

Symposium

How Does the Brain Implement Adaptive Decision Making to Eat?

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Adaptive decision making to eat is crucial for survival, but in anorexia nervosa, the brain persistently supports reduced food intake despite a growing need for energy. How the brain persists in reducing food intake, sometimes even to the point of death and despite the evolution of multiple mechanisms to ensure survival by governing adaptive eating behaviors, remains mysterious. Neural substrates belong to the reward-habit system, which could differ among the eating disorders. The present review provides an overview of neural circuitry of restrictive food choice, binge eating, and the contribution of specific serotonin receptors. One possibility is that restrictive food intake critically engages goal-directed (decision making) systems and “habit,” supporting the view that persistent caloric restriction mimics some aspects of addiction to drugs of abuse.

Key words: anorexia; decision making; dependence; reward; obesity; serotonin

Significance Statement

An improved understanding of the neural basis of eating disorders is a timely challenge because these disorders can be deadly. Up to 70 million of people in the world suffer from eating disorders. Anorexia nervosa affects 1–4% of women in United States and is the first cause of death among adolescents in Europe. Studies relying on animal models suggest that decision making to eat (or not) can prevail over actual energy requirements due to emotional disturbances resulting in abnormal habitual behavior, mimicking dependence. These recent studies provide a foundation for developing more specific and effective interventions for these disorders.

Introduction

Feeding behavior results from a combination of factors from the internal and external environments and is a typical motivated behavior. Feeding behavior maintains the body weight of an organism to a threshold specific to one’s species (as for temperature; Kupfermann, 1991). From this comes the complexity: food intake depends on homeostatic rules and also on other internal states, motivational states also called “drives” (Kupfermann, 1991). Motivation is expressed when it triggers goal-directed behavior. When individuals feel hungry, they are motivated to ob-

tain food. Feeling hungry then translates into the demand for energy. Hunger impels the organism to display goal-directed behavior to seek and consume foods and thus survive. Individuals do not make the decision to feel hungry, but can decide to satisfy or not satisfy hunger.

For some individuals, eating behavior can be chronically disordered and can include persistent food restriction and/or excessive intake despite negative consequences, suggesting disturbances of motivation and of goal-directed behavior (decision making). Food is a basic primary reward, requiring motivation to obtain it (“wanting”; Hoebel, 1997). Some investigators suggest that excessive consumption of foods, regardless of whether it is associated with obesity (Corwin et al., 2011), mimics addiction (Avena, 2010). However, whether binge eating represents a kind of addiction remains unclear (Corwin, 2011).

Common molecular mechanisms also exist between anorexia and addiction. Indeed, drugs of abuse (e.g., cocaine, amphetamine) trigger adaptive responses including an increased activity of the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling pathway in the nucleus accumbens (NAc), a

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critical brain structure of the reward system (Koob and Nestler, 1997; Nestler, 2005; Chen et al., 2009). The resultant phosphorylation of the cAMP-response element binding protein (CREB) dampens rewarding effects. Therefore, the sensitivity to subsequent drug exposures decreases (tolerance) with increased activity of reward pathways (dependence) to the point that drugs removal triggers depressive states (Nestler, 2004). Stimulation of the cAMP/PKA/cocaine- and amphetamine-regulated transcript (CART) pathway in the NAc after local stimulation of the serotonin (5-hydroxytryptamine, 5-HT) 4 receptors (5-HTR₄) provokes anorexia (Jean et al., 2007). This pathway is also involved in anorexia induced by the 3,4-*N*-methylenedioxymethamphetamine, the psychogenic compound of ecstasy (Jean et al., 2007). The ability of cocaine-addiction-related animal models (Rocha et al., 1998) to eat less despite an early period (3 d) of deprivation further depends on a gain-of-function of 5-HTR₄ with CART overexpression in the NAc (Jean et al., 2012b). Considering the involvement of CART in motivational properties of cocaine (Couceyro et al., 2005; Rogge et al., 2009), these findings evidence a “shared neural signal foul-up” between drug dependence and anorexia that is consistent with deficits in neural networks underlying addiction in patients with anorexia nervosa (Kaye et al., 2009; Nestler, 2013). The rewarding effect of anorexia has been described in humans at the onset of anorexia nervosa symptoms (Brockmeyer et al., 2013). Indeed, the brain can implement food restriction until death as the result of maladaptive decision making. Because the prospect of receipt of a positive reward is capable of inducing risky, and potentially lethal behavior, potential neural deficits that restrict food intake to a lethal point could be included in those of dependence, which requires further testing.

Examination of the activity of neural centers involved in the recognition of rewards and the development of habits is therefore relevant (Walsh, 2013). A recent report described goal-directed decision making as a complex process and argued that reward-based decisions depend on the habit and goal-oriented systems (Solway and Botvinick, 2012). The habit system “stores” stimulus–response associations based on past rewards and the goal-oriented system selects one action by anticipating the positive and negative outcomes (Solway and Botvinick, 2012). Because “addiction is a form of learning and relapse is a persistent memory of the drug experience” (Wikler, 1961), feeding behavior appears to result from integrated activity of an autonomous and voluntary nervous systems informed by the sensory nervous system of external environment states. However, excessive and restrictive intake of food can prevail over homeostatic rules. Studying neural substrates of feeding behavior is therefore critical to better understand how neural systems interact to make adaptive decisions to eat or not in the face of environmental changes (i.e., stressors). Indeed, responses to stress include reduced food intake despite requirements for energy (Stone et al., 1984; Shibasaki et al., 1988; Shimizu et al., 1989; Grignaschi et al., 1993; Haleem et al., 1998), macronutrient selection (Wang, 2002), and increased consumption of food (Rowland and Antelman, 1976; for review, see Morley et al., 1983).

Our understanding of brain functions often comes from clinical descriptions of symptoms in humans. Indeed, symptoms of anorexia nervosa make visible a likely “crosstalk” between different cerebral structures. We will use “anorexia” instead of “anorexia-like behavior” for animals. Animals display anorexia that is operationally defined as reduced food intake despite the physiological energy demand; that is, after partial or total food deprivation (Jean et al., 2012b). Patients with anorexia nervosa can reduce food intake and even starve to death and often display

emaciation, amenorrhea, motor hyperactivity or “overexercise” (Beumont et al., 1994; Casper, 2006), anxiety (Godart et al., 2000; Kaye et al., 2004), harm avoidance [excluding possible harm due to anorexia (Fassino et al., 2002)], perfectionism (Friederich and Herzog, 2011), obsessionality (Anderluh et al., 2003; van den Heuvel et al., 2005), and depression (Casper, 1998). Individuals suffering from anorexia nervosa can also struggle with bulimia (i.e., overeating with purging). The symptomatology of anorexia nervosa is complex, especially when food restriction alternates with bulimia that differs from binge eating (Corwin et al., 2011). Binge eating involves uncontrollable consumption of large amounts of food, but is not followed by food purging. Understanding anorexia is a major challenge because restrictive feeding aggravates numerous diseases and is the first cause of death of adolescents in Europe (Papadopoulos et al., 2009). Indeed, personality traits (anxiety, harm avoidance, obsession, perfectionism) often occur in childhood before the onset of eating disorders and likely implement biological predisposition and account for ~50–80% of the risk of developing eating disorders (Bulik et al., 2006; Kaye et al., 2009).

In this mini-review, we will consider first the most known molecular mechanisms that have been observed in the hypothalamus and the NAc, two respective critical brain areas related to the autonomic and voluntary nervous system. In addition, although numerous peptidergic systems are involved, we will focus on serotonergic systems that are also known to have a prime role in survival mechanisms because of their clear involvement in adaptive responses to stress, emotional states, and feeding behavior. Mainly based on recent results, we suggest that voluntary control processes in the nervous system (underlying decision and motivation) can be modified to prevail over cerebral autonomous control of hunger, compromising survival. To better understand how the brain implements adaptive decision making to eat, we will consider the neural circuitry involved in persistent restrictive food choice, consistently with the fact that an altered balance between reward and inhibition may favor extremes in food intake. At a molecular level of analyses, we will then describe particular mechanisms in the NAc that could underlie the switch from undereating to overeating in animal models. Finally, we will show that these brain activities depend on environmental factors transmitted via the sensory system (e.g., individuals with obesity vs lean) show differential neural responses to visual and auditory food cues of high- and low-palatability foods.

Critical brain areas of the CNS control food intake: autonomous versus voluntary control

The main area of current research remains the delineation of subcircuits in the hypothalamus that regulate the autonomic nervous system and control energy homeostasis. In summary (Schwartz et al., 2000), hypothalamic neurons in the arcuate nucleus coexpress either neuropeptide (NPY) and agouti related-peptide (AgRp) or CART and POMC and their respective activation increases and decreases food intake upon the influence of numerous messengers, including those secreted by peripheral organs (leptin, ghrelin, orexin, etc.). In turn, AgRp-containing neurons in the arcuate nucleus mainly target neurons in the paraventricular nucleus that express melanocortin 4 receptors (MCR4; Garfield et al., 2015). Stimulation of the MCR4 decreases food intake (Adan and Kas, 2003; Lubrano-Bertheliet et al., 2003; Srinivasan et al., 2004; Kim et al., 2008).

In parallel, accumulating evidence shows a critical influence of 5-HT on food intake (for review, see Compan, 2013). In the

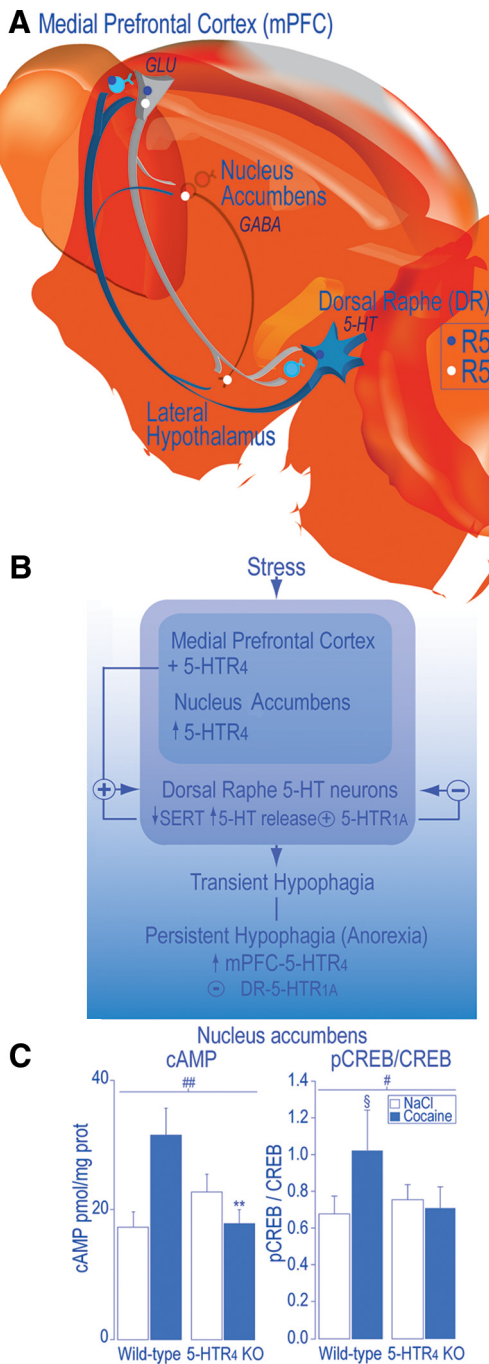


Figure 1. A working hypothesis: decision making to eat could partly depend on neural pathways concerned with dealing with stress. **A**, Efferent neurons of the mPFC mainly target the DR (Sesack et al., 1989; Peyron et al., 1998; Vertes, 2004) and contain glutamate (GLU) (Lee et al., 2003). With regard to the reciprocal descending projections, 5-HT neurons in the mPFC mainly arise from the DR and send axon collaterals to the NAc (Van Bockstaele et al., 1993). In the mPFC, 60% of pyramidal efferent neurons express both 5-HTR₄ and 5-HTR_{1A} mRNA (Feng et al., 2001). In the mPFC, 5-HTR₄ mRNA are mainly expressed by GLU-expressing efferent neurons (Penas-Cazorla and Vilaro, 2014). In the NAc, 5-HTR₄ are localized on GABA-expressing efferent neurons to the lateral hypothalamus (Jean et al., 2007). In the mPFC, the 5-HTR_{1A} is localized, in the mPFC, in glutamatergic pyramidal efferent, local GABA-expressing interneurons (Czyrak et al., 2003; Amargós-Bosch et al., 2004; Santana et al., 2004) and on 5-HT terminals and, in the DR, on DR 5-HT neurons (Miquel et al., 1992; Pompeiano et al., 1992). **B**, From the mPFC, 5-HTR₄ exert a tonic positive influence on the firing activity of DR 5-HT neurons in rodents (Lucas and Debonnel, 2002; Lucas et al., 2005; Conduictier et al., 2006). From the DR and mPFC, 5-HTR_{1A} exert a negative feedback on DR 5-HT neurons (Sprouse and Aghajanian, 1987; Haj-Dahmane et al., 1991; Bortolozzi et al., 2004). We found that mPFC 5-HTR₄ overexpression induced decreases in the levels of plasma membrane 5-HT transporter (SERT) and increases in 5-HT release, which

hypothalamus, stimulation of the 5-HT_{2C} receptors (5-HTR_{2C}), likely located on CART/POMC neurons, induced increases in the α -melanocyte-stimulating hormone release and reduced food intake (Heisler et al., 2002). Consistently, lorcaserin, a 5-HTR_{2C} agonist, appears effective in reducing obesity and possibly abuse of substances in humans (Higgins et al., 2013; Howell and Cunningham, 2015), in agreement with an enhanced cocaine self-administration in the 5-HTR_{2C} knock-out (KO) mice (Rocha et al., 2002). Stimulating 5-HTR_{1B} in the hypothalamus also reduces food intake and may favor the inhibitory control of 5-HTR_{2C} (Doslikova et al., 2013). In contrast, activation of the 5-HTR_{1A} and 5-HTR_{2B} in the arcuate nucleus, expressed by POMC neurons, increases food intake (Yadav et al., 2009; Yadav et al., 2011). Nonetheless, 5-HTR_{1A}/5-HTR_{2B} could be “modulators” between two “anorectic factors,” leptin and MCR4 in the hypothalamus. Leptin inhibits 5-HT cells activity in the brainstem and thus reduces the inhibitory control of 5-HTR_{1A} on MCR4 mRNA expression in the hypothalamus, resulting in reduced food intake (Kumar et al., 2010).

Autonomous control of food intake appears to depend largely on the hypothalamus, including likely important downstream pathways between the parabrachial nucleus and the central nucleus of amygdala (Carter et al., 2013), but the involvement of the voluntary system, including the NAc and medial prefrontal cortex (mPFC), is less clear. However, the critical role of the NAc and mPFC in motivation and goal-directed behavior suggests that both structures could trigger increased or decreased intake of foods that could override actual energy needs (in opposition to the hypothalamus).

Analyses have been mainly conducted in the NAc and show that, in addition to the hypothalamus, peptides influence food intake (e.g., CART, NPY, galanin, melanocortins, glucagon-like peptide, opioids; Zhang and Kelley, 1997; Jean et al., 2007; Woolley et al., 2007; Picciotto, 2008; Pandit et al., 2011; Reddy et al., 2014; van den Heuvel et al., 2015). In addition, over the last few years, dopamine has been often related to “food addiction” and obesity (for review, see Salamone and Correa, 2013), whereas a 5-HT-dependent addictive pathway in the NAc (Jean et al., 2007) involving a 5-HTR₄ and 5-HTR_{1B} interrelation supports anorexia (Jean et al., 2012b). Nonetheless, and as observed in the hypothalamus for different 5-HT receptor subtypes, stimulation of the 5-HTR₆ provokes overeating (Pratt et al., 2009).

A key question is what are the neural substrates that initiate the transition from transient to persistent restrictive food intake; that is, those that would abnormally favor an “early decision making” to not eat. We suspected impaired activity of a network governing goal-directed behavior (decision making), the ascend-

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 activates DR 5-HTR_{1A} that prevent the transition from a transient to a sustained hypophagia (“early anorexia”), introducing anorexia as an antidepressant (5-HT accumulation resulting from 5-HTR_{1A} desensitization and SERT reduction; Jean et al., 2012a, unpublished data). In addition, stimulation of 5-HTR₄ in the NAc enhanced the activity of an addictive signaling pathway (cAMP/PKA/CART), which provokes anorexia and motor hyperactivity (Jean et al., 2007, 2012b), suggesting that neural substrates of anorexia are included in those of dependence. **C**, Consistently, acute intraperitoneal administration of cocaine (30 mg/kg) failed to increase, in the NAc, cAMP levels and pCREB/CREB ratio, in 5-HTR₄ KO compared with wild-type mice. Data are means \pm SEM, $n = 5–8$ mice of both genotypes per each group. A significant treatment effect is noted: $\$p < 0.05$, $\$\$p < 0.01$ compared with NaCl, a genotype effect ($*p < 0.05$) and genotype \times treatment interaction, $\#p < 0.05$, $\#\#p < 0.01$ after significant two-way ANOVA. We posit that decreased activity of the mPFC-5-HTR₄ (among many other factors) could favor a subcortical influence; that is, an autonomous control without adaptive decisional control regardless of the requirement for energy (Compan, 2013).

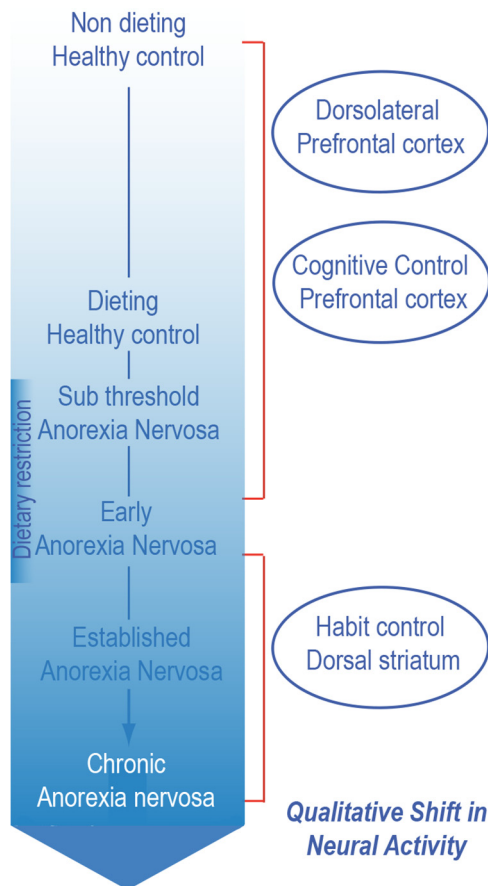


Figure 2. Reproduced with permission from Steinglass and Foerde (2015) (and see Foerde et al., 2015).

ing serotonergic inputs from the dorsal raphe nucleus to the mPFC for several reasons: (1) this network supports an adaptive “decision” to avoid adverse effect of stress and then depressive states (Amat et al., 2005; Robbins, 2005; Euston et al., 2012); (2) eating disorders are stress related (for review, see Hardaway et al., 2015); and (3) eating disorders are often associated with depression (Micali et al., 2015). Our working hypotheses are schematized in Figure 1 (Jean et al., 2012a, unpublished data), introducing the idea that processes within the voluntary nervous system (underlying decision, motivation) could be modified to prevail over a cerebral autonomous control of hunger, compromising survival. This study suggests a primary mechanism that could support the onset of a persistent hypophagia (“an early anorexia”) whereby individuals shift from adaptive to persistent maladaptive food choice as in anorexia nervosa (Walsh, 2013; Fig. 2).

Neural circuitry involved in persistent restrictive food choice

One of the major unanswered questions about anorexia nervosa is how to account for its persistence. The salient behavioral feature of anorexia nervosa is the avoidance of high-fat foods (Walsh, 2011). This pattern of behavior is consistent across individuals and not difficult to measure objectively. Even after individuals with anorexia nervosa have become accustomed to routinely consuming such foods during treatment in structured settings such as hospital units and day programs, have gained significant weight, and have exhibited substantial psychological improvement, they continue to avoid consuming high-fat food when they can (Walsh, 2013). This behavior is a substantial con-

tributor to the high rate of relapse after successful acute treatment in such programs.

The Columbia group has taken a top-down approach in attempting to understand the neural underpinnings of this phenomenon, using emerging knowledge from cognitive neuroscience regarding the acquisition and maintenance of behavior. Specifically, we have suggested that the dieting behavior of anorexia nervosa begins in response to stresses experienced during adolescence and adulthood (Walsh, 2013) and is initially highly rewarding because the resultant weight loss is viewed as a rare accomplishment and evidence of impressive self-control (Steinglass et al., 2012b) and it helps the individual to cope with difficult-to-manage stressors. However, we posit that, over time, as the dieting behavior is repeated and continues to be reinforced, at least intermittently, it becomes engrained via the mechanisms underlying stimulus–response learning; that is, habit formation (Walsh, 2013). This model suggests that, once the behavior has become well established, it engages the dorsal striatum, a striatal subregion associated with habitual behavior (Fig. 2).

To test these hypotheses, we reframed the avoidance of high-fat foods characteristic of anorexia nervosa as a choice about what food to eat. We adapted a previously published food choice task (Hare et al., 2009) and expanded it to include photographs of 76 foods, half of which had a high fat content (>37% of calories from fat). The task has three phases and was conducted during fMRI: in the first two phases, subjects are asked to rate each food on “health” and on “taste” using a 5-point Likert scale. From the foods rated neutral by that subject on both health and taste, a “reference food” is randomly chosen. In the third phase of the task (the choice phase), the subject is shown 75 pairs of photographs and asked to indicate which of the two foods they prefer, also using a 5-point Likert scale. The photograph of the reference food is always shown on the left and the 75 other foods are sequentially displayed on the right. At the end of the task, one of the subject’s actual choices is randomly selected and that food presented to the subject, who is asked to eat it. On the following day, the subject is asked to select foods from a multi-item buffet and eat these foods for lunch.

We have completed an initial study examining 21 young-adult women hospitalized for treatment of anorexia nervosa and 21 healthy women. As expected, both groups rated the high-fat foods as significantly less healthy than the low-fat foods. On average, the controls rated the high-fat and low-fat foods equally tasty, but the patients rated the high-fat foods less tasty, leading to a significant group \times taste interaction. In the choice phase, patients with anorexia nervosa chose high-fat foods far less frequently than did the controls, leading to a highly significant group \times choice interaction. Furthermore, the proportion of times that patients chose high-fat foods versus the reference food was significantly correlated with the caloric content of the lunch that they chose to consume the following day. These results indicate that the food choice task effectively captures the salient behavioral feature of anorexia nervosa.

Analysis of fMRI data revealed several important findings. First, during the choice phase, individuals with anorexia nervosa engaged the dorsal striatum significantly more than did controls, consistent with our hypothesis. In contrast, there were no differences between groups in activity in the dorsal striatum during the health and taste phases. Second, during the choice phase, there was no difference between groups in activity in the ventral striatum, a subregion associated with goal-directed actions.

The current results are consistent with the possibility that persistent, maladaptive food choice in anorexia nervosa is linked to

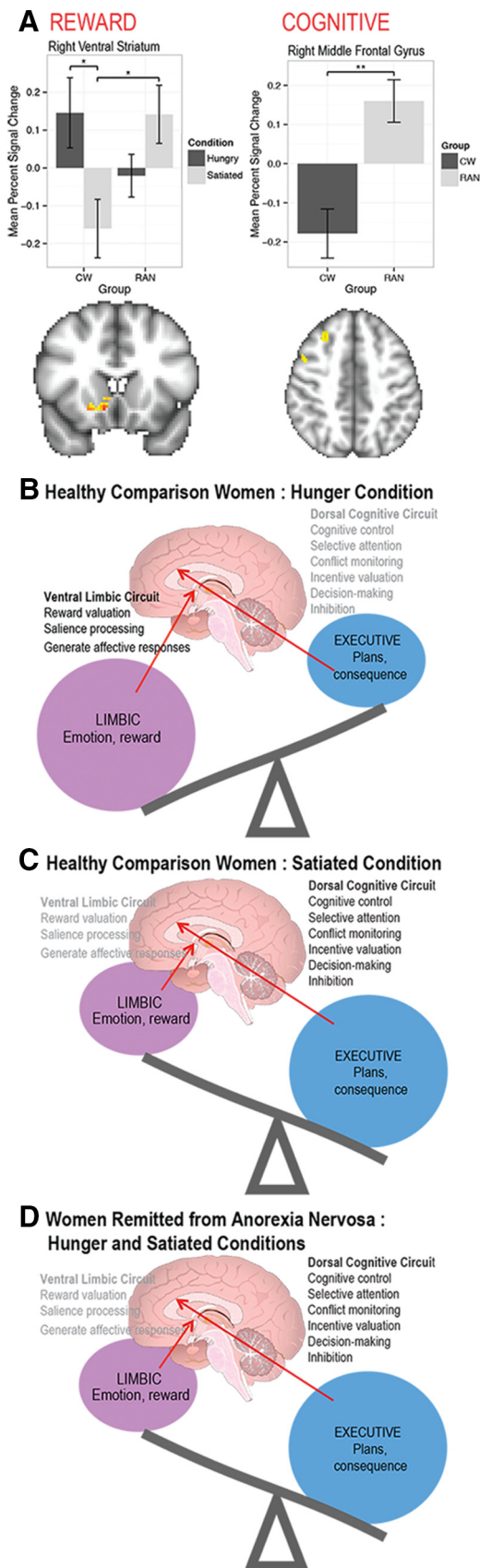


Figure 3. *A*, Left, Region-of-interest analysis showing that, for “immediate reward valuation” within the right ventral striatum, healthy comparison women (CW) had a greater response when hungry than when satiated; when satiated, remitted anorexia nervosa (RAN) had a greater response than CW. Right, Cognitive-related region-of-interest analysis for the “all

activity in the frontostriatal networks crucial for the development of habitual behavior. A similar hypothesis has been proposed regarding substance use and other disorders. The current data suggest that food choice in anorexia nervosa is not guided simply by frontal-striatal activity associated with goal-based, rewarding behaviors and support continued examination of the neural basis of persistent maladaptive food choice in this disorder.

Altered balance between reward and inhibition may favor extremes consumption of food

Another key question is what factors, such as personality traits, predispose to the development of inappropriate restriction of food intake? The fact that such traits persist after recovery from the eating disorder suggest that they may be predisposing factors for the development of chronic eating disorders. Individuals with anorexia nervosa often report that there is an anxiety-reducing character to dietary restraint and reduced daily caloric intake (Vitousek and Manke, 1994; Kaye et al., 2003; Steinglass et al., 2010), whereas eating stimulates dysphoric mood (Frank and Kaye, 2012).

Symptomatology of individuals with anorexia nervosa suggest potential altered balance among limbic, cognitive, and salience neural circuits. These circuits interact to value reward, assess future consequences of one’s behavior, and integrate and evaluate reward prediction to guide decisions using cognitive control and inhibition (Phillips et al., 2003). Simply put, patients with anorexia nervosa have a diminished reward and salience response and increased cognitive control and inhibition. For example, they have long been noted to be anhedonic and ascetic, able to sustain self-denial of food and most of the comforts and pleasures in life (Frank et al., 2005). Moreover, patients with anorexia nervosa have an enhanced ability to delay reward (i.e., show less reduction in the value of a monetary reward over time) compared with healthy volunteers (Steinglass et al., 2012a). They also tend to be overcontrolled, overconcerned about consequences, and have high punishment sensitivity in the ill and recovered states (Claes et al., 2006; Harrison et al., 2010; Harrison et al., 2011; Jappe et al., 2011; Matton et al., 2013; Glashouwer et al., 2014).

Data from imaging studies support the argument that enhanced cognitive control and ability to delay reward may help to maintain persistent food restriction. Animal studies show that the ventral striatum processes motivational aspects of stimuli by modulating the influence of limbic inputs on striatal activity (Schultz, 2004; Yin and Knowlton, 2006). In this way, even secondary rewards such as money activate the ventral striatum proportionally to the reward amount or deviation from an expected payoff (Montague et al., 2004). Our group (Wierenga et al., 2015) investigated brain activation during delay discounting in recovered anorexia nervosa when hungry and when satiated (Fig. 3). It is important to emphasize that hunger influences behavioral choice in healthy individuals by increasing the appetitiveness of rewarding stimuli (Goldstone et al., 2009; Wang and Dvorak, 2010; Levy et al., 2013; Tal and Wansink, 2013). Compared with healthy women, recovered anorexia nervosa patients failed to

← decisions” analysis. Within the right middle frontal gyrus, RAN responded more strongly than CW for all trials. Error bars represent the SE for each group. * $p = 0.05$; ** $p = 0.01$. *B–D*, Comparison of ventral limbic and dorsal cognitive circuits in CW showing hunger (*B*) enhances limbic and reduces cognitive activity whereas satiety (*C*) reverses these neural processes. However, in RAN, there is (*D*) reduced limbic and enhanced cognitive function whether hungry or satiated (Wierenga et al., 2015).

increase activation of reward valuation circuitry when hungry and showed elevated response in cognitive control circuitry regardless of metabolic state (Wierenga et al., 2014). This finding is consistent with our previous studies (Wagner et al., 2007; Wagner et al., 2010; Bischoff-Grethe et al., 2013) and other studies showing that limbic regions are underactive for motivational behavior in ill anorexia nervosa patients (Zastrow et al., 2009). That is, hunger does not make salient stimuli more appetitive in anorexia nervosa. Moreover, difficulties in valuating emotional salience may contribute to inability to appreciate the risks inherent in this deadly disorder.

In addition, imaging studies show that altered reward and salience processing is associated with eating pathology. A growing body of research (Kaye et al., 2013) suggests that ill and recovered anorexia nervosa adults have an enhanced anxiety response to anticipated food cues and diminished insula and striatal response to receipt of food (Wagner et al., 2008; Cowdrey et al., 2011; Vocks et al., 2011; Frank et al., 2012; Oberndorfer et al., 2013a, 2013b). A study of response to pain confirms a mismatch between anticipation and objective responses in recovered anorexia nervosa patients (Strigo et al., 2013). That is, there may be a reduced response to “code” reward, but an exaggerated anticipation that is often anxious in nature. An exaggerated response to stimulus cues may be a mean to predict and manage the anxiety elicited by subjectively aversive stimuli, similar to the anticipatory sensitivity linked with stimulus avoidance that is seen in highly anxious individuals (Simmons et al., 2006).

Finally, based on growing evidence from behavioral and imaging studies, individuals with anorexia nervosa could have an impaired ability to identify the emotional significance of a stimulus but increased traffic in neural circuits concerned with planning and consequences, which is associated with anxiety (Wierenga et al., 2014). This overreliance on cognitive brain circuits involved in linking action to outcome may constitute an attempt at “strategic” (as opposed to hedonic) means of responding to reward stimuli.

It is appropriate here to mention the critical implication of 5-HT systems in anxiety that is prevented when 5-HTR_{1A} is expressed during the early postnatal period (Gross et al., 2002); conversely, the absence of 5-HTR₄ induces anxiety-like behavior in stressful conditions and leads to decrease in 5-HTR_{1A} levels in the dorsal hippocampus (Compan et al., 2004; Conductier et al., 2006). Interestingly, cocaine administration increased the phosphorylated CREB (pCREB)/CREB ratio in the NAc in wild-type mice but not in 5-HTR₄ KO animals (Fig. 1), suggesting that these receptors enhance CREB phosphorylation. Considering that inhibition of the transcription factor CREB in the NAc has been associated with anxiety-like behavior (Barrot et al., 2005), anorexia induced by stimulation of 5-HTR₄ in the NAc could favor the “anxiety-reducing character to dietary restraint” (Vitousek and Manke, 1994; Kaye et al., 2003; Steinglass et al., 2010). In contrast, reduced activation of 5-HTR₄ could enhance anxiety that is provoked by overeating.

Particular molecular mechanism underlies the transition from undereating to overeating

The mechanism that underlies the transition from undereating to overeating depends on a peculiar property of G-protein coupled receptors (GPCRs) that was described *in vitro* by Lefkowitz (2007). Like other GPCRs, 5-HTR₄ displays an active form (G-protein coupled, symbolized by R^{*}) and inactive form (G-protein uncoupled, R) in the plasma membrane, mostly described *in vitro* (Claeyssen et al., 2000; Kenakin, 2004), with the unique exception

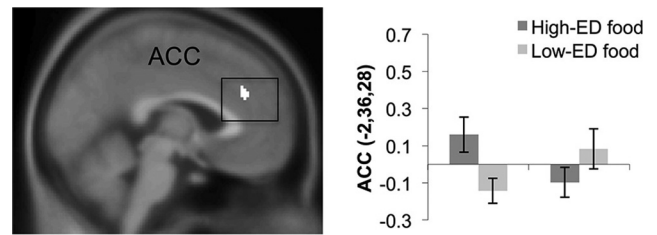


Figure 4. Greater activation in response to high-ED versus low-ED food cues in binge eaters compared with nonbinge eaters in a conjunction of visual and auditory modalities, in the dorsal anterior cingulate cortex (dACC). The bar graph shows β estimates for voxels in the dACC in binge eaters (BE) and nonbinge eaters (non-BE) for high-ED (vs baseline) and low-ED (vs baseline) (Gelibter et al., 2015).

of the MCR4 that have been shown to be constitutively active *in vivo* (Kim et al., 2008). Some GPCRs then can exhibit an autonomous capacity (or agonist-independent activity called “constitutive activity”) to regulate their own intracellular signaling pathways without agonist stimulation. Inhibiting this autonomous capacity of 5-HTR₄ reduces the activity of their intracellular signaling pathways and stabilizes their R form. An inverse agonist inhibits the constitutive activity, and displaces the significant amount of R^{*} form toward R. Agonists then enrich R^{*} whereas inverse agonists stabilize R, and antagonists equilibrate R/R^{*}. However, the physiological consequences of the R^{*}/R transition (“toggling”) was unknown. We found that inactivating totally (“silencing”) the NAc-5-HTR₄, i.e., injecting a specific inverse agonist of 5-HTR₄ in the NAc of behaving mice, provoked overeating (competitive antagonist suppressed this response). We hypothesize that the two extremes of the R^{*}/R of 5-HTR₄ in the NAc correspond to two extremes of feeding patterns: restrictive diet and overeating. Our results indicate that silencing 5-HTR₄ causes overeating while, as mentioned above, activation of the main signaling pathway (cAMP/PKA) of 5-HTR₄ in the NAc (R^{*}) favors anorexia (Jean et al., 2007; Jean et al., 2012b; Laurent et al., 2012). From R^{*} to R, cAMP levels increase then decrease in the NAc. Analyses of downstream molecular signals show that silencing NAc-5-HTR₄ decreases the levels of cAMP, decreases CART and increases the mRNA levels of the orexigenic neuropeptide Y (NPY). siRNA-mediated NPY knock-down in the NAc suppresses overeating induced by silencing 5-HTR₄ (Compan, 2015).

Consistently, humans with obesity display increased levels of 5-HTR₄ in the NAc (Haahr et al., 2012), suggesting either an accumulation of 5-HTR₄ in their inactive state and/or an adaptive compensatory increase in 5-HTR₄ in response to decreases in 5-HT contents that are suspected to be lower in humans with obesity (Björntorp, 1995; Strömbom et al., 1996). This is consistent with the inverse correlation between 5-HT and 5-HTR₄ contents in rats, pigs, and humans (Compan et al., 1996; Etrup et al., 2011; Haahr et al., 2014). During one year without bulimic and purging episodes, the levels of 5-HIAA in CSF were higher in patients who were suffering from bulimia than in controls (Kaye et al., 1998). The levels of 5-HIAA are also reduced in CSF of patients with anorexia nervosa, but normalized over the recovery of their body weight (Kaye et al., 1984; Kaye and Weltzin, 1991). Altogether, we suggest that sustaining high constitutive activity of 5-HTR₄ induces persistent anorexia, a corollary to our observation that inhibition of the constitutive activity of 5-HTR₄ triggers excessive food intake. As mentioned above, a maladaptive food choice is associated with changes in the activity of the dorsal, but not the ventral striatum. Whether the absence of increased neural

activity in the ventral striatum could be associated with low release of 5-HT and high constitutive activity of 5-HT₄ in patients with anorexia nervosa is unknown. The following section provides evidence that, on the other side of the weight spectrum, in individuals with obesity, there is increased brain activity in the dorsal striatum in response to high-calorie food cues.

Differential neural responses to visual and auditory food cues in obesity and binge eating

We compared fMRI brain activity in response to food cues in obese and lean individuals who had consumed a fixed meal for lunch 3 h earlier. The obese participants were more likely to show increased brain activity in the putamen (dorsal striatum) and ventral tegmental area (VTA, midbrain), two components of the dopaminergic reward pathway, when shown images (visual cues) or when hearing words (auditory cues) associated with highly energy-dense (ED) food cues such as chocolate cake, ice cream, or french fries compared with low ED foods such as carrots, cucumbers, or apples. That this occurred across different modalities of vision and audition suggests that the effects are independent of sensory input (Geliebter et al., 2006; Carnell et al., 2014). Greater putamen activation in obese versus lean women in response to high-ED compared with low-ED visual stimuli were also noted in another fMRI study (Rothmund et al., 2007). In addition, in a PET study, obese (vs lean) individuals showed greater regional cerebral blood flow in the midbrain in response to a small taste of a liquid meal (DelParigi et al., 2005).

A greater proportion of obese individuals are binge eaters compared with those who are lean (de Zwaan, 2001) and binge eating often precedes obesity (Mussell et al., 1995). When we compared binge eaters with nonbinge eaters, a similar pattern emerged as for comparing obese with lean subjects (Geliebter et al., 2015). That is, there was greater responsiveness to cues of high-ED, more palatable foods than low-ED foods, in this case in the dorsal anterior cingulate (Fig. 4), an area involved in guiding reward-based decision making (Bush et al., 2002). In addition, in a PET study, there was more dopaminergic activity in the dorsal striatum of obese binge eaters than obese nonbinge eaters when a taste of a preferred food was given after oral methylphenidate to enhance dopamine levels (Wang et al., 2011).

After Rouen Y gastric bypass surgery to treat obesity, there was a marked reduction in fMRI activity in the reward areas of the brain associated with dopaminergic pathways [including the VTA and putamen, as well as the dorsolateral prefrontal cortex, ventrolateral and dorsomedial PFC, ventral striatum, and lenticular nucleus (i.e., putamen and pallidum)] in response to high-ED versus low-ED food cues (Ochner et al., 2011; Geliebter, 2013), suggesting that surgery helped to normalize the neural responses in those with obesity. Surgery may induce hormonal changes (e.g., orexin, ghrelin, etc.), which could in turn modify neural activity. The change in neural activity was apparently not due to weight loss per se because it was noted even after statistically controlling for weight change and was also seen in the surgery group only compared with a control group who lost weight by dieting. We have also examined whether the surgery effect differed between those who binge eat and those who do not, and found that after surgery, the brain responses were similarly reduced in both groups for high-energy food cues. This may be because gastric restriction from the surgery virtually prevents binge eating.

Conclusion

In sum, neural substrates of dependence could interfere with homeostasis and favor maladaptive decision making to not eat or overeat and eventually lead to eating disorders. The neuronal network underlying eating behaviors is part of a larger network implicating reward and decision-making systems that react to environmental cues. Accordingly, environmental changes (i.e., stressors) associated with biological predisposition could alter motivation and adaptive decision making, including the excessive restriction of food intake or types of foods. If adaptive responses to stress depend on the 5-HT system, then eating disorders could emerge when 5-HT neurons reach the limit of their adaptive capacities. We suggest that a predominance of a cortical control reflects an adaptive process to prevent “negative emotional states” when facing an acute stress at the onset of anorexia nervosa, which could be supported by a shared signal foul-up with drugs of abuse. In the face of chronic stress, limits of this adaptive process could “submerge” cortical control and “release the influence of the subcortical areas” such as the NAc (autonomous control without adaptive decisional control), in which uncontrolled oscillating changes in common molecule levels (cAMP, CREB: all controlled by GPCRs) could lead to an anarchic consumption of foods (from anorexia to bulimia and/or binge eating).

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