Review

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Escaping the Golden Cage: Animal Models of Eating Disorders in the Post–*Diagnostic and Statistical Manual* Era

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ABSTRACT

Eating disorders (EDs) are severe, life-threatening mental illnesses characterized by marked disturbances in body image and eating patterns. Attempts to understand the neurobiological basis of EDs have been hindered by the perception that EDs are primarily socially reinforced behaviors and not the result of a pathophysiologic process. This view is reflected by the diagnostic criteria of anorexia nervosa and bulimia nervosa, which emphasize intrapsychic conflicts such as "inability to maintain body weight," "undue influence of body weight or shape on self-evaluation," and "denial of the seriousness of low body weight" over neuropsychological measures. The neuropsychological constructs introduced within the research domain criteria (RDoC) matrix offer new hope for determining the neural substrate underlying the biological predisposition to EDs. We present selected studies demonstrating deficits in patients with EDs within each domain of the RDoC and propose a set of behavioral tasks in model systems that reflect aspects of that deficit. Finally, we propose a battery of tasks to examine comprehensively the function of neural circuits relevant to the development of EDs.

Keywords: Animal behavior, Anorexia nervosa, Binge eating disorder, Bulimia nervosa, Eating disorder, RDoC

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Despite the clear involvement of biological factors, such as sex (predominantly female) and energy homeostasis, in the development of an eating disorder (ED), the neurobiological basis of EDs remains poorly understood. The lack of well-defined animal models is one important limitation toward understanding the neurobiology of ED-related behaviors. To date, the most commonly used behavioral paradigm is the activity-based anorexia model, in which concomitant calorie restriction and access to a running wheel leads to a rapid increase in locomotor activity, reduced food intake, and, frequently, death (1). Although the model offers predictive and face validity in the study of certain ED-related behaviors, it has limited capacity to study the psychological processes that often underlie the development of EDs. The research domain criteria (RDoC) system was created to facilitate dimensional studies of such neuropsychological measures. We present constructs within the RDoC matrix relevant to the development of EDs and discuss their potential research applications.

NEGATIVE VALENCE

The negative valence system contains several constructs, including acute threat (fear) and potential threat (anxiety), with substantial research supporting dysfunction in patients with EDs.

Clinical Evidence

There is a clear temporal relationship between the development of anorexia nervosa (AN) and anxiety disorders. Of girls who eventually develop AN, 58% have a diagnosable Axis I anxiety disorder by age 10, an average of 5 years before the onset of the ED (2). In a separate study of 68 women with AN, 60% were found to have a comorbid anxiety disorder, and 90% of these women developed the anxiety disorder before the occurrence of AN (3).

This strong temporal relationship suggests that the appearance of anxiety symptoms may represent the first presentation of a neurobiological process that predisposes an individual to developing AN. A structured diagnostic interview of patients with EDs found an increased rate of several anxiety disorders, including social phobia (20%), specific phobia (15%), and generalized anxiety disorder (10%) (4). Independent of DSM diagnosis, multiple studies demonstrated increased anxiety levels using self-report measures such as the State-Trait Anxiety Inventory. One study found elevated trait anxiety on the State-Trait Anxiety Inventory in subjects across all ED diagnoses, including AN restricting subtype (AN-R), AN binge/purge subtype, bulimia nervosa (BN), and binge eating disorder, compared with control subjects (5). The score on the State-Trait Anxiety Inventory scale correlates with the severity of ED symptoms (6,7), increases with stress-induced exacerbation of ED symptoms (8), and improves with weight restoration (9). Similarly, higher rates of agoraphobia and social phobia were found to be correlated with ED symptoms using the Marks and Matthews Fear Questionnaire (6).

Finally, analysis of anxiety symptoms in patients with AN who did not meet criteria for an anxiety disorder found much

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higher levels of traits such as harm avoidance and perfectionism in this group than in a control group of healthy women (4). Keel *et al.* (10) further assessed this association using a discordant monozygotic twin study to examine the relationship between EDs and other psychiatric syndromes, including depression, anxiety, and substance abuse. Their data support a model of shared transmission of EDs with anxiety, but not depression or alcohol, nicotine, or drug abuse. Other constructs within the negative valence domain may also prove to be relevant to the development of EDs. In particular, clinicians treating patients with EDs frequently observe elements within sustained threat and loss constructs, such as increased conflict detection, decreased appetitive behaviors, and shame/guilt. Further studies examining the association between these constructs and EDs would be of interest to the field.

RDoC Correlates With Animal Behavior

The neural circuitry underlying fear and anxiety responses are well studied, in part because of the high degree of conservation between humans and model systems such as rodents (11). Behaviors such as fear conditioning, elevated plus maze, open field test, and light-dark box are robust tasks with face and predictive validity that have allowed for a dimensional examination of specific pathways, such as corticoamygdalar circuits (12) and the corticotropin-releasing factor/hypothalamic-pituitary-adrenal axis (13), in these processes. Several signaling molecules implicated in appetite regulation, such as estrogen (14), brain-derived neurotrophic factor (15), orexin (16), and endogenous opiates (17), also affect measures of fear and anxiety, suggesting the possibility of a shared neural substrate that may link appetite dysregulation with a vulnerability to fear and anxiety disorders.

POSITIVE VALENCE

Although disturbances within the negative valence system are frequently associated with the development of EDs, deficits within the positive valence system may be equally important for their manifestation. Constructs within this domain include aspects of appetitive behaviors and reward and habit learning that are core features of EDs.

Clinical Evidence

An episode of bingeing, defined as 1) eating an amount of food within a discrete period of time that most people would not eat under comparable conditions and 2) a sense of loss of control over the eating during the episode, is a key diagnostic feature of multiple EDs, including BN, binge eating disorder, and frequently AN binge/purge subtype. Several constructs within the positive valence domain relate to the "wanting" and "liking" of calorically dense foods observed during bingeing episodes (18). With regard to "wanting," reward valuation is the measure of the preference of one option (e.g., high-calorie food) versus another (e.g., low-calorie food), whereas effort valuation/willingness to work gauges the amount of effort an individual is willing to expend to obtain an objective. In contrast, "liking" refers to the hedonic enjoyment or pleasure obtained from consumption of the object. Both increased "wanting" and "liking" of calorically dense foods are associated with the binge eating trait of the Binge Eating Scale (19) indicating that both processes are relevant to understanding the neurobiology of EDs.

Conversely, it has long been debated if patients with AN-R have disturbances in appetite. Some researchers argued that the presence of food-related thoughts and behaviors such as cooking and food handling are evidence of hunger (20). In contrast, a study of patients with EDs using a multidimensional scaling method found that patients with EDs displayed a decreased preference for high-fat foods, and patients with AN-R showed the greatest degree of aversion (21). Using a visual analog scale, patients with EDs displayed reductions in the "wanting" and "liking" to eat measures of high-calorie food compared with control subjects (22). In a group of patients with AN-R, wanting of high-calorie food measured by analog rating was reduced more than liking before and after weight restoration (23). Using an open questionnaire method, food aversions were assessed in patients with AN and BN compared with control subjects. Patients in both ED groups displayed aversions to multiple food categories with aversion to the high-protein group (meat, fish, eggs, milk) being a distinguishing characteristic of AN and BN (24). Finally, patients with AN displayed increased ability to delay reward in a monetary reward task (25), a food-independent measure of reward valuation, demonstrating that the deficits observed in patients with AN in the positive valence system are not restricted to food-related rewards.

More recently, functional and structural imaging studies mapped these deficits in processing of taste stimuli to specific neural circuits. Wagner *et al.* (26) found that pleasantness of sucrose administration correlated with activation of the insular cortex in control subjects but was diminished in patients with AN-R. A similarly designed study found that patients with AN-R displayed blunted activation of the anterior insula in response to sucrose administration, whereas patients with BN exhibited significantly enhanced activation, suggesting that disruptions in nutrient sensing by taste centers of the brain may underlie the opposing behavioral phenotypes observed in these two populations (27). Finally, a structural study reported that increased volume of the gyrus rectus within the medial orbitofrontal cortex correlated with rating of taste pleasantness (reward value) in patients with AN-R and patients with BN, suggesting a shared neural substrate may mediate dysfunction in both disorders (28).

Although alterations in behaviors related to food rewards may intuitively be the most relevant to EDs, several studies identified dysfunction in other constructs within the positive valence system in patients with EDs, including reward learning and habit. Behaviors relevant to the development of EDs within these constructs range from impaired interpretation of positive and negative feedback to behavioral rigidity and perseveration (29,30). Wagner *et al.* (31) observed reduced activation of the anterior ventral striatum in response to positive and negative events in a monetary reward task in recovered patients with AN compared with control women. The authors concluded that striatal dysfunction in patients with AN may lead to difficulty distinguishing positive and negative feedback and impair their ability to process appropriately the valence of emotional stimuli. Fladung *et al.* (32)