unfair offers when study participants perform the Ultimatum Game, an experimental economics game, in which one player proposes a division of a sum of money and another player can accept or reject the offer.<sup>14</sup> This decrease supports a bias toward the right PFC in the suppression of self-oriented behaviors and the integration of moral reasoning and fairness judgment in decision making. The implications for the control of food intake may be especially relevant in industrialized societies, where food oversupply coexists with a continuous flow of health- and food-related information through the mass media. This body of information creates attitudes and beliefs about food among the general population. Values of eating “well” or “poorly” are generally assigned to different diets according to their expected impact on long-term health or body appearance. A right PFC dysregulation could result in a failure to appropriately weigh the adverse consequences of indulging in a bad diet, thus facilitating obesogenic habits.

The PFC is also an important node in the neural circuits mediating self-recognition, with a preferential involvement of the right hemisphere,<sup>15</sup> where visuospatial information, perception of human bodies, and self body image are conveyed through prefrontal-parietal and prefrontal-temporolimbic channels. Asymmetric atrophy of the right frontal lobe in patients with dementia can cause a disturbance in body image and changes in other facets of self, including food preferences.<sup>16</sup> Miller et al<sup>16</sup> reported the case of a 54-year-old woman who developed a second personality and weight gain coincident with the beginning of frontotemporal dementia, with predominant involvement of the right frontal lobe. The patient described her alternate personality as socially inappropriate, unfashionable, fond of fast foods, and an overeater.

On the other hand, successful weight-loss maintainers, who have a high degree of dietary restraint and body image awareness and monitoring, show more activation of the right dorsolateral PFC after consumption of a meal, as compared with nondieters.<sup>17</sup> Some data suggest that obesity may be associated with a lower level of bodily awareness and a dysfunction of this right hemispheric system of body image monitoring. For example, overweight and obese individuals misperceive their body-size status more than lean individuals, and this “weight estimate error” (defined as measured weight minus self-reported weight) correlates positively with BMI.<sup>18</sup> Misreporting of caloric intake and physical activity in those who fail to lose weight and self-report as diet-resistant may indeed reflect an impairment in these mechanisms.<sup>19</sup> Additionally, BMI has been negatively correlated with decreased or disturbed sensitivity for several bodily signals, such as the ability

to perceive heart action,<sup>20</sup> and this reduced sensitivity may help explain the increased prevalence of psychosomatic health complaints in the obese population. The PFC is also an area in which emotions are integrated with self-scheme, the ability to predict what another is thinking or may know in a given social context to ultimately acquire a self-conscious dimension. Lack of embarrassment, which may perpetuate an “inappropriate” body size, has been associated with decreased activity of the PFC, despite preserved basic emotional responses.<sup>21</sup>

### Toward a Human Brain Model of Obesity

The consistency of the link between the right PFC and obesity and the emerging role for this area in cognitive processes relevant for food intake and physical activity suggest that a dysfunction of the right PFC may represent a central event in the etiology of human obesity. Beyond dysregulation of appetite and overactivity of food-related reward and motivation loops, it is possible that disruption of the right PFC is a critical mechanism sufficient to cause a positive switch in energy balance, favoring an increase in body weight in modern societies.

Human eating can be conceptualized as a dual model (Figure), in which “reflexive eating” represents implicit automatic impulses to overeat in preparation for future food shortage. This phylogenetically older eating mode is controlled by the hypothalamus and brain circuits involved in reward and motivation under the influence of a variety of neurotransmitters and neuropeptides and is balanced by a superimposed “reflective eating” mode. Reflective eating is essentially human and incorporates a cognitive dimension related, for example, to social expectations of body shape, appropriate collective acts, and long-term health goals. In this scenario, a decrease in the activity of the right PFC can underlie a switch into a self-centered, reflexive mode of eating that could lead to obesity in industrialized societies, where food is widely available. The amount of activity in the right PFC may determine the degree of inhibition over downstream circuits that promote overeating.

Recent findings provide indirect evidence that the cortex could be also targeted by appetite mediators. For example, leptin replacement in adults who are genetically deficient in this hormone has been shown to increase gray matter density in several cortical areas that include the PFC.<sup>22</sup> In addition, a potential role of insulin in brain glucose metabolism has been recently reported.<sup>23</sup> This mechanism appears to be regionally selective, with the PFC as a major target that undergoes enhanced metabolic rate in response to insulin.<sup>23</sup> Although little is known about the effect of ghrelin and other appetite-related humoral signals on the PFC, these recent studies raise the possibility that, in response to a given nutritional state, an extensive brain response may be initiated. This response may comprise effects on homeostatic hypothalamic circuits, reward pathways, and certain influence on cortical areas involved in the control of behavioral aspects of food intake and physical activity.



## Causes of Right Prefrontal Dysregulation

The mediator of right prefrontal dysregulation in obese individuals and its predicted higher prevalence in the current obesity epidemic is unknown. Genetic factors may play an important role in PFC functioning. However, a genome change cannot be responsible for the exponential increase of obesity worldwide in such a relatively short period, and environmental factors need to be considered. In higher vertebrates, the stress response acts as a driver of brain plasticity at the interface between environment and behavior and provides a feasible mechanism by which environment could affect PFC function. Epidemiologic and experimental data link obesity to a chronic activation of the stress response through the hypothalamic-pituitary-adrenal axis.<sup>24</sup> In the PFC, cortisol modulates dopaminergic activity with remarkably lateralized effects. Dopaminergic projections to the right hemisphere display an enhanced sensitivity to stressors that are specifically perceived as severe and uncontrollable, such as those that arise from social conflict.<sup>25</sup> In today's industrialized society, shame, defeat, frustration, and fear of social rejection are commonly perceived by people because of unattainable social models of success. Thus, chronic psychosocial stress, characterized by a threat to self-esteem and the anticipation of an impending and lasting challenge, may disinhibit reflexive circuits through a cortisol-induced right PFC dysfunction that is caused by a prolonged activation of the hypothalamic-pituitary-adrenal axis. Other mechanisms may also play important roles in right prefrontal dysregulation, stress response, and obesity, such as genetic interindividual differences, social structure, and cultural habits.

## Conclusion

The right brain hypothesis for obesity may serve to foster interaction among cognitive neuroscientists and researchers studying energy balance and inspire future translational studies to unravel a most important unmet clinical need. Given the heterogeneity of obesity, it remains uncertain whether this model can be extended to the general obese population or applied only to a subset of individuals (eg, total vs central obesity, certain ranges of the BMI, obesity associated with binge-eating disorder). The right PFC represents an interesting therapeutic target to explore in future studies in obesity research. Neuromodulation-based approaches may help assess the potential benefit of enhancing the activity of right PFC. Increasing the activity of the right PFC might decrease appetite and reestablish inhibitory mechanisms controlling eating, as well as improve long-term adherence to interventions such as diet or exercise therapy, which is a major barrier that limits the success of any attempt to treat obesity.

**Financial Disclosures:** Dr Alonso-Alonso reports that he was accepted in the Clinical Investigator Training Program, which supports his salary and provides formal training in various aspects of clinical research. This program was set up as a joint venture of the Harvard-MIT Division of Health Sciences and Technologies and the Beth Israel Deaconess Medical Center, supported by unrestricted educational grants from Pfizer and Merck Inc. During 2006, he was funded by the Fundación para la Investigación y Desarrollo del Complejo Hospitalario Universitario de Vigo (FICHUVI), Galicia, Spain. Dr Pascual-Leone reported no financial disclosures.

**Funding/Support:** The work on this article was partly supported by grants from the Boston Obesity and Nutrition Research Center (P30 DK46200), National Institutes of Health grant K24 RR018875, and the CITP Program.

**Role of the Sponsor:** None of the funding organizations played a role in the design and conduct of this work; collection, management, analysis, interpretation of the data; or the preparation, review, and approval of the manuscript.

**Acknowledgment:** We thank Clifford B. Saper, MD, PhD, Harvard Medical School and Beth Israel Deaconess Medical Center; Eleftheria Maratos-Flier, MD, Harvard Medical School and Beth Israel Deaconess Medical Center; Christos Mantzoros, MD, DSc, Harvard Medical School and Beth Israel Deaconess Medical Center; and Jeffrey S. Flier, MD, Harvard Medical School and Beth Israel Deaconess Medical Center, for valuable comments and suggestions. None received compensation for their feedback in the development of this article.

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