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Stress as a common risk factor for obesity and addiction

Rajita Sinha, PhD[1,2,3] and **Ania M. Jastreboff, MD, PhD**[4,5]

[1]Department of Psychiatry Yale University School of Medicine, Yale Stress Center, 2 Church Street South, Suite 209, New Haven, CT 06519

[2]Child Study Center, Yale University School of Medicine, New Haven, CT 06520

[3]Department of Neurobiology, Yale University School of Medicine, New Haven, CT 06520

[4]Department of Internal Medicine, Section of Endocrinology, 333 Cedar Street, Yale University School of Medicine, New Haven, CT 06520

[5]Department of Pediatrics, Section of Pediatric Endocrinology, 333 Cedar Street, Yale University School of Medicine, New Haven, CT 06520

Abstract

Stress is associated with obesity and the neurobiology of stress overlaps significantly with that of appetite and energy regulation. This review will discuss stress, allostasis, the neurobiology of stress and its overlap with neural regulation of appetite and energy homeostasis. Stress is a key risk factor in the development of addiction and in addiction relapse. High levels of stress changes eating patterns and augments consumption of highly palatable (HP) foods, which in turn, increases incentive salience of HP foods and allostatic load. The neurobiological mechanisms by which stress affects reward pathways to potentiate motivation and consumption of HP foods as well as addictive drugs is discussed. With enhanced incentive salience of HP foods and over-consumption of these foods, there are adaptations in stress and reward circuits that promote stress-related and HP food-related motivation as well as concomitant metabolic adaptations, including alterations in glucose metabolism, insulin sensitivity, and other hormones related to energy homeostatsis. These metabolic changes in turn may also affect dopaminergic activity to influence food motivation and intake of HP foods. An integrative heuristic model is proposed wherein repeated high levels of stress alter the biology of stress and appetite/energy regulation, with both components directly affecting neural mechanisms contributing to stress-induced and food cue-induced HP food motivation and engagement in overeating of such foods to enhance risk of weight gain and obesity. Future directions in research are identified to increase understanding of the mechanisms by which stress may increase risk of weight gain and obesity.

Keywords

Obesity; Stress; Addiction; Metabolism; Neuroendocrine; Reward

Correspondence to: Rajita Sinha; Ania M. Jastreboff.

Corresponding author: Rajita Sinha, Ph.D., Yale Stress Center, 2 Church Street South, Suite 209, New Haven, CT 06519, Tel: 203-737-5015, Fax: 203-737-1272.

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Obesity and addiction: the integral role of stress

Addiction to alcohol and drugs continues to be a significant public health problem with devastating medical, social and societal consequences (1). Stress is a critical risk factor affecting both the development of addictive disorders and relapse to addictive behaviors, hence jeopardizing the course and recovery from these illnesses (2).Obesity is a global epidemic, and the United States is at the forefront of the pandemic with two-thirds of its population classified as overweight or obese (BMI > 25kg/m^2) (3). The development of both obesity and addiction involves genetic, environmental and individual lifestyle characteristics that all contribute to this pandemic (4); (5). While previous reviews focus on these factors, this paper explores the role of stress, food cues and food motivation in contributing to overeating in obesity.

Stress and allostasis

Most simply, *stress* is the process by which any highly challenging, uncontrollable and overwhelming emotional or physiological event or series of events result in adaptive or maladaptive processes required to regain homeostasis and/or stability (6), (2). Examples of emotional stressors include interpersonal conflict, loss of a meaningful relationship, unemployment, death of a close family member, or loss of a child. Some common physiological stressors include hunger or food deprivation, insomnia or sleep deprivation, severe illness, extreme hyperthermia or hypothermia, psychoactive drug effects and drug withdrawal states. Stress-related adaptation involves the concept of *allostasis*, which is the ability to achieve physiological stability through change in internal milieu and to maintain apparent stability at a new physiological set point (6); (7)). According to McEwen and colleagues, there are ongoing adjustments of internal milieu, with fluctuations in physiology, mood, and activity as individuals respond and adapt to environmental demands (7). Excessive stress to the organism, termed as increased *allostatic load*, results in “wear and tear” of the adaptive regulatory systems resulting in biological alterations that weaken stress adaptive processes and increase disease susceptibility (7). Thus, high levels of uncontrollable stress and conditions of repeated and chronic stress promote sustained allostatic load resulting in dysregulated neural, metabolic and biobehavioral states that contribute to maladaptive behaviors and physiology outside of the homeostatic range {McEwen, 2007 #4}.

Stress, chronic adversity, and increased vulnerability to obesity

Similar to the effects of repeated and chronic stress on increasing addiction vulnerability (2), considerable evidence from population-based and clinical studies indicates a significant and positive association of high uncontrollable stressful events and chronic stress states with adiposity, BMI and weight gain (8), (9), (10), (11). This relationship also appears to be strongest among individuals who are overweight and those who binge eat (8), (9), (12). Using a comprehensive interview assessment of cumulative and repeated stress in a community sample of healthy adults (n=588), we found that higher numbers of stressful events and chronic stressors (see Table 1) over the lifetime was associated with excessive alcohol use, being a smoker and a higher BMI, after controlling for age, race, gender and socioeconomic status variables (see Figure 1).

As stress affects weight gain and BMI, we also assessed its effects on basal glucose, insulin and insulin resistance. Morning screening of fasting plasma glucose (FPG) and insulin was assessed in a large subgroup of these healthy community volunteers and homeostasis model assessment (HOMA-IR) was calculated as an index of insulin resistance. We found that cumulative stress was associated with BMI-related changes in higher levels of glucose,

insulin and HOMA-IR (Figure 2). These data indicate stronger associations between cumulative total stress and metabolic dysfunction among individuals in higher compared to lower BMI categories. These findings are similar to previous research indicating stronger effects of stress on increased substance use in individuals who are regular to heavy as compared to light or recreational users (2). Together, these findings suggest that cumulative and repeated stress increases obesity risk and that individuals with higher BMIs may be more vulnerable to stress-related food consumption and subsequent weight gain.

Stress and eating behaviors

Acute stress significantly alters eating (13); (10); (9). While some studies show decreases in food intake under acute stress, acute stress can also increase intake, especially when HP, calorie-dense foods are available (9, 13), (14), (15), (16). For example, by self-report alone, 42% of students reported increase food intake with perceived stress, and 73% of the participants reported increase in snacking during stress (17). One third to half of animal or human laboratory studies show increases in food intake during acute stress, while others show no change or reduce intake (18), (11). Thus, while increased food intake with acute stress does not occur in everyone, certainly it does affect many individuals. Additionally, it is important to note that a number of experimental factors may contribute to research on these differential effects on acute stress-induced eating (19), (20), (12). These factors include the specific type of stressor used in the manipulation, length of stress provocation, length of time of exposure to food intake and the amount and type of foods offered in the experiment, as well as the satiety and hunger level at the start of the study. These factors may contribute to the variability in results of the laboratory experiments that model stress effects on food intake.

There is significant evidence suggesting potentially detrimental effects of stress on eating patterns (e.g., skipping meals, restraining intake, binging) and food preference (10). Stress can increase consumption of fast food (21), snacks (22), calorie-dense and highly-palatable foods (23), and stress has been associated with increased binge eating (12). The effects of stress may be different in lean as compared to obese individuals (8, 24–26). Stress-driven eating has been found to be exacerbated in obese women whereas stress-driven eating appears to have an inconsistent effect on food consumption in lean individuals (24). Furthermore, changes in eating patterns may relate to carbohydrate metabolism and insulin sensitivity (27). In healthy lean women, binge eating increases fasting glucose, insulin response, and alters the diurnal pattern of leptin secretion (28). Irregular meal frequency has been found to increase insulin in response to a test meal after a period of irregular eating patterns (27). Taken together, this research suggests that stress may promote irregular eating patterns and alter food preference and that overweight and obese individuals may be more vulnerable to such effects, possibly via weight-related adaptations in energy regulation and homeostasis.

The overlapping neurobiology of stress and energy homeostasis

The physiological responses to acute stress are manifested through two interacting stress pathways. The first is the hypothalamic-pituitary-adrenal (HPA) axis, in which corticotropin-releasing factor (CRF) is released from the paraventricular nucleus (PVN) of the hypothalamus, stimulating secretion of adrenocorticotrophin hormone (ACTH) from the anterior pituitary, which subsequently stimulates the secretion of glucocorticoids (GC) (cortisol or corticosterone) from the adrenal glands. The second is the autonomic nervous system, which is coordinated by the sympathoadrenal medullary (SAM) and the parasympathetic systems. Both components of these stress pathways also influence inflammatory cytokines and immunity (2); (6).

The release of CRF and ACTH from the hypothalamus and the anterior pituitary during stress results in GC release from the adrenal cortex, which in turn, supports energy mobilization and gluconeogenesis. Stress-related sympathetic arousal increases blood pressure and a diversion of blood flow from the gastrointestinal tract to skeletal muscles and the brain. The acute effects of stress on CRF and ACTH is terminated by GC negative feedback, supporting a return to homeostasis, and under such acute stress conditions, there is significant evidence that there is a decrease, rather than an increase, in food intake (19), (9). The hypothalamus is responsive to GCs via negative feedback, but also to insulin, secreted from the pancreas and integral to glucose metabolism and energy storage (29), (9), and to other hormones, like leptin which inhibits appetite, and ghrelin which promotes appetite (5); (9); Currie, 2005). Glucocorticoids increase plasma leptin and ghrelin levels, and ghrelin also increases with stress and is involved in regulating anxiety and mood (30). Furthermore, a number of hypothalamic neuropeptides, such as CRF, propriomelanocortin (POMC), the orexigenic neuropeptide Y (NPY), and agouti-related peptide (AgRP), as well as the melanocortin receptors involved in regulating the stress response, also play a role in feeding (31). Glucocorticoids alter the expression of these neuropeptides that regulate energy intake (32), (31). For example, bilateral adrenalecomy reduces food intake, and GC administration increases food intake by stimulating the release of NPY and inhibiting CRF release (31). Furthermore, food restriction and high fat diets alter HPAaxis responses to stress and GC gene expression in a number of brain regions involved in energy homeostasis and stress (33), (20), (18), (34), (35). Thus, the hypothalamus is a critical region in the stress circuit as well as in the regulation of feeding and energy balance.

Chronic and high levels of repeated and uncontrollable stress results in dysregulation of the HPA axis, with changes in GC gene expression (6), (36), which in turn, also affect energy homeostasis and feeding behavior. Chronic activation of the HPA axis is known to alter glucose metabolism and promote insulin resistance, with changes in a number of appetite-related hormones (e.g. leptin, ghrelin) and feeding neuropeptides (e.g. NPY) (37), (38), (39), (40). Chronic stress persistently increases GCs, and promotes abdominal fat, which in the presence of insulin, decreases HPA axis activity (9), (38) (33). Basic science studies have shown that adrenal steroids increase glucose and insulin levels as well as selection and intake of high caloric foods (13), (14), (15), (41). Chronic high GCs and increases in insulin have synergistic effects on increasing HP food intake and abdominal fat deposition (23), (9); (42). High levels of repeated stress also result in sympathetic overactivity, and stress-related increases in autonomic responses are related to insulin levels and insulin resistance in adolescents and adults (43).

Stress effects on food reward, motivation and intake

The hypothalamic stress circuits are under the regulation of extrahypothalamic cortico-limbic pathways modulated by CRF, NPY and noradrenergic pathways. The stress response is initiated via the amygdala and stress regulation occurs via GC negative feedback to the hippocampus and medial prefrontal cortical (mPFC) regions (6). The extrahypothalamic projections of CRF are involved in subjective and behavioral responses to stress, while release of orexigenic NPY during stress and increased NPY mRNA in the arcuate nucleus of the hypothalamus, amygdala and hippocampus, increases feeding, but also decrease anxiety and stress (31). Stress and GCs potentiate dopaminergic transmission and impact reward seeking and intake in laboratory animals (18), (13) (2). Acute stress increases acquisition of food reward, intake of high fat diets (11), (16), and compulsive food seeking of HP foods (25), and promotes reward dependent habits (44). Stress also potentiates craving for desserts, snacks and higher HP food intake in satiated overweight individuals relative to lean individuals (25).

Increased drug taking and high fat diets alter CRF, GC and noradrenergic activity to increase sensitization of reward pathways (including the ventral tegmental area [VTA], nucleus accumbens [NAc], dorsal striatum and the mPFC regions) which influences preference for addictive substances and HP foods and increases drug/food craving and intake (45), (2),(46). More importantly, this motivational circuit overlaps with limbic/emotional regions (eg. the amygdala, hippocampus, and insula) that play a role in experiencing emotions and stress, and in learning and memory processes involved in negotiating behavioral and cognitive responses critical for adaptation and homeostasis (2); (47). For example, amygdala, hippocampus and insula play an important role in coding of reward, reward cue-based learning and memory for high emotional and reward cues and potentiating emotion and reward cue-based feeding (48), (49). On the other hand, the medial and lateral components of the prefrontal cortex (PFC) are involved in higher cognitive and executive control functions and also in regulating emotions, physiological responses, impulses, desires and craving (50). High and repeated stress alters structural and functional responses in these prefrontal and limbic brain regions, providing some basis for the effects of chronic stress on cortico-limbic regions that modulate food reward and craving (51); (52). These findings are consistent with behavioral and clinical research indicating that stress or negative affect decrease emotional, visceral and behavioral control, increase impulsivity (2) which, in turn, is associated with greater engagement in alcohol, smoking, and other drug abuse as well as increased intake of HP foods (23); (53); (54). With increasing focus on food addiction and how craving for sweets and fat may promote obesity (55), it would be important to consider whether vulnerability to food addiction is also exacerbated by chronic stress.

Food cues, food reward, motivation and intake

Highly palatable food cues are ubiquitous in the current obesogenic environment. Exposure to these HP food cues may increase food intake and contribute to weight gain (49). Such foods are rewarding, stimulate the brain reward pathways and, via learning/conditioning mechanisms, increase the likelihood of HP food seeking and consumption (56), (57), (58). Animals and humans can become conditioned to seek out and consume these HP foods, particularly in the context of stimuli or ‘cues’ associated with HP foods in the environment (55), (59), (57). Such increases in conditioning and related increases in intake of HP foods result in adaptations in neural reward/motivation pathways, which occur with increased salience of these HP foods, and in turn, result in greater ‘wanting’ and seeking of HP foods, similar to the incentive salience processes that occur with increasing alcohol and drug intake (60). A plethora of animal research and growing human neuroimaging research now clearly shows the involvement of brain reward regions and increased dopaminergic transmission with HP food cue exposure, with concomitant increases in food craving and motivation (61), (62), (63), and greater responsivity of brain reward regions and food craving among individuals with higher BMI (64), (65), (66), (67).

With greater consumption of HP foods, the concomitant changes in carbohydrate and fat metabolism, insulin sensitivity and appetite hormones that modify energy homeostasis also influence neural reward regions involved in increasing salience, wanting and motivation for food intake (68), (57), (69), (70), (71), (72), (73). For example, in healthy individuals food-related rise in plasma glucose stimulates insulin secretion, enabling glucose uptake into peripheral tissues; interestingly central infusion of insulin has been shown to suppress appetite and feeding (74); (75);(76);(77);(78). However, chronic high levels of peripheral insulin and insulin resistance, as is observed in many individuals with obesity, may promote food craving and intake as well as alter dopaminergic activity in reward regions such as the VTA, NAc and dorsal striatum (78), (79), (80), (81). Similarly, leptin and ghrelin influence dopaminergic transmission in brain reward regions and food seeking behavior in animals, and activate brain reward regions in humans (69), (70), (71), (73). Insulin resistance and

T2DM are also associated with changes in the function of neural reward circuits and their response to food cues (82), (79), (80). We recently showed increased limbic and striatal reactivity to stress and food cues in obese relative to lean individuals (81) (see Figure 3). Furthermore, higher activity in the insula and dorsal striatum correlated with higher insulin levels, insulin resistance and with food craving when participants were exposed to favorite food contexts (81). Together, these findings support the notion that there may be parallel and related adaptations in metabolic and neural motivation circuits that closely interact to dynamically influence hunger, food choices and selection, motivation for HP foods and overeating of HP foods.

Increasing evidence suggests that hormones involved in appetite and energy homeostasis (e.g., leptin, ghrelin, insulin) may also play a role in craving, reward and compulsive seeking of alcohol and drugs (49);(57); (58); (68); (69);(72); (71) These associations have generated interest in exploring the idea of “addiction transfer”, or replacing one “addiction”, in this case certain foods, for another, such as alcohol or other substances (83). For example, a recent study found alcohol use increased following rapid, significant weight loss as is seen in patients who undergo bariatric surgery (84). Thus, future research on the potential cross-sensitization of food and addictive substances in vulnerable individuals may shed light on the mechanisms underlying these phenomena.

Weight and diet-related metabolic and stress adaptations: influences on food craving and intake

Increasing levels of weight above healthy lean levels and overeating of HP foods, result in changes in glucose metabolism, insulin sensitivity and in hormones, regulating appetite and energy homesostasis (85), (57), (58). As indicated in the previous sections, these metabolic factors not only influence neural reward regions to impact motivation, but also affect hypothalamic circuits, interacting with the overlapping stress and energy regulation circuitry. Thus, it is not surprising that increased weight, insulin resistance and high fat diets are associated with blunted GC responses to stress challenges and altered autonomic and peripheral catecholamine responses (43), (20), (33) (34). As noted previously, high levels of stress and glucocorticoids increase glucose and insulin levels and also promote insulin resistance. Similarly, chronic high levels of insulin have been shown to downregulate HPA axis responses and increase basal sympathetic tone (43), (86), (42), (87). Additionally, evidence indicates that stress affects glucose levels and variability in both patients with type 1 and 2 diabetes (88), (89), (90), while ghrelin, which via signaling of reward pathways promotes appetite and feeding (71), is also involved in stress-induced food reward and food seeking (30) (73). Thus, weight-related metabolic shifts in set-points may increase allostatic load with increased autonomic basal tone and altered HPA axis activity (18), (91), (40), (6).

Consistent with this previous work showing BMI and stress adaptations affecting food reward and motivation, we recently showed that acute stress increases amygdala activity and blunted medial orbito-frontal cortex response to milkshake vs. tasteless receipt, but this effect was moderated by high cortisol levels and by high BMI respectively (92). Using a hyperinsulinemic clamp, we also showed that mild hypoglycemia potentiated activation of brain reward and limbic regions (hypothalamus, striatum, amygdala, hippocampus and insula) preferentially to HP food cues, an effect that correlated with increasing cortisol levels, while it decreased medial prefrontal activation, an effect that correlated with lowered glucose levels (93). As mild hypoglycemia may be considered a physiological stressor, our findings suggest that glucose utilization may occur differentially in the brain with increasing stress, with enhanced motivation and limbic signaling in the presence of food cues but decreased neural response in self-control and regulatory prefrontal regions. Furthermore, this neural pattern was more striking in healthy obese individuals suggesting that such

adaptations occur with increasing weight, perhaps setting the course for weight-related metabolic, neural and stress-related adaptations that influence HP food motivation. This study combined with earlier cited evidence suggests an exquisitely orchestrated neuroendocrine-metabolic-reward axis which under normal healthy conditions, coordinates physiological and psychological aspects of feeding and energy homeostasis, but with increasing risk factors and adaptations in these pathways, the regulatory circuits in each of these systems may be “hijacked”, thus promoting increased HP food motivation and intake.

Summary and proposed model

The converging lines of evidence presented suggest that ubiquitous HP food cues and high levels of stress may alter eating behaviors and affect brain reward/motivation pathways involved in wanting and seeking HP foods. Such behavioral responses may further promote changes in weight and body fat mass. Growing evidence supports weight-related bio-behavioral adaptations in interacting metabolic, neuroendocrine and neural (cortico-limbic-striatal) pathways, to potentiate food craving and intake under conditions of HP foods and related cues and with stress. Thus, a heuristic model is proposed of how HP foods, food cues and stress exposure may alter metabolic, stress and reward-motivation pathways in the brain and body to promote HP food motivation and intake (see Figure 4). As described in previous sections, stress-responsive hormones (CRF, GCs) and metabolic factors (insulin, ghrelin, leptin) each influence brain dopaminergic transmission, and with weight-related adaptations (chronic changes), these factors may promote higher levels of HP food motivation and intake, via potentiation of brain reward activity. Thus, a ***sensitized feed-forward process*** may ensue in which weight-related adaptations in metabolic, neuroendocrine and cortico-limbic striatal pathways promote HP food motivation and intake in vulnerable individuals. Such a sensitized process with increased HP food motivation and intake, would in turn, also promote future weight gain, thereby potentiating the cycle of weight-related adaptations in stress and metabolic pathways, and increased sensitization of brain motivation pathways in the context of HP food cues or stress, to promote HP food motivation and intake. In addition to weight and BMI, individual differences in genetic and individual susceptibility to obesity, eating patterns, insulin resistance, chronic stress, and other psychological variables may further moderate this process.

Future directions

While there is growing scientific attention on the complex interactions between stress, energy balance, appetite regulation, and food reward and motivation and their effects on the obesity epidemic, there are significant gaps in our understanding of these relationships. A number of key questions remain unanswered. For example, it is not known how stress-related neuroendocrine changes in cortisol, ghrelin, insulin and leptin, influence HP food motivation and intake. If chronic stress downregulates the HPA axis responses, as shown in previous research, how do these changes influence food craving and intake? It would be beneficial to examine if weight-related changes in stress, neuroendocrine and metabolic responses alter HP food motivation and intake, and whether such changes predict future weight gain and obesity. Identifying specific biomarkers and developing quantifiable measures to assess biobehavioral adaptations associated with stress and food addiction could assist in guiding optimal clinical care as well as targeting specific vulnerable subgroups with novel public health interventions. Furthermore, evidence on neuromolecular changes that occur in stress and metabolic pathways as they pertain to high-fat diets, and chronic stress, and how they relate to food intake and weight gain, would be critical in understanding the role that stress and metabolic adaptations play in food motivation, overeating and weight gain.

There is also a paucity of data on mechanisms underlying failure to maintain weight loss or relapse to overeating HP foods and weight gain, and on which obesity treatments are most suitable for which subgroup of individuals. The addiction field provides important clues on the neurobiological adaptations that promote addiction relapse and treatment failure. As failure to maintain weight loss has been discussed in the context of relapse to maladaptive behaviors (94, 95), it is possible that similar mechanisms may be driving relapse to overeating of HP foods and weight gain, but specific studies on this topic are rare. There is also a dearth of information on metabolic adaptations and their related effects on reward and stress neurobiology which may occur with the variety of weight-loss interventions, including gradual weight loss, rapid weight loss via “crash diets”, or various bariatric surgery interventions. Additionally, a number of stress-related illnesses, such as mood and anxiety disorders, are associated with obesity and T2DM, and interestingly, medications for such conditions (i.e. certain antidepressants) increase the risk of weight gain, but there is little evidence to elucidate the underlying mechanisms for these phenomena. In the setting of T2DM, tight glycemic control with exogenous insulin therapy often promotes weight gain. As hyperinsulinemia, insulin resistance, or the long-term effects of insulin resistance may potentiate motivation-reward neural pathways and food craving in obese, insulin-resistant individuals, it would be beneficial to investigate therapeutic approaches that may be less likely to promote HP food craving and intake to diminish further weight gain in these susceptible individuals.

Finally, there are new advances in behavioral and pharmacologic management of obesity but it is unclear how they relate to normalizing stress, metabolic and reward disturbances in vulnerable obese individuals. For example, recent evidence suggests that weight maintenance is associated with low stress level and better ability to cope with stress (96); (97). As stress promotes food craving and binge eating, stress reduction interventions may be useful in effective weight management programs, and some pilot behavioral stress reduction studies in obesity and T2DM are showing positive effects on improving stress, food craving and physiologic function (98, 99). However, such research is in its infancy and requires greater attention in the future. Also, medications used to treat drug abuse are also being considered as potential interventions for weight loss (100). Indeed, future research on increasing our understanding of the neuro-behavioral-metabolic mechanisms underlying stress, addiction and obesity would be of tremendous benefit in the development of novel therapies to attenuate HP food motivation, intake and weight gain.

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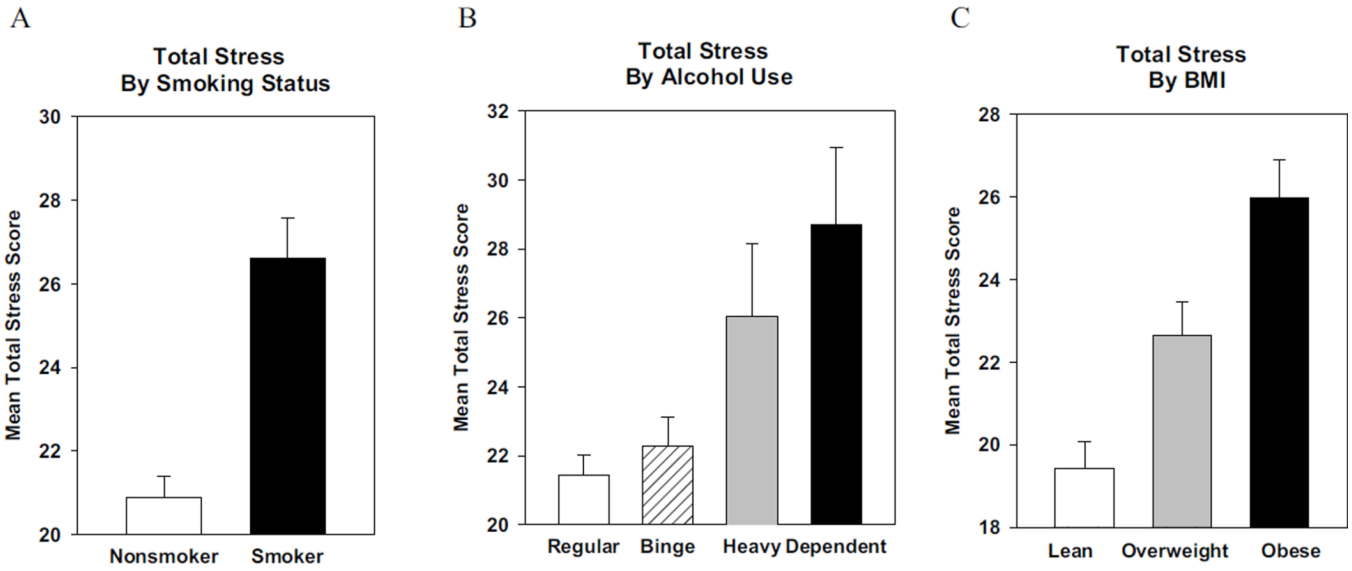

Figure 1.

Total stress scores for cumulative adverse life events and chronic stress associated with (a) current smoking status (X^2 = 31.66, df=1, P < 0.0001; Odds Ratio =1.196 {95%CI: 1.124–1.273}); (b) current alcohol use as categorized by NIAAA alcohol use criteria for regular, binge and heavy levels of consumption and DSM-IVR diagnosis for alcohol dependence (X^2 =15.37, df=1, P < 0.0001; OR =1.113 {95%CI: 1.055–1.173}); and (c) current body mass index (BMI) groups for lean (206), overweight (199) and obese (183) (X^2 = 25.47, df=1, P < 0.0001, OR =1.146 (95%CI: 1.087–1.208)) assessed in a community sample of 588 participants.

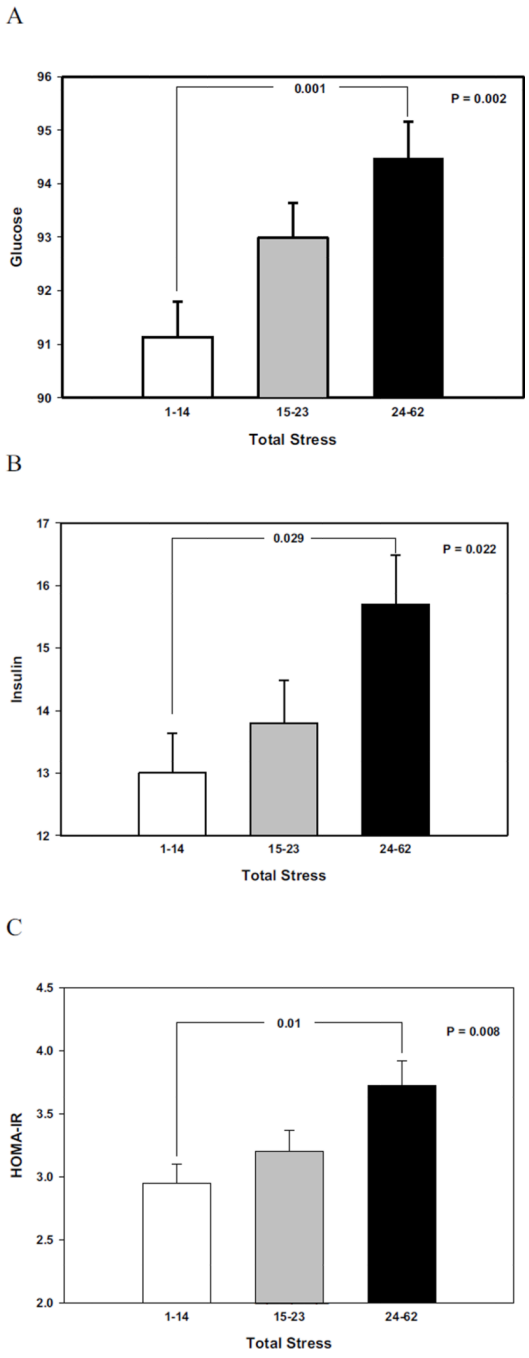

Figure 2.

Greater total cumulative stress significantly predicts log transformed (a) fasting plasma glucose levels (adjusted R^2 = 0.0189; t=2.88. p<.004), (b) fasting insulin (adjusted R^2 = 0.016; t=2.74, p<.007), and, (c) HOMA-IR (adjusted R^2 = 0.0210, t=3.02, p<.0027) in a subsample of the 380 healthy non-diabetic subjects. Figures show raw data for FPG, insulin and HOMA-IR comparing the low, medium and high total stress groups (p values corrected for multiple comparisons using Tukey tests).

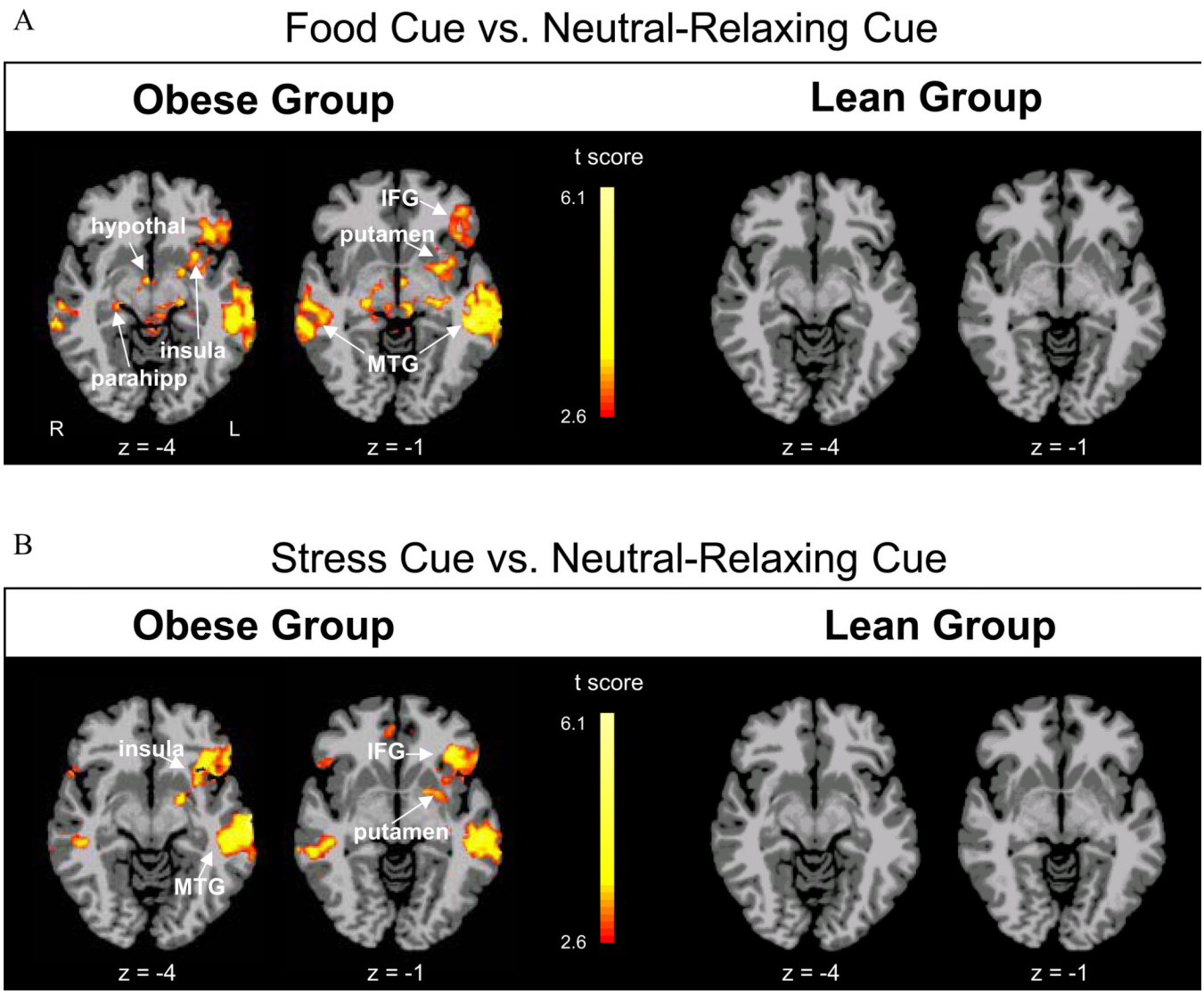

Figure 3.

Axial brain slices in the obese and lean groups of neural activation differences observed in contrasts comparing favorite-food cue vs. neutral-relaxing conditions (A) and stress versus neutral-relaxing conditions (B) (threshold of $p<0.01$, FWE corrected). Obese individuals show increased activation in the insula, putamen, IFG, and MTG in both contrasts; lean individuals do not show such increased activations. The color scale provides t values of the functional activity. Talairach z levels indicated. hypothal, hypothalamus; IFG, inferior frontal gyrus; L, left; MTG, middle temporal gyrus, parahipp, parahippocampus; R, right. (reprinted with permission from (81))

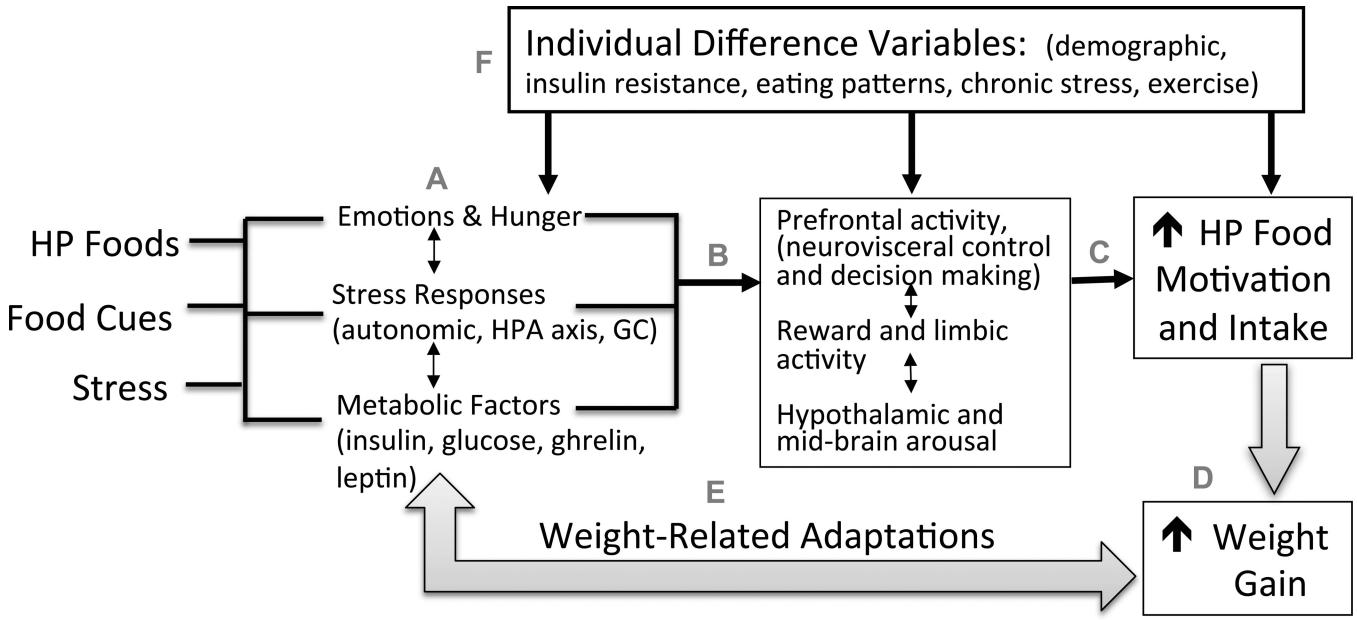

Figure 4.

A heuristic model is proposed of how HP foods, food cues and stress exposure may increase subjective (emotions, hunger) and also activate metabolic, stress and motivation systems in the brain and body to promote HP food motivation and intake (A). Stress-responsive hormones (ACTH, cortisol) and metabolic factors (insulin, ghrelin, leptin) influence brain limbic and striatal reward regions (emotion and signaling) to influence dopaminergic signaling, activate hypothalamic and midbrain arousal regions and prefrontal cortical circuits involved in reward prediction, self control and decision making (B). With weight-related adaptations in metabolic, neuroendocrine and subjective/behavioral responses, a vulnerable individual becomes highly susceptible to food cues-related and stress-related HP food craving which predicts HP food intake in these susceptible individuals (C). Such a sensitized process with increased HP food motivation and intake would in turn also promote weight gain (D), thereby potentiating the cycle of weight-related adaptations in stress and metabolic pathways (E), and increased sensitization of brain motivation pathways, to promote HP food motivation and intake, especially under conditions of food cue or stress exposure. Individual differences variables may further moderate these relationships as shown in F.

Table 1

List of Cumulative Stressful Events and Perceived Chronic Stressors Assessed in the Cumulative Adversitv Interview*

Major Life Event (lifetime)	Recent Life Event (within the last 12 months)	Life trauma	Perceived Chronic Stress
• Parents' divorce and/ or conflict • Loss of parent or significant other • Loss of child by death or removed • Unfaithful significant other • Separation from one or both parents • Family or significant other with substance abuse issues • Educational setback – failure • Isolation and abandonment • Loss of home to natural disaster • Victim of gun shooting or other violent acts • Observing violent victimization	• Relationship difficulties - significant increase in arguments - unfaithful significant other - divorce or separation - ending of close relationship • Death of a loved one - child or significant other - close family friend • Job-related stress - demotion/ worse job - pay loss - job loss • Financial crisis - bankruptcy - going on welfare • Legal difficulties • Poor school performance - failure or dropout • Living-situation stress - moved to worse neighborhood - kicked out of house - kicked child out of house • Natural disaster – loss of home • Physical assault • Serious accident or injury • House/car broken into • Unwanted pregnancy	• Physical abuse/assault - threatened or witnessed assault - exposure to war or combat - kidnapping • Death - immediate family member or significant other (including suicide) • Emotional abuse • Serious accident - self/ witnessed one • Sexual abuse/assault • Trauma related to natural disaster	• Relationship problems - divorce/ separation - child-related stress • Chronic health/medical problems • Job/employment related stress • Financial difficulties - unemployment • Legal problems • School-related stress • Living-situation stress

Major Life Event (lifetime)	Recent Life Event (within the last 12 months)	Life trauma	Perceived Chronic Stress
	- abortion/ miscarriage		

* Cumulative Adversity Interview assesses subject's experience of the above major and recent life events, life traumas and perceived chronic stressors and cumulative adversity scores are predictive of psychiatric disorders and development of addictions in prospective longitudinal studies (Turner RJ, Lloyd DA. Stress burden and the lifetime incidence of psychiatric disorder in young adults: racial and ethnic contrasts. *Arch Gen Psychiatry*. 2004, May;61 (5):481-8;
Turner RJ, Lloyd DA. Cumulative adversity and drug dependence in young adults: racial/ethnic contrasts. *Addiction* 2003; 98:305-15; Lloyd DA, Turner RJ. Cumulative lifetime adversities and alcohol dependence in adolescence and young adulthood. *Drug & Alcohol Dependence* 2008; 93:217-26)