Stress and Reward Neural Networks, Eating, and Obesity

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Introduction<1>

Stress is becoming increasingly recognized as a factor leading to overeating and obesity. Here we present the evidence that stress-related eating follows well defined neural pathways that involve control over volitional behavior (prefrontal cortex or PFC), and subcortical areas controlling stress arousal and energy storage (limbic hypothalamic-pituitary-adrenal axis or L-HPA) and strong motivational drive and impulsivity (nucleus accumbens). The limbic system and PFC each inhibit activity in the other, promoting a balance between slower reflective analytic reasoning, necessary to promote goal-directed behavior, and quick reactive survival instincts. Shifts in activity of this neural network, what we call here the "**PFC/limbic balance**," has well demonstrated effects on cognition and behavior during acute stress.[1] It is now becoming clear that this neural network shapes eating behavior. We propose that a low PFC/limbic balance can lead to energy imbalance, and in particular, abdominal obesity.

We first review neural and hormonal control over eating during basal conditions and then under stressful circumstances, showing that stress affects in large part activation of reward pathways, and impairs attempts to control eating. We conclude with suggestions for treatment of this widespread common behavior.

Basic mechanisms underlying stress related overeating.<1>

Homeostatic eating (H-EAT), and non-homeostatic influences.<2>

We are equipped with highly evolved regulatory systems that monitor the amount of stored energy and attuned to the need to find and eat more calories. In chordates, this system resides primarily in the brainstem and hypothalamus, and is sensitive to hormonal and nutrient signals acting directly on neuronal receptors within this network. Regulation of homeostatic eating is covered in detail elsewhere [2]. Left alone, the homeostatic regulation of feeding behaviors is remarkably accurate and over weeks, months and years the organism neither gains nor loses much weight. Despite the complex coordination

between gut, pancreas, vagus, and brain, this homeostatic regulatory system is easily overridden by our emotions. As more brain was added to mammals, such as limbic and cortical networks, regulation of food intake became far more complicated, and far less driven by homeostasis of maintaining fat stores. The higher brain structures also innervate the brainstem and hypothalamic network and, at each level, can subvert or reinforce their normal operation of maintaining energy homeostasis. In particular, eating for reward, or hedonic eating, contributes to a large proportion of our caloric intake. We pose that stress is a major factor that promotes hedonic eating and strengthens networks toward tonic hedonic overeating. This makes sense in that the stress response is likely a mere subset of the metabolic networks that maintain caloric balance, our primary survival need.[3] The focus of this review is the mechanisms for stress eating, and outcomes of energy balance and fat distribution.

Stress drives specific intake of comfort food.<2>

Both acute, single stressors and chronic, sustained stressors are likely to change feeding behaviors in people and rats. Roughly 40% of people reduce and 40% increase their total caloric intake during stressors, with only 20% maintaining intake at normal levels.[4, 5] Rats and mice, given only chow to eat, uniformly decrease food intake during stressors. However, if supplied with highly palatable foods to eat, rats still decrease chow intake but eat the same or more palatable food, as people do. Whether they decrease or increase caloric intake, people change the type of food ingested, with negative emotion driving a shift away from healthy foods toward highly palatable food – usually sweet, sometimes salty, and high fat, and sometimes moderated by high dietary restraint.[6-9]

The Stress-hedonic Eating (S-EAT) Model.<1>

In Figure 1, we pose a simplified version of the neural networks regulating stress-induced hedonic eating. There are interactive connections between structures regulating eating – the limbic system, reward system, basal ganglia, and PFC. Differential patterns of activation shape two distinct types of eating behavior – stress-induced hedonic eating **(S-EAT)** vs. homeostatic eating **(H-EAT),** which is eating

solely in response to caloric need.

Insert Figure 1 around here

Limbic structures, stress, and regulation by the stress hormone cortisol<2>.

Stressors engage a network of limbic (phylogenetically ancient) structures that reflect interoceptive as well as exteroceptive inputs: the insula, extended amygdala, anterior cingulate cortex as well as thalamic, hypothalamic and lower brainstem sites.[10] This recruitment of the stress-network appears to depend on the actions of glucocorticoids (GC) secreted from the adrenal cortex in response to stressors and the network is engaged to a large extent through the positive actions of GC on corticotropic releasing factor (CRF) expression in extrahypothalamic neurons. Acute cortisol reactivity appears to acutely promote comfort food intake both in the lab and naturalistically.[11, 12]

Both acute and chronic stressors increase synapses and dendritic bushing in the amygdala and ACC, and reduce synaptic contacts with dendritic atrophy in the hippocampus and PFC[13-15] further sculpting the chronic stress network toward limbic-biased stress responses. Chronic stress effects on the brain may alter eating tonically toward greater comfort food. Women reporting greater chronic stress report greater hunger drive and greater high fat intake.[16]

Stress stimulates the reward system.<2>

Exposure to psychological stressors can induce a hefty immediate stress response. Stress activates the limbic system, in particular the amygdala and corticotropin releasing factor (CRF), from the hypothalamus, consequently the hypothalamic pituitary adrenal axis (L-HPA axis). Activation of the L-HPA is linked to activation of the mesolimbic reward area activity. There are several examples of the tight interconnection between stress and reward areas. Anatomically, increased CRF secretion resulting

from activation of this central stress response network impinges on DA neurons in the VTA, and increases dopamine secretion over the nucleus accumbens (NAC) that is stimulated by drugs, and possibly stressors.[17, 18] Stress is linked to craving and drug addiction in people (see Singha, this volume). In humans exposed to a lab stressor during a PET study, stress exposure, as well as cortisol release, both enhanced dopamine release from the NAC.[19] In another study on acute stress, those who responded with greater cortisol reactivity released more dopamine in the ventral striatum, showing a very strong coupling of the two.[20]

In turn, the experience of dopamine stimulation is one of craving or drive for pleasure, and food is the most available and inexpensive drug around – a "natural" reward. For example, rats which had opioids injected into their reward area respond by overeating.[21]

S-EATING is maintained through negative feedback: Short term gain to well being with long term cost to health.<2>

Stress eating may be motivated by negative reinforcement, seeking distraction from distress or a stressful situation[22] or seeking reward and relaxation. In rat studies, eating palatable foods reduces both subsequent stress-induced behavioral and neuroendocrine responses.[23-26] and makes people feel better. [27, 28] Eating palatable foods triggers increased dopamine secretion in the mesolimbic pathway, from the ventral tegmental area (VTA) to the NAC -- a highly rewarding pleasurable experience, activating dopamine and opioid secretion from neurons throughout the homeostatic feeding network. Thus, as shown in Figure 1, eating palatable foods after a stressor reduces activity in the central stress-response network, and serves as feedback to sharpen the activity of the network and reduce the duration of its activity. The long-term cost of S-EAT is high -- abdominal fat deposition and related metabolic derangements.

Stress eating can promote habit-driven comfort food eating in the absence of active stress.<2>

These strong opioid and dopamine responses in the reward center during stress promote encoding of habits in the basal ganglia, the home of habit.[29] Thus, either acute or chronic stressors might augment wanting, pleasure and memories associated with palatable food intake. Memories of responses to stimuli are stored both in the cortex, where flexibility of response is engendered by the knowledge of outcome and in the basal ganglia, where habit is expressed, and a learned response follows the stimulus [30-32].

Stress subjugates the Prefrontal Cortex: Impaired PFC/Limbic balance.<2>

The prefrontal cortex is a key player in stress neural networks. During normal conditions, the PFC reigns, and cognition is dominated by reflective cognition. During stress, however, the PFC activity is dampened and the amygdala and limbic circuitry dominates, promoting automatic behavior geared toward survival including being vigilant for food cues. In rats, the PFC neurons inhibit both dopamine from the NAC and the Limbic-HPA axis cortisol response.[33]

Conversely, stressors lead both to reduction of PFC function and increased habit expression,[1, 30 13] thus reinforcing the likelihood of seeking and eating sweet foods after a stressor whether or not the stressed individual is high on dietary restraint.[6, 26] The stressed brain expresses both strong drive to eat and impaired capacity to inhibit eating -- a potent formula for obesity.

Dietary Restraint: Adaptive regulator or additional stressor?<1>

The construct of dietary restraint is an important individual difference that moderates many of the relationships in Figure 1. Dietary restraint is defined as voluntary and cognitive control over one's eating to restrict food intake to control body weight. [34] Restraint is necessary to have in our abundantly palatable food environment but on the other hand, is linked to overeating in states of stress.

A critical distinction is the difference between flexible versus rigid restraint.[35] We pose that high PFC/limbic balance is related to high levels of "adaptive restraint," or the type of flexible dietary restraint behaviors that promote appropriate control over eating. This high balance allows the volitional flexible control needed to self monitor and adjust to changes in one's food environment and behavior, such as

awareness of how much one has eaten and then adjusting accordingly. Flexible restraint is associated with less disinhibited eating, less frequent/severe binge eating, lower weight, and lower energy intake.[35] In contrast, maladaptive or "rigid restraint," reflects severe behaviors to control eating, based on inflexible cognitive rules such as having forbidden foods, and skipping meals. Rigid restraint is associated with disinhibited eating, higher BMI, and greater binge eating.[35] Those high in rigid restraint, therefore, may reflect low PFC/limbic balance and be particularly vulnerable to S-EAT processes.[36, 37]

Rigid restraint may *itself* serve as a stressor, since rigid restraint represents frequent cognitive load or demands on attention and working memory, and violations of one's desires to eat less. Restraint has been associated with perceived stress as well as increased cortisol.[38, 39] Further, chronic stress is associated with greater rigid and lower flexible restraint.[16] While high stress may promote more rigid restraint, it is also likely that high levels of rigid restraint chronically activates the limbic-HPA pathways, leading to physiological stress and strengthening the low PFC/high limbic imbalance, promoting a vicious cycle of overcontrol and loss of control.

Putting it all together: Contrasting Stress Eating (S-EAT) vs. Homeostatic Eating (H-EAT).<1>

Ingestive behavior can involve many processes, from hunger and satiety detection, to food choice, and cessation of eating. Given that eating is largely a habitual behavior, often done unintentionally with little awareness,[40] it is regulated in part by the PFC/limbic balance, and thus affected by states of stress. Table 1 summarizes how eating processes are regulated differently under stress vs. non-demanding conditions.

Insert Table 1 around here

The PFC, particularly the right frontal PFC, plays a crucial role in eating behavior, as demonstrated by certain neurological conditions.[41] Interoceptive awareness of hunger and satiety cues

uses somatosensory perception, relying on the anterior insula cortex[10] and for satiety, the orbitofrontal cortex.[42] PFC also promotes inhibition of undesired responses, so is crucial in control over eating. Those with successful weight loss maintenance have higher activity in certain frontal regions and secondary visual cortex in response to food images than those who are obese.[43-45] The PFC also drives top down decision making about food choices, enabling one to plan for healthy choices based on goals and nutrition knowledge.

In contrast, stress can disinhibit aspects of PFC circuitry so necessary for self-regulation of eating. Emotional states can be misinterpreted as hunger. The limbic brain, amygdala and hypothalamus drive salience for survival related cues, making food cues salient and increasing the arousal drive to consume.[2] Stress may thwart careful self regulation (flexible control) over food portions. Conversely, people with rigid control tend to lose that control under stress, and overeat, at least in laboratory studies.[37] Instead of being a result of thoughtful decisions, S-EATing is driven by VTA-driven impulse, and habit circuitry, focused in the basal ganglia.[30, 46] For the stressed brain, food 'choices' seem to become predetermined or habitual search for dense calories or highly palatable food, rather than a conscious choice.

Consequences of a chronically stressed society and interventions for S-EATING. <1>

Living in increasingly stressful times creates a potent formula for low PFC/limbic balance, impaired flexible restraint, and sustained excess energy intake, preferentially stored as 'stress fat,' in the visceral area. Although it is hard to determine how pervasive S-EATING vs. H-EATING may be, it could account for a large proportion of our societal caloric excess and the obesity epidemic. Given that S-EAT patterns may be initiated by historical stressors, or provoked by the mildest of daily stressors, and masquerade as habit, it is hard to identify the unique contribution of S-EATING to one's total caloric intake, at least in people.

Psycho-educational strategies are not enough to counter the strong habitual forces of S-EAT, especially when the food environment is likely the most powerful influence on eating behavior. Exercise

improves function of the PFC[41] but may not be enough to counter the epidemic. Re-training of the brain to pay effortful attention to eating and to emotions is probably a necessary but not sufficient component in any obesity intervention. Experimental work supports the potential role of techniques that work on re-appraisal of emotional stressors, and even simply labeling emotions verbally, in establishing a stronger PFC/limbic balance and control over eating. Mindfulness, nonjudgmental attention to the present moment, promotes more reflective cognition, awareness of emotions, and separation of emotions from hunger. Mindful eating can reduce binge eating.[47] People high on dispositional mindfulness show stronger PFC/limbic balance (high PFC, low amygdala activity) when simply labeling emotions.[48] Structural data shows that meditation is associated with greater volume of right orbital prefrontal cortex, insula, and hippocampus, which are important in self control.[49, 50] We are currently testing if mindful eating and mindful stress reduction can reduce S-EAT in obesity. However, given the pervasive exposure of both the toxic food environment and societal-wide chronic stress, it is likely that food policy and policies that reduce societal stress are both necessary to tide the epidemic.

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Table 1: Contrasting eating-relevant behavior in Homeostatic Eating vs. Stress Eating

Process	HOMEOSTATIC-EATING (H-EAT) (PFC driven, somatosensory cortex)	STRESS-EATING (S-EAT) (Amygdala, Limbic, Hypothalamus driven)
Hunger	Awareness of hunger level, Sensitivity to somatosensory cues	Confusion of emotions with hunger (arousal drive), blunted awareness of somatosensory cues
Control over onset and cessation of eating	Flexible restraint	Rigid restraint and loss of control
Decision making about food choices	Reflective eating enables healthy choices (Goal directed behavior)	Reflexive eating of highly palatable food, pursuit of comfort food (Habit driven behavior)
Satiety	Awareness of sensations of satiety, physical cues	Blunted sensitivity to satiety and physical cues

Figure 1. Stress-induced hedonic eating.