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Integrated circuits and molecular components for stress and feeding: implications for eating disorders

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Abstract

Eating disorders are complex brain disorders that afflict millions of individuals worldwide. The etiology of these diseases is not fully understood, but a growing body of literature suggests that stress and anxiety may play a critical role in their development. As our understanding of the genetic and environmental factors that contribute to disease in clinical populations like anorexia nervosa, bulimia nervosa and binge eating disorder continue to grow, neuroscientists are using animal models to understand the neurobiology of stress and feeding. We hypothesize that eating disorder clinical phenotypes may result from stress-induced maladaptive alterations in neural circuits that regulate feeding, and that these circuits can be neurochemically isolated using animal model of eating disorders.

Keywords

Animal models; anorexia nervosa; anxiety; binge eating disorder; bulimia nervosa; eating disorders; feeding; neural circuits; plasticity; stress

Stress phenotypes involve the interplay between physical and psychological events, and can play a role in facilitating both rewarding and punishing outcomes, resulting in both positive/adaptive (Lemos *et al.* 2012) and negative/maladaptive (Haramati *et al.* 2011) behavior. Some stressors, such as those seen following traumatic events, drug or alcohol withdrawal, or other stimuli, result in maladaptive behaviors. The link between stress and drug addiction is a large focus of the neuroscience field (for review, see Volkow & Li 2004); however, we propose that stress adaptations may represent a broader etiological factor in psychiatric disorders. Clinical studies indicate an association between stress and eating disorder (ED) onset and symptom expression, similar to what has been observed for stress and drug addiction. Taken as a whole, these findings suggest that stress may impact common neuronal circuitry that is involved in both EDs and drug addiction. Because of this, both EDs and drug addiction may respond to similar treatments (Koob *et al.* 2014; Volkow & Wise 2005).

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However, though a considerable body of research and societal emphasis has been placed on prevention and intervention of both stress-related behaviors and EDs, the combination of the two has only recently come to the forefront of scientific and clinical aims. This review will briefly highlight major EDs and relevant background (Part 1), discuss rodent models of feeding and EDs and global behavioral work (Part 2), explore the circuitry of feeding behaviors and how stress manipulations may shift specific aspects of this circuit (Part 3) and identify some overlapping stress and feeding-related molecular systems (Part 4).

Part 1: stress contributions to eating disorders

Overview

The three primary EDs as presented in the Diagnostic and Statistical Manual of Mental Disorders– 5th edition (DSM-5) (American Psychiatric Association 2013) are anorexia nervosa, bulimia nervosa and binge eating disorder (BED). Anorexia nervosa is characterized by a persistent restriction of food intake that results in low body weight and body mass index. This behavior is often accompanied by an irrational fear of weight gain, excessive exercise, distorted body image and menstrual dysfunction in women (Yilmaz *et al.* 2014). Anorexia nervosa prevalence is estimated to be between 0.3 and 0.9%, around 90% of cases are female (Yilmaz *et al.* 2014), and it carries the highest mortality rate of any psychiatric illness with suicide being a common cause of death (Arcelus *et al.* 2011; Chesney *et al.* 2014; Franko *et al.* 2013; Preti *et al.* 2010; Smink *et al.* 2013; Sullivan 1995). Bulimia nervosa is characterized by recurrent episodes of binge eating (i.e. excessive food intake paired with a sense of loss of control), together with compensatory behaviors such as self-induced vomiting, laxative use, excessive exercise, or food restriction. Bulimia nervosa prevalence estimates range from 0.8 to 2.9% and, similar to anorexia nervosa, is more common in females. Like anorexia nervosa, bulimia nervosa is also associated with elevated mortality, though not as extreme as anorexia (Berg *et al.* 2013; Smink *et al.* 2013; Smyth *et al.* 2007; Yilmaz *et al.* 2014). BED, the newest ED addition to the DSM-5, is characterized by recurrent binge episodes in the absence of recurrent compensatory behaviors, is the most prevalent ED with lifetime prevalence estimates between 2 and 3.5%, and is more evenly distributed between sexes than the other eating disorders (Hudson *et al.* 2007; Kessler *et al.* 2013). Binge eating disorder patients are often overweight or obese and have an elevated risk for type II diabetes, cardiovascular disease and metabolic syndrome (Dingemans *et al.* 2002; Gluck *et al.* 2004; Hudson *et al.* 2010). All of these conditions can lead to adverse long-term health outcomes.

For all EDs, psychological treatment options such as family based therapy and cognitive behavioral therapy provide some improvement in patient outcome, and SSRIs such as fluoxetine have been used to treat bulimia nervosa and BED (American Psychiatric Association 2006; Watson & Bulik 2012). Though outcome studies clearly indicate that current treatments provide improvement over time, only ~50% of patients with anorexia nervosa or bulimia nervosa fully recover and more than 20% develop chronic EDs (Steinhausen 2009). These observations underscore that significant advancements in pharmacotherapeutic approaches that target the core symptomology of the disorders are still

lacking and ultimately necessary to provide lasting remission and improved health for those suffering from EDs.

Eating disorder etiology

Eating disorders are complex brain disorders that are influenced by both genetic and environmental factors. Family and twin studies reveal that EDs run in families and are heritable (Yilmaz *et al.* 2014). Although genome-wide association studies (GWAS) have not yet yielded significant results for anorexia, samples sizes have not yet reached contemporary standards and no GWAS for bulimia or BED have been conducted (Yilmaz *et al.* 2014). Among the environmental factors that contribute to ED etiology, severity, and treatment are sociocultural factors like a 'Western' ideal of thinness and attractiveness that promotes sexual objectification, socioeconomic status, and personality traits like perfectionism, impulsivity and anxiety (Claridge *et al.* 1998; Kent & Waller 2000; Lunner *et al.* 2000; Polivy & Herman 2002; Schmidt *et al.* 1997; Spencer 2013; Striegel-Moore & Bulik 2007; Woerwag-Mehta & Treasure 2008). Ultimately, genetic risk alleles for EDs and environmental factors combined may account for the development of EDs, but precisely how biopsychosocial components combine to influence ED etiology is yet unknown. Comorbid psychiatric conditions, however, may provide insight into a repertoire of brain pathways upon which ED risk factors, genetic or environmental, ultimately converge.

Acute stress effects on eating disorder symptomology

Acute daily stressors contribute to overall negative affect and increase the risk of disordered eating. Patients with anorexia nervosa experience elevated pre-meal anxiety relative to healthy controls, and anxiolytic medications can be prescribed to reduce anxiety and promote intake during the refeeding process (Kruger & Kennedy 2000; Steinglass *et al.* 2010; Striegel-Moore & Bulik 2007). Social appearance anxiety is also associated with anorexia nervosa symptomology (Bulik 2010; Kaye *et al.* 2004; Levinson & Rodebaugh 2012; Pallister & Waller 2008; Steinglass *et al.* 2011), and a multifactorial neurodevelopmental model incorporates interpersonal stress as a key component in anorexia nervosa etiology (Connan *et al.* 2003). For bulimia nervosa, studies using momentary assessments of negative and positive affect, anger/hostility, and stress show that binges and vomiting episodes are more likely to occur on days with lower positive affect and higher negative affect, anger/hostility, and stress (Berg *et al.* 2013; Smyth *et al.* 2007). Furthermore, decreasing positive affect and increasing negative affect often precede both binge and purge episodes. In laboratory settings, patients with disordered eating report an elevated desire to binge in response to verbal, interpersonal and audiovisual stressors relative to healthy controls despite no difference in autonomic and cardiovascular responses (Cattanach *et al.* 1988). Physiological stressors like cold stress are known to increase blood cortisol levels, hunger, and desire to eat in individuals with BED (Gluck *et al.* 2004). Similarly, individuals with bulimia nervosa display increased hunger and desire to binge relative to restrained eaters in an imagery task designed to provoke feelings of loneliness and rejection (Tuschen-Caffier & Vögele 1999).

Chronic stress effects on eating disorder symptomology

Chronic stress and trauma contribute to the development, maintenance, and treatment of EDs. Although of some debate, precipitating events and adverse life events such as prenatal nutrition, loss of a loved one, physical or emotional abuse, interpersonal stressors, or aversive sexual experiences are known to contribute to ED risk (Claridge *et al.* 1998; Kent & Waller 2000; Lunner *et al.* 2000; Polivy & Herman 2002; Schmidt *et al.* 1997; Spencer 2013; Woerwag-Mehta & Treasure 2008). In a large cohort of individuals with anorexia nervosa, 13.7% of participants met diagnostic criteria for post-traumatic stress disorder with the first traumatic event occurring prior to the onset of the ED. Of those anorexic patients with comorbid post-traumatic stress disorder, the most common trauma was sexually related occurring in childhood or adulthood (Reyes-Rodríguez *et al.* 2011). Even in healthy individuals, chronic psychosocial stressors like job demands and strained family relationships are known to be associated with increasing body mass index (Block *et al.* 2009).

Anxiety disorder comorbidity

As outlined above, stress itself can have a large impact on ED symptomology. One trait that is commonly linked with stress is anxiety. Interestingly, other than mood disorders, the most common psychiatric disorders, individuals with EDs often present with comorbid anxiety disorders (Bulik 2010; Kaye *et al.* 2004; Pallister & Waller 2008; Reyes-Rodríguez *et al.* 2011; Steinglass *et al.* 2011). Patients with anxiety disorders share common symptoms in that they all display intense fear of normally innocuous objects or situations (Shin & Liberzon 2009). Although patterns of anxiety disorder comorbidity vary somewhat across ED subtypes, obsessive compulsive disorder, social phobia, generalized anxiety disorder and post-traumatic stress disorder are commonly reported (Block *et al.* 2009; Franko *et al.* 2013; Godart *et al.* 2002; Reyes-Rodríguez *et al.* 2011; Smink *et al.* 2013; Steinhausen 2009). Interestingly, among ED patients with at least one comorbid anxiety disorder, the anxiety disorder often emerges first (Bulik *et al.* 1997; Godart *et al.* 2000; Polivy & Herman 2002; Raney *et al.* 2008; Schmidt *et al.* 1997; Woerwag-Mehta & Treasure 2008). These findings suggest that anxiety disorders may represent an etiological pathway into eating disorders. In the case of anorexia nervosa, patients report higher rates of anxiety and depression that increase eating disorder severity, and contribute to disease chronicity (Hudson *et al.* 2007; Kessler *et al.* 2013; Pollice *et al.* 1997; Yacobovitch-Gavan *et al.* 2009). We propose that anxiety and other forms of stress promote long-term maladaptive alterations in neural circuits that regulate food intake and that these forms of plasticity underlie the presentation of ED endophenotypes.

Importantly, the aforementioned studies highlight the effects of stress defined as biological or environmental events that contribute to negative affect and possess biological hallmarks like activation of neuroendocrine and sympathetic systems. We propose a broader definition of stress: a shift from a homeostatic set point shaped by prior experience and encoded by biological components. Although we do believe that EDs are simply diseases of appetite dysregulation, alterations in food intake patterns are nonetheless a central diagnostic criterion. We posit that maladaptive ED endophenotypes are partly the result of stress-induced plasticity of genetically and anatomically defined neural circuits that result in

homeostatic imbalance of feeding. Therefore, the study of neural circuits in genetically accessible animal models of feeding and EDs in conjunction with stress represents a critical step in establishing causal roles for these pathways and in identifying novel therapeutic targets for the treatment of EDs.

Part 2: rodent models of disordered eating and behavioral implications

In humans with EDs, actual food consummatory behavior is intertwined with cognitive and social variables, which often leads to diagnostically relevant psychological states such as low self-esteem, shame, embarrassment and other cognitive states as discussed above. The focus of animal studies, however, is typically on the actual consumption of food (an increase or decrease) following a manipulation (Patterson & Abizaid 2013). Interactions between stress and EDs have focused globally on two common behavioral models of stress: (1) withdrawal from or alteration of access to food as a stressor, and (2) manipulations of the environment as a stressor. Importantly, acute and chronic stressors may differentially affect key brain areas involved in feeding (Chagra *et al.* 2011), suggesting the need for caution when interpreting and comparing stress and feeding studies utilizing different models.

Withdrawal from or alteration of access to food

Caloric restriction has been shown to reprogram stress and orexigenic pathways (Pankevich *et al.* 2010) (see Table 1). Similarly, palatable foods like those high in fat or containing sugar are known to induce alterations in behavior to maximize consumption (Avena & Hoebel 2003; Czyzyk *et al.* 2009). Teegarden and Bale (2007) demonstrated that acute withdrawal from access to highly palatable preferred food produced both stress and affective responses (Teegarden & Bale 2007). Interestingly, intermittent intake of sucrose attenuated neuronal markers of stress (Christiansen *et al.* 2011), and in a similar model, attenuated stress-induced hypophagia (Martin & Timofeeva 2010). Palatable foods may have a protective effect as well: ingestion of palatable foods may mitigate stress effects (Foster *et al.* 2009), with notable peptidergic changes in key stress-related regions as discussed below. The results by Foster *et al.* were similar to those published later by MacKay *et al.* (2014), revealing that protracted effects of stress can be mitigated by consumption of highly palatable foods. Recent work, however, demonstrated that chronic exposure to a high-fat diet for 12 weeks in mice increased anxiety-like behavioral phenotypes, such as decreased open arm time in the elevated plus maze and increased immobility in a forced swim test, classical markers of anxiety-like behavior (Sharma & Fulton 2013). Rats exposed to a high-fat diet displayed exaggerated responses to a mild stressor, similar to animals previously exposed to chronic or acute stress (Legendre & Harris 2006), as well as other markers for increased hypothalamic-pituitary-adrenal (HPA) axis activity (Tannenbaum *et al.* 1997). When placed on an intermittent access schedule to 10 or 25% sucrose, rats escalate their intake and display withdrawal-like symptoms as measured by a decrease in immobility during forced swim in response to naloxone; animals also showed sensitization similar to that seen with drugs of abuse (Avena & Hoebel 2003; Colantuoni *et al.* 2001). Taken together, both withdrawal from food as well as variable or inconsistent access to food can be used as a stressor, particularly high-fat diet and sugar manipulations.

Manipulation of the environment

Physical stress, in both acute and chronic forms, such as chronic variable stress (CVS), restraint stress, social defeat and forced swim stress (FSS) have been used to shift the consumption or motivation for food (Table 1).

Chronic restraint stress in both rats and mice has been consistently shown to decrease body weight (Chiba *et al.* 2012; Chotiawat *et al.* 2010; Harris *et al.* 2002; Jeong *et al.* 2013; Kim *et al.* 2013; Rybkin *et al.* 1997), food intake (Haque *et al.* 2013; Rybkin *et al.* 1997), and sucrose preference (Chiba *et al.* 2012). Interestingly, Kim *et al.* (2013) demonstrated that increased plasma CORT levels following restraint stress correlated with decreased body weight. This stress-induced decrease in weight appears to be independent of the hormone leptin (Harris *et al.* 2002). Stress induced increases in consumption of highly palatable foods is reversed by diazepam, a classical treatment for depression (Ely *et al.* 1997). Other groups have demonstrated that chronic stress increases behavioral measurements of anhedonia, but not behavioral despair (Lim *et al.* 2013), demonstrating the relationship between stress and other neuropsychiatric conditions may be nuanced.

CVS and its variants (mild, unpredictable, etc.) have been shown to impact feeding (Pankevich *et al.* 2010; Teegarden & Bale 2008). CVS, in addition to reducing body weight, also decreases the consumption of highly palatable foods (Patterson *et al.* 2010) (though note that Pankevich and colleagues saw an increased consumption of highly palatable foods). Chronic variable stress is thought to deregulate function of the hypothalamic paraventricular nucleus of the hypothalamus (PVN), possibly through norepinephrine (Flak *et al.* 2014). Herman *et al.* (2008) noted that the PVN is likely to play a role in coordinating responsiveness to stressors.

Forced swim stress has often been used as an acute, mild stressor in both the anxiety and feeding literature (Diane *et al.* 2008). Juvenile rats exposed to a three day FSS showed increased anxiety during adulthood, but this was mitigated by palatable food exposure (MacKay *et al.* 2014). Food deprived mice show altered novelty-suppressed feeding behavior following a relatively short 3-min FSS (Barfield *et al.* 2013).

Interestingly, social stress has also been used to modulate food intake effectively (Bhatnagar *et al.* 2006). For example, social defeat stress decreases weight gain in male rats (Haller *et al.* 1999). Conversely, social defeat models have been shown to increase key peptides related to feeding behavior, NPY and AGRP, discussed in more detail below. Interestingly, Patterson *et al.* (2013) demonstrated that submissive animals overeat following social defeat stress, adding another layer of complexity to the stress/feeding interaction (Patterson *et al.* 2013).

The relationship between stress and food consumption may not be strictly linear. Pecoraro *et al.* (2004) demonstrated that stress promotes consumption of highly palatable food while reducing overall consumption. In addition, rats exposed to a combination of high-fat diet and stress show interacting effects (Macedo *et al.* 2012). This is consistent with work conducted in humans showing that chronic stress shifts consumption toward high carbohydrate, high saturated fat foods, which may be driving increased weight (Roberts *et al.* 2013), and that

stress may push people to have an increased ‘drive to eat’ or encourage individuals to eat in the absence of hunger (Groesz *et al.* 2012; Rutters *et al.* 2012). As much of the human literature shows stress-induced increases in food consumption, it will be important to demonstrate the precise relationship between stress and aberrant feeding behavior, both as manipulation models and as outcome variables.

In addition, caution must be taken when comparing home cage feeding assays (such as changes in body weight) vs. planned feeding assays (such as binge eating episodes or novelty-suppressed feeding) as these may actually be two different types of consumption behavior, and thus may be shifted differently following stress. For example, rats exposed to a combination of stressors show increased latency to feed in a novelty-suppressed feeding assay, whereas their home cage consumption increased (Roth *et al.* 2012). In a similar study, rats exposed to CVS showed decreased consumption in novelty-suppressed feeding, but no changes in home cage food or water consumption (Gamaro *et al.* 2002). Therefore, interpretations of stress-induced alterations in food intake across different feeding measurements (home cage vs. test condition) are difficult, and only tentative conclusions may be drawn.

Part 3: mapping of conserved nuclei and neural circuits for feeding

Feeding is driven by a complex network of signals distributed throughout the central nervous system and in the gut, and can be broadly classified by the motivation to satisfy either metabolic or hedonic drives (Berthoud 2004, 2011; Chambers *et al.* 2013; Williams & Elmquist 2012). Hedonic, or non-homeostatic reward-based feeding, often involves the consumption of highly palatable foods, the excessive consumption of which may produce physiological states that share characteristics of drug and alcohol addiction like tolerance, dependence and withdrawal (Johnson & Kenny 2010; Kenny 2011; Krashes & Kravitz 2014). While homeostatic feeding is governed primarily by peripheral signals and discrete neuronal populations in hypothalamic nuclei critical for signaling hunger or satiety (for review, see (Sternson 2013) and (Elmquist *et al.* 2005) and Table 2 for comprehensive list), we propose that stress modulation of hedonic feeding circuits represents a critical node in the etiology of EDs and focus much of our review on these nonhypothalamic sites.

Studies of immediate early gene activation after feeding

Neurons are known to increase the expression of specific genes following acute activation (Sagar *et al.* 1988). Multiple studies have demonstrated an increase in Fos-like immunoreactivity (FLI) in specific forebrain and hindbrain regions following an episode of feeding. Fraser *et al.* (1993) demonstrated that a meal increases FLI in the nucleus of the solitary tract (NTS) and that this induction was independent of cholecystokinin signaling (Fraser & Davison 1993). Several other groups have observed similar activation of the NTS and proximally located nuclei like the area postrema following food intake (Emond & Weingarten 1995; Olson *et al.* 1993; Rinaman *et al.* 1998; Zittel *et al.* 1994). Anorexigenic signals like cholecystokinin, glucagon-like peptide 1, and stimulation of the vagal nerve complex via gastric distension increase FLI in brain areas like the NTS (Fraser & Davison 1993), central amygdala (CeA; Olson *et al.* 1993; Turton *et al.* 1996), bed nucleus of the stria terminalis (BNST; Olson *et al.* 1993), and PVN (Olson *et al.* 1993; Turton *et al.* 1996).

Neuropeptide Y (NPY), discussed later, induced feeding increased FLI in various hypothalamic populations like the PVN and extrahypothalamic sites like the BNST, lateral division of the CeA, and lateral division of the parabrachial nucleus (PBN; Lambert *et al.* 1995; Li *et al.* 1994).

To determine if there are brain areas whose activation is regulated by highly palatable and calorically dense foods, Park and Carr (1998) exposed rats to a highly palatable meal containing fat and sucrose, and examined FLI in 20 different brain areas. They observed an increase in FLI in nuclei including the lateral hypothalamus (LH), ventral tegmental area (VTA) and medial preoptic area, while they observed a decrease in the medial and lateral habenula in response to the palatable meal. Entrained or limited access to highly palatable food also increases FLI in the CeA, PFC and NTS (Bello *et al.* 2009; Mendoza *et al.* 2005). As a whole, these studies reveal a complex network of hypothalamic, forebrain and hindbrain nuclei containing cells in the NTS, CeA, BNST, PVN, PBN and LH that are activated following perturbations that illicit or inhibit feeding. Although these studies provide a strong relevance for the aforementioned brain areas in feeding, the interpretation of these data, however, is limited by (1) an incomplete understanding as to the particular feeding-related stimulus that evokes activation of these neurons, (2) the lack of immunocytochemical identification of many of these cells and (3) a lack of a complete wiring diagram of genetically defined cell types in these brain areas. To better understand how these brain areas and circuits are modified by stress and their potential contributions to EDs, there is a salient need to interrogate the effects of these networks using exogenous activation or inhibition.

Exogenous circuit manipulation

The advent of tools for the direct manipulation of genetically and anatomically defined cell types in the brain has ushered in a new era of identifying behaviorally causal neural circuits (Fig. 1). Techniques like genetically encoded neurotoxins, optogenetics, and designer receptors exclusively activated by designer drugs (DREADDs) have been particularly effective in identifying neural circuits that are sufficient to drive or inhibit feeding (Gropp *et al.* 2005; Luquet *et al.* 2005; Sternson & Roth 2014; Tye & Deisseroth 2012; Yang *et al.* 2013; Fig. 1). For example, optogenetic activation of fibers in the LH from GABAergic neurons in the BNST is sufficient to drive feeding that is enhanced in the presence of calorically dense and palatable food (Jennings *et al.* 2013). The authors suggested a specificity of the GABA^{BNST->LH} circuit in optogenetically-induced feeding, as excitation of GABA^{BNST->VTA} terminals did not evoke feeding. However, GABA^{BNST} neurons make up a very heterogeneous population and are known to project to additional sites like the periaqueductal gray (PAG), PBN, and CeA. Additionally, the precise population of neurons in the LH receiving GABA^{BNST} inputs is unclear, however, a recent study demonstrated that DREADD-mediated activation of orexin neurons in the LH is sufficient to increase feeding, leading to a mild increase in weight gain (Inutsuka *et al.* 2014). Land *et al.* (2014) showed that Dopamine Receptor 1 expressing neurons in the prefrontal cortex (PFC) have elevated FLI following food deprivation induced hyperphagia, that optogenetic stimulation of D1^{PFC} neuron cell bodies or axon terminals in the basolateral amygdala is sufficient to slightly

increase feeding, that inhibition of these neuron inhibits food intake, and that stimulation of D1^{PFC} axon terminals in the BLA similarly increases food intake.

Conversely, there are now multiple circuits that are sufficient to drive anorexic responses following activation. Carter and colleagues identified a population of calcitonin gene-related peptide neurons in the PBN that are activated during conditions that normally suppress appetite, inhibit feeding when activated, are capable of driving starvation following chronic activation, and orchestrate anorexic behavior through glutamatergic axon terminals that project to the CeA (Carter *et al.* 2013). Interestingly, projections from CGRP^{PBN} neurons were also visible in the BNST, however, the authors did not observe an increase in food intake following stimulation of CGRP^{PBN->BNST} axon terminals. The CeA may represent a critical integrator for anorexic behavior as PKC- δ expressing neurons are activated following suppression of feeding by either cholecystokinin, lithium chloride, or lipopolysaccharide mediated suppression of feeding (Cai *et al.* 2014). The authors also demonstrated that DREADD-mediated inhibition of PKC- δ neurons blocked anorexic responses to cholecystokinin and lithium chloride and that optogenetic inhibition of these neurons is sufficient to slightly increase food intake, while not affecting behavioral measures of anxiety. Moreover, via Cre-dependent monosynaptic rabies tracing, they demonstrated that PKC- δ neurons receive presynaptic inputs from cells in the insula, basolateral amygdala and the lateral PBN. The latter population was also demonstrated to express CGRP. Lastly, they showed that PKC- δ neurons release GABA and that local GABAergic signaling is required for optogenetic inhibition-induced feeding. The PBN represents a critical node for integration of multiple hunger signals as they receive inputs from both arcuate nucleus AGRP-expressing neurons, glutamatergic inputs from the NTS, and glutamatergic inputs from the PVN. Wu *et al.* (2009, 2012) demonstrated that ablation of AGRP neurons results in severe anorexia and eventually starvation, and that this phenotype could be blocked by several perturbations: local antagonism of 5HT₃ signaling, viral genetic deletion of tryptophan hydroxylase in the NTS or Raphe magnus/obscurus, direct delivery of bretazenil (a positive allosteric modulator that acts on the benzodiazepine site of the GABAA receptor) into the PBN, or local genetic deletion of vGlut2 either in the PBN or NTS. The PBN also receives glutamatergic inputs from cells in the PVN that express single-minded 1 (*Sim1*) and the anorexigenic receptor melanocortin 4 (MC4R), although the functional significance of the excitatory *Sim1*/MC4R^{PVN->PBN} in inhibition of feeding is yet unknown (Shah *et al.* 2014). These studies illustrate that an interwoven network of brain nuclei are critical for regulating feeding, however the function of these circuits in driving behavior in animal models of EDs is an open topic for study.

Many of the brain regions containing behaviorally sufficient neural circuits overlap with brain regions altered by or required for orchestrating responses to stress. Multiple groups have demonstrated overlapping brain regions exhibiting FLI following various forms of physical or social stressors (Ceccatelli *et al.* 1989; Cullinan *et al.* 1995; Kovács 1998; Martinez *et al.* 2002). We hypothesize that neuron ensembles within areas like the BNST and CeA are critical for orchestrating stress-induced alterations in feeding through outputs to hypothalamic and hindbrain nuclei. Circuits within these brain regions, therefore, represent important areas for study in the context of stress and animal models of EDs.

Part 4: potential molecular mechanisms underlying stress modulation of eating

Much of the work on both stress and EDs has focused on molecular mechanisms, providing much insight into the potential interactions between these two traits, as well as common targets for treatment. Notably, key transmitters have provided insight into the overlapping mechanisms of EDs and stress-related responses. Here, we focus on major peptides and hormones involved in both of these disorders: CRF, NPY, AGRP, dynorphin and glucocorticoids.

Corticotrophin releasing factor

Most notably, corticotrophin releasing factor (CRF) plays a key role in both stress and EDs. The CRF receptors, known for being a key component of the stress and the HPA axis response (and key for the final stage of the HPA axis response, glucocorticoid release), have also been shown to modulate food intake (for in-depth review, see Stengel & Taché 2014). The CRF system is known to mediate anxiety-like symptoms involved in drug withdrawal (George *et al.* 2007). Pharmacological manipulations of the CRF system have further demonstrated the interaction between the two disorders. Converging evidence implicates the CRF2 receptor in reduced feeding. Infusion of a CRF1/2 receptor agonist directly into the lateral septum reduced feeding while increasing anxiety-like behaviors in rats (Bakshi *et al.* 2007). In addition, food restriction (in itself a notable stressor) results in altered CRF expression in the hypothalamus (Lenglos *et al.* 2013). In this study by Lenglos *et al.*, food restricted and restraint stressed males showed decreased body weight. Interestingly, repeated restraint stress did not decrease body weight in female rats, an important sex difference that should be further investigated. Similarly, administration of urocortin-1 (the endogenous CRF2 receptor agonist) results in anorexic behaviors in rats, which was blocked by 5-HT_{2c}R activation (Harada *et al.* 2014). CRF1 receptor antagonism reversed overeating following a restriction paradigm (Cottone *et al.* 2009). Sharma *et al.* (2012) found that exposure to a high-fat diet increased weight and anxiety in male mice, and interestingly, decreased CRF1 receptor expression levels. In addition, blockade or deletion of the CRF1 receptor reduces food intake and overall caloric consumption (Giardino & Ryabinin 2013), and work by Chotiawat *et al.* (2010) demonstrated that CRF1 receptor knockout mice do not lose weight following restraint. These studies place the entire CRF system at a key position to modulate feeding and stress interactions. Novel CRF antagonists may prove useful for the treatment of both EDs and anxiety.

Neuropeptide Y

Neuropeptide Y (NPY) has been historically characterized as an anxiolytic and orexigenic peptide, and is often considered a functional antagonist to CRF. Decades of work has demonstrated NPY's role in feeding behaviors, demonstrating that elevated levels of NPY lead to increased food intake (Levine & Morley 1984; Stanley & Leibowitz 1985) and the increased storage of energy as adipose tissue (Billington *et al.* 1991; Gehlert 1999). Administration of NPY increases food consumption in rats that requires downstream opioid signaling (Hanson & Dallman 1995; Levine *et al.* 1990), whereas inhibition of NPY via

insulin signaling inhibits food intake in rats (Strack *et al.* 1995). Elevated levels of NPY have been seen in animal models of obesity (for further reading, see (King & Williams 1998)). Interestingly, much research has also been done on the global role of NPY and stress: stress has been shown to engage the NPY system (Pleil *et al.* 2012). Following 8 hours of maternal separation, neonate pups display elevated expression of NPY mRNA in the arcuate nucleus (and expectedly, a decrease in corticotropin-releasing hormone mRNA expression in the PVN; Schmidt *et al.* 2008). Miller *et al.* (2002) demonstrated overconsumption of highly palatable foods increased NPY in the hypothalamus, and reduced anxiety-like behavior in the open field test, highlighting the nuanced interactions between NPY, stress and feeding. NPY-1R antagonists may attenuate stress-induced eating (Goebel-Stengel *et al.* 2014). Acute restraint produces higher corticosterone levels in NPY^{-/-} mice compared to WTs (Forbes *et al.* 2012). As NPY appears to play a protective role against anxiety, but may increase feeding, therapeutic treatments for either anxiety disorders or EDs must carefully weigh the effects on one another.

Agouti-related peptide

The agouti-related peptide (AGRP) has been heavily studied in regards to feeding behaviors (importantly, AGRP and NPY are co-expressed in the arcuate nucleus). Excitatory projections onto AGRP neurons in the arcuate nucleus of the hypothalamus drive hunger (Krashes *et al.* 2014). Feeding increases are also seen when stimulating AGRP neurons directly, or their downstream projections to the PVN of the hypothalamus, BNST or lateral hypothalamus (Aponte *et al.* 2011; Atasoy *et al.* 2012; Betley *et al.* 2013; Krashes *et al.* 2011, 2013). Interestingly, decreased levels of AGRP in the arcuate nucleus are seen in a mouse model of maturity-onset obesity (Bäckberg *et al.* 2004). Providing another piece of evidence of a complex AGRP/NPY interaction, Kas *et al.* demonstrated that following inescapable foot shock, AGRP mRNA levels were downregulated, while NPY mRNA levels were upregulated, despite the strong overlap of these peptides in the arcuate nucleus (Kas 2005).

Dynorphin

Dynorphin, the ligand for the kappa opioid receptor, as well as other opioids have been implicated in both stress-related disorders and EDs, with increasing emphasis being placed on the two disorders together. Wise and Raptis (1986) demonstrated that the opioid antagonist naloxone inhibits feeding in mammals. Similarly, rats maintained on a food-restricted diet showed increased plasma CORT levels, but this was blocked by the kappa opioid receptor antagonist norBNI (Allen *et al.* 2012). Swim stress has been shown to increase food consumption in rats while decreasing dynorphin levels in the hypothalamus (Vaswani *et al.* 1988). Treatment with norBNI has also been shown to block food deprivation induced heroin reinstatement (Sedki *et al.* 2014), further highlighting the complex interactions among feeding, anxiety and other neurological disorders.

Notably, the dynorphin system has been shown to interact with other molecules to influence stress and feeding. Orexin neurons in the lateral hypothalamus co-express dynorphin at a high rate (above 90%) (Chou *et al.* 2001), and when LH orexin neurons are selectively ablated, mice become severely obese (Hara *et al.* 2001; Inutsuka *et al.* 2014). However,

further work needs to be conducted to understand the relationship between dynorphin and orexin in these neurons, and whether both are involved in the obesity phenotype seen with ablation. Additionally, the dynorphin/NPY systems have been shown to interact in modulating these behaviors. Dynorphin/NPY double knockouts have significantly greater body weight and increased adipose tissue, but no differences in food intake (Nguyen *et al.* 2014). The dynorphin and kappa opioid receptor system has been identified as a major player in the stress response system, indicating that antagonism of the dynorphin system may influence both anxiety, addiction and feeding-related behaviors.

Glucocorticoids

Glucocorticoids, notably corticosterone, are types of hormones heavily involved in feeding and stress. A number of studies have explored the role of glucocorticoids in stress-induced HPA axis activation (e.g. see Noguchi *et al.* 2010; Oitzl *et al.* 2010; Ridder *et al.* 2005; Shishkina *et al.* 2014; Veldhuis *et al.* 1985). Not only does glucocorticoid secretion lead to increased food seeking and appetite (McEwen 2004), but food consumption in turn is known to modulate HPA axis function (Leal & Moreira 1997). In Addison's disease, glucocorticoid levels are low and this is associated with symptomatic anorexia and loss of appetite (Nieman & Chanco Turner 2006). Glucocorticoids can also control feeding behavior through regulation of orexigenic and anorexigenic peptides, such as CRF and NPY (la Fleur 2006). Hisano *et al.* (1988) demonstrated that glucocorticoid receptors and NPY colocalize in rat hypothalamus, providing insight into their interactions. Chronic administration of glucocorticoids increased NPY levels, while decreasing CRH levels, in the hypothalamus of rats (Zakrzewska *et al.* 1999). Therefore, glucocorticoids may serve to regulate the orexigenic NPY and anorexigenic effects of CRF, via direct actions and feedback loops. It is likely that stressors, via their activation of the HPA axis and downstream glucocorticoids, modulate both of these crucial peptides. However, distinct stressors (and feeding contexts) may modulate the HPA axis differently, leading to regulation of these peptides.

Work conducted addressing peptide interactions with stress and EDs provides promising therapeutic potential for co-targeting these traits. The literature has begun to elucidate the role of key peptides, notably CRF, NPY, AGRP, Dynorphin and the glucocorticoids, as potential targets for intervening in both stress and feeding-related conditions.

Conclusions

Stress has profound effects on the complex circuitry that influences feeding behaviors through discrete molecular mechanisms. This may inform discrete targets that could influence the circuitry related to feeding behavior. The literature suggests bidirectional causality between stress and EDs: maladaptive eating such as chronic consumption of a high-fat diet can drive and influence behavioral responses to stress and exposure to various forms of stress can influence maladaptive eating behaviors and perpetuate binge eating or other unhealthy eating patterns, further perpetuating the cycle. Therefore, we propose and encourage further research on the interactions between these two prevalent traits, with a focus on common treatment targets. Future research should focus on potential therapeutic

treatments for co-morbid stress and EDs, with an emphasis on modulation and homeostasis of peptide levels.

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Figure 1. Wiring diagram of exogenously mapped feeding circuits in mice

Using genetically modified strains of mice, multiple lines of research using cell-specific ablations, optogenetics and DREADDs implicate the illustrated pathways in regulating feeding. See Table 1 for details on the neuronal populations within these brain regions, their effect on feeding, and the accompanying reference.

Abbreviations: ARC – arcuate nucleus, BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; LH, lateral hypothalamus; NTS, nucleus of the solitary tract; PAG, periaqueductal gray; PBN, parabrachial nucleus; PFC, prefrontal cortex; RMg, raphe magnus.

Table 1

Summary food and environmental manipulations and stress effects

Feeding manipulation	Length	General effect	Reference
Caloric restriction	3 weeks	↑ stress	Pankevich <i>et al.</i> (2010)
24 hr HED access	multiple weeks	↑ binge of HED food, ↔ body weight	Czyzyk <i>et al.</i> (2009)
12 hr access 10% sucrose	21 days	↑ amphetamine response	Avena <i>et al.</i> (2003)
High fat, protein, carb diet	4 weeks	↓ stress sensitivity	Teegarden <i>et al.</i> (2007)
	4 weeks + withdrawal	↑ stress sensitivity	
Twice daily 30% sucrose	2 weeks	↓ of HPA axis response	Christiansen <i>et al.</i> (2011)
Intermittent access to sucrose	6 weeks	↑ sucrose licking, ↓ restraint stress-induced activation of lateral septum	Martin <i>et al.</i> (2010)
Highly palatable food	7 days	↓ ACTH, ↓ CORT responses, ↓ stress systems	Foster <i>et al.</i> (2009)
High fat diet	6 weeks	↑ anxiety	Sharma <i>et al.</i> (2012)
High fat diet	4 days	↑ weight gain, ↑ anxiety	Legendre <i>et al.</i> (2006)
High fat diet	1–12 weeks	↑ anxiety	Tannenbaum <i>et al.</i> (1997)
		↑ HPA response to stress	

Stress manipulation	Length	General effect	Reference
Restraint stress	6 h day × 28 days	↓ body weight, ↑ anxiety	Chiba <i>et al.</i> (2012)
Restraint stress	2 h × 15 days	↓ body weight, ↑ anxiety	Jeong <i>et al.</i> (2013)
Restraint stress	2 weeks	↓ body weight	Kim <i>et al.</i> (2013)
Restraint stress	3 h × 10 days	↓ body weight ↓ food intake	Harris <i>et al.</i> (2002)
Restraint stress	3 h	↓ body weight, ↓ food intake	Rybkin <i>et al.</i> (1997)
Restraint stress	3 days	↓ body weight, ↑ anxiety	Chotiwat <i>et al.</i> (2010)
Restraint stress	2 h	↓ body weight, ↑ anxiety	Haque <i>et al.</i> (2013)
Restraint stress	3 h for 3 days	↓ body weight	Kim <i>et al.</i> (2013)
Restraint stress	3–4 h day/7–8 days	↑ anhedonia	Lim <i>et al.</i> (2013)
Restraint stress	3 h day/5 days	↑ highly palatable food, ↓ overall consumption	Pecoraro <i>et al.</i> (2004)
Chronic variable stress	17 days	↑ high fat diet consumption	Teegarden <i>et al.</i> (2008)
Chronic variable stress	14 days	↓ caloric intake, ↓ body weight	Patterson <i>et al.</i> (2010)
Chronic variable stress	2 weeks	↓ body weight	Flak <i>et al.</i> (2014)
Chronic variable stress	3 days	↑ anxiety	MacKay <i>et al.</i> (2014)
Acute swim stress	15 min × 3 days	variable (gender)	Diane <i>et al.</i> (2008)
Acute swim stress	3 minutes	↑ anxiety	Barfield <i>et al.</i> (2013)
Social defeat	7 days	variable, ↑ food intake	Bhatnagar <i>et al.</i> (2006)
Social defeat	4 h × 4 days	↓ weight gain	Haller <i>et al.</i> (1999)
Social defeat	21 days	↑ weight gain, ↑ caloric intake	Patterson <i>et al.</i> (2013)

Both food manipulations (top) and environmental manipulations (bottom) impact feeding and anxiety related behaviors.

ACTH, e; CORT, corticosterone; HED, high energy diet; HPA, hypothalamic pituitary adrenal; h, hours.

Table 2

Summary of exogenous genetically-defined circuit manipulations on food intake

Brain region	Cell population	Targeting strategy	Terminal sites	Effect on food intake	Reference
ARC	AGRP/NPY	Ablation	n/a	↓	Wu <i>et al.</i> (2009)
		ChR2	Somatic	↑	Aponte <i>et al.</i> (2011)
		hM3D	Somatic	↑	Krashes <i>et al.</i> (2011)
		ChR2	PVN	↑	Atasoy <i>et al.</i> (2012) and Betley <i>et al.</i> (2013)
PVN	POMC		BNST	↑	Betley <i>et al.</i> (2013)
			LH	↑	Betley <i>et al.</i> (2013)
		ChR2	Somatic	↓	Aponte <i>et al.</i> (2011)
		hM3D	Somatic	↓	Zhan <i>et al.</i> (2013)
		Ablation	n/a	↑	Zhan <i>et al.</i> (2013)
		hM3D	Somatic	↔	Kong <i>et al.</i> (2012)
	RIP	hM4D	Somatic	↑	Atasoy <i>et al.</i> (2012)
	SIM1	hM4D ^{trxn}	PAG	↑	Stachniak <i>et al.</i> (2014)
	TRH	hM3D	Somatic	↑	Krashes <i>et al.</i> (2014)
	PACAP	hM3D	Somatic	↑	Krashes <i>et al.</i> (2014)
BNST	AVP	hM3D	Somatic	↓	Pei <i>et al.</i> (2014)
	vGAT	ChR2	LH	↑	Jennings <i>et al.</i> (2013)
PFC	D1	ChR2	Somatic	↑	Land <i>et al.</i> (2014)
LH	vGLUT2		BLA	↑	
		ChR2	Somatic	↓	Jennings <i>et al.</i> (2013)
		hM3D	Somatic	↑	Inutsuka <i>et al.</i> (2014)
		Ablation	Somatic	↓	Inutsuka <i>et al.</i> (2014)
PBN	CGRP	ChR2 and hM3D	Somatic	↓	Carter <i>et al.</i> (2013)
CeA	PKC δ	hM4d	Somatic	↑	
		ChR2	CeA	↓	
		eNpHR	Somatic	↑	Cai <i>et al.</i> (2014)
		ChR2	Somatic	↓	

See Fig. 1 for brain region abbreviations.

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AGRP, agouti related protein; AVP, arginine vasopressin; CGRP, calcitonin gene related peptide; ChR2, Channelrhodopsin 2; D1, dopamine receptor 1; eNpHR, Halorhodopsin; hM3D, Gq coupled humanized muscarinic type 3 receptor; hM4D, Gi-coupled humanized muscarinic type 4 receptor; ORX, orexin; PACAP, pituitary adenylylate cyclase-activating peptide; PKC δ , protein kinase C delta; POMC, proopiomelanocortin; RIP, rat insulin promoter; TRH, thyroid releasing hormone; vGAT, vesicular GABA transporter; vGLUT2, vesicular glutamate transporter 2.