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Central nervous system regulation of eating: Insights from human brain imaging☆,☆☆

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ABSTRACT

Appetite and body weight regulation are controlled by the central nervous system (CNS) in a rather complicated manner. The human brain plays a central role in integrating internal and external inputs to modulate energy homeostasis. Although homeostatic control by the hypothalamus is currently considered to be primarily responsible for controlling appetite, most of the available evidence derives from experiments in rodents, and the role of this system in regulating appetite in states of hunger/starvation and in the pathogenesis of overeating/obesity remains to be fully elucidated in humans. Further, cognitive and affective processes have been implicated in the dysregulation of eating behavior in humans, but their exact relative contributions as well as the respective underlying mechanisms remain unclear. We briefly review each of these systems here and present the current state of research in an attempt to update clinicians and clinical researchers alike on the status and future directions of obesity research.

Obesity is an increasing concern worldwide and was declared a global health epidemic in 2003 by the World Health Organization. Particularly pronounced in industrialized countries including the United States, a third or more of the population presents with obesity and an additional third is overweight [1]. Other nations are rapidly following with a lag phase that reflects their degree of westernization. In order to understand and develop effective therapeutics for this medical condition, it is necessary to understand the central nervous system (CNS) mechanisms underlying eating behaviors and how these mechanisms become dysregulated.

Current research indicates that the brain circuitry which controls eating in humans is regulated not only by homeostatic mechanisms, but also by the reward, emotion/memory,

Abbreviations: CNS, central nervous system; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalogram; EEG, electroencephalogram; PET, positron emission tomography; D2, dopamine-2; POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine-related transcript; AgRP, agouti-related protein; NPY, neuropeptide Y; VTA, ventral tegmental area; SN, substantia nigra; OFC, orbitofrontal cortex; pre-SMA, pre-supplementary motor area; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; AgRP, agouti-related peptide; ARC, arcuate nucleus; AVP, arginine-vasopressin; BDNF, brain-derived neurotrophic factor; CART, cocaine- and amphetamine-regulated transcript; DMH, dorsomedial hypothalamus; LH, lateral hypothalamus; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY; TRH, thyroid-releasing hormone; VMH, ventromedial nucleus.

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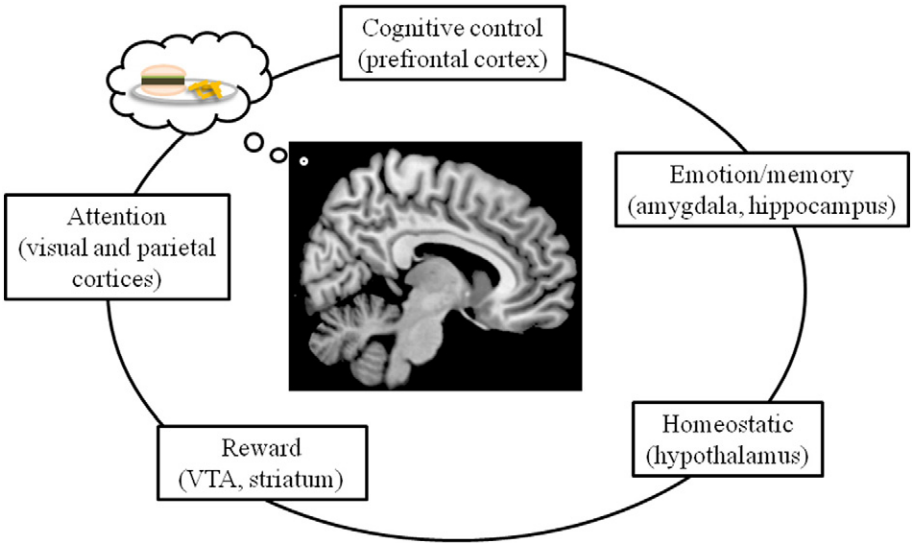

Fig. 1 – Control of eating in human brain involves several brain systems including the homeostatic brain systems (hypothalamus), attention systems (including the parietal and visual cortices), emotion and memory systems (such as the amygdala and hippocampus), cognitive control (including the prefrontal cortex), and the reward network (including the VTA and striatum).

attention, and cognitive control systems (Fig. 1). These circuits interact to control energy intake and expenditure. Here, after introducing the techniques that are employed to study the human brain, we will describe each of these systems, beginning with the homeostatic control of eating in the hypothalamus and ending with the prefrontal processes of cognitive control.

1. Techniques to Study the CNS in Clinical Research

The most commonly used techniques to examine the appetitive processes in human brains include neurocognitive testing and functional magnetic resonance imaging (fMRI). Neurocognitive testing can be described simply as targeted computer games which aim to capture a certain mental skill through a specific task. By simplifying real world experiences into these tasks, researchers obtain outcome measures of each of the cognitive components described above. For instance, the stop signal task or go/no-go task is often used to measure cognitive or inhibitory control [2–4] and can be combined with fMRI to study these complex mechanisms in the brain. Previous studies have found longer stop signal reaction times (SSRTs), which represent poorer inhibitory control, to correlate with future weight gain [5]. Intensive lifestyle changes decrease SSRTs, representing improved inhibitory control, in adolescents [6]. However, neurocognitive testing alone is limited in scope. While specific outcome measures may provide basic information about cognitive performance/state, they do not describe how different brain areas or networks are involved or may be altered in disease states. These neural phenotypes can be captured when neurocognitive tasks are combined with fMRI. For example, even though there may be no difference in performance on neurocognitive tasks, obese and lean individuals display different patterns of brain activations to the same challenges during fMRI [4,7–10]. These findings suggest that activations of specific brain areas may be altered or act to compensate in order to maintain neurocognitive performance. These changes in brain activations are related to real-life decisions in eating. For example, despite no difference on the cognitive control-related Stroop task, obese as compared to lean participants showed greater activation of the frontal cortex including the insula during incongruent stimuli, and this was related to reported binge eating [9].

Neuronal activations require an increased supply of oxygenated blood. fMRI relies on the differences in the magnetic properties of the oxygenated versus deoxygenated hemoglobins to create an image of the brain and detects functional activation by observing shifts in the magnetic signals. Thus, this represents an indirect measure of neural activity, which assumes that recently active brain areas use more oxygen. fMRI captures brain activity in the cortex with good spatial and acceptable temporal resolution but is susceptible, by nature, to artifacts from the sinuses, throat, and eyes. It is thus difficult to identify activity in some areas of interest to obesity research, including the hypothalamus [11] and orbitofrontal cortex [12]. Nonetheless, fMRI is considered to be one of the best tools currently available for the detection of regional brain activations to specific cues or tasks. As mentioned earlier, fMRI is frequently conducted in conjunction with a behavioral task. In terms of studying the control of eating, the most common paradigms involve the presentation of food images or food delivery (such as giving a milkshake). For instance, brain responses to viewing food images have been repeatedly shown to be different between obese and lean individuals in the reward, emotional and cognitive control circuits [13–18]. Oral food presentation has also been observed to modulate brain activity in these circuits [19,20]. fMRI can be expanded to study not only the activation of the human brain but also how these brain centers are