Review


Michael Lutter, Anna E. Croghan, and Huxing Cui

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

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
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 binging, 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 binging 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)
also assessed brain activity in patients with AN and control subjects after exposing them to images of underweight, normal-weight, and overweight individuals. Control subjects preferred viewing normal-weight images, which was associated with enhanced activation of their ventral striatum. By contrast, patients with AN demonstrated the opposite response, with an increased preference for viewing underweight individuals associated with increased activation of the ventral striatum.

Researchers have long appreciated the association of AN and obsessive-compulsive disorder (OCD) because of the frequent comorbidity of the two disorders (33,34) and several features shared in common, including recurrent intrusive thoughts, excessive need for structure and order, ritualistic behaviors, rigid and inflexible coping strategies, and increased sensitivity to error detection (30). Converging methodologies indicate that dysfunction within the habit construct may underlie the shared features of OCD and AN. Roberts et al. (35) used a composite score of set-shifting ability as a measure of cognitive-behavioral flexibility to demonstrate that patients with EDs have poor set-shifting ability (AN-R, 22.9%; AN binge/purge subtype, 45.5%; BN, 36.7%) compared with healthy controls (9.1%). Finally, patients with poor set-shifting ability displayed a longer duration of illness (10.44 years) compared with patients with intact set-shifting ability (6.96 years), suggesting that behavioral flexibility is an important contributor in recovery from the illness. Zastrow et al. (36) used a target-detection task to examine cognitive-behavioral flexibility in patients with AN. They found that patients with AN had higher error rates during behavioral-response shifting, which corresponded with hypoactivity in several brain regions, including the anterior cingulate cortex, ventral striatum, and thalamus. Together these studies suggest that dysfunction within the habit construct may underlie the shared neural substrate in the development of OCD and AN.

**RDoC Correlates with Animal Behavior**

Several well-established models of animal behavior correspond to constructs within the positive valence system. In particular, models of “wanting” of palatable diet are already commonly employed within the fields of substance abuse research and diet-induced obesity. The diet preference test and macronutrient selection test are used to measure preference for foods of different calorie content (37). A model of binge eating has been developed in which intermittent access to a high-energy diet leads to binge eating–like bouts when the diet is present in rats (38) and mice (39). This model does not require previous caloric restriction to trigger bouts of binge eating, modeling aspects of human EDs in which the binge frequently occurs in the absence of hunger (38,39). Estrogen signaling in brain reward circuits appears to suppress these “bingeing” episodes in mice (40) providing construct validity for the model because the frequency of binge eating episodes in humans increases during midluteal and premenstrual phases when estradiol levels decrease and progesterone levels increase (41). Conditioned place preference for a high-fat diet is a complementary food preference that includes a component of associative learning (42). Operant responding or self-administration of high-sucrose or high-fat pellets is the best method for assessing willingness to work for palatable food because the mice must exert increasing effort to obtain successive pellets (42,43). Additionally, acquisition of operant responding can be used to assess reward learning (44). Methods to assess “liking” of food are more difficult in mice because of the subjective nature of the experience. However, Berridge (45) developed a method observing reactions to pleasant (tongue protrusion) versus bitter (mouth gape) tastes that are ethologically conserved across species from human newborn infants to orangutans and rats.

Several measures of behavioral perseveration have been adapted to study features of diseases such as OCD and autism. Compulsive grooming was used as an antidepressant-responsive task relevant to the study of corticostriatal dysfunction and OCD (46,47). Energy homeostasis pathways in the brain were shown to modulate the SAPAP3-null model of compulsive grooming (48), perhaps identifying a link between appetite dysregulation and behavioral compulsivity relevant to the pathophysiology of EDs. Behavioral rigidity or preservation was also evaluated by changing the spatial location of the reinforcer in the Morris water maze or T-maze and measuring the time to learn the new location (49).

**COGNITIVE SYSTEMS**

Deficits in cognitive functioning are frequently observed in patients with EDs. Most studies compare cognitive functioning in patients during the acute phase of the illness and after recovery, although it is often difficult to distinguish an underlying cognitive impairment from the sequelae of chronic malnutrition. In this section, we discuss selected cognitive deficits reported in patients with EDs with a particular focus on constructs that translate well in rodent models.

**Clinical Evidence**

Several studies reported impairments in attentional processes in patients with AN, including reduced psychomotor speed and the power of attention measure on the Cognitive Drug Research battery (50). Likewise, patients with BN exhibited reduced psychomotor speed (51) and more inattentiveness than healthy control subjects in the Cognitive Drug Research battery (50), which may contribute to the higher rates of comorbid attention-deficit disorder and impulsivity seen with this diagnosis (51,52). Decreased attentiveness is associated with greater severity of ED symptoms (52). Although patients with either AN or BN seem to display reduced levels of sustained attention/vigilance, both groups have been reported to display increased attention to words associated with food and body weight and shape (51). Several studies also reported impairments in executive functioning, such as planning, problem solving, and set shifting, in patients with EDs (53–57). This finding suggests that poor cognitive flexibility may contribute to the behavioral rigidity observed in patients with EDs and promote maintenance of the illness. Finally, some studies found cognitive impairments in other constructs, including verbal learning and fluency, visuospatial ability, and speed of information processing (58), although others reported highly variable findings (51).
RDoC Correlates with Animal Behavior

Several measures of impulsivity or response inhibition have been validated for use in rodents, including the go/no-go task, the delay discounting task, and the stop task (59,60). The 5-choice serial reaction time task is another, more intensive task that can be modified to measure aspects of visual attention and inhibitory control (61). Reversal learning is a measure with relevance to set-shifting ability in which the rodent must suppress a learned response while engaging actively in a response to obtain reward (62). Reversal learning can be applied to food-rewarded tasks, such as instrumental responding (62), and non–food-rewarded tasks, such as maze learning (62). Finally, the attentional set-shifting task requires the rodent to discriminate among various factors (e.g., smell, digging medium, texture) during several trials. Reversal learning can be measured by changing the value of a stimulus within the same domain (intradimensional) or across a new domain (extradimensional) (63). Extradimensional shifts are more difficult to learn and generally require more trials.

SOCIAL PROCESSES

Problems with social functioning commonly contribute to the onset and maintenance of EDs (64,65), whereas improvement in social relationships is frequently cited as a key factor in recovery (66,67). The social processes domain encompasses multiple aspects of social functioning ranging from facial and nonfacial communication to attachment and self-knowledge. We outline findings with the largest effect sizes and the greatest relevance to rodent models of neuropsychiatric illness. For a systematic review of social process dysfunction in EDs, the reader is directed to a recent excellent review by Caglar-Nazali et al. (68).

Clinical Evidence

Multiple neuropsychological studies demonstrate that patients with AN and BN report high degrees of insecure attachment and separation anxiety (69–73). This insecure sense of attachment is manifested as decreased parental bonding as well as increased experience of parental overprotection (68). Within the domain of social communication, the most prominent deficits occurred in the constructs of production and reception of facial communication. Several studies using tasks such as the emotion recognition task reported impairment in reception of facial communications in patients with AN (74–79). In contrast, the results were mixed with BN with some studies finding superior recognition and others finding impairments (74,76). Additionally, patients with AN displayed reduced expression of facial emotion and increased avoidance of facial emotion compared with healthy control subjects (68,80). Two subconstructs within perception and understanding of self, agency and self-knowledge, consistently showed significant differences in patients with EDs. Agency, defined as “the ability to recognize one’s self as the agent of one’s actions and thoughts, including recognition of one’s own body/body parts,” was reduced in patients with EDs in several studies (81–85). Several functional imaging studies linked impairments in interoception, or the sensitivity to stimuli originating inside of the body, in subjects with EDs to altered activation of the insular cortex (27,86–88). Within the subconstruct of self-knowledge, patients with EDs exhibited dramatically increased levels of self-negativity (89) and reduced emotional awareness (alexithymia) (90). Through use of self-evaluation assessments, such as the Submissive Behavior Scale, patients with EDs reported feeling higher levels of shame and social inferiority than control subjects (91–97).

RDoC Correlates with Animal Behavior

Although new to the field of ED research, rodent models of social behavior have been used widely in the study of monogenic models of autism (98). Given the complexity of human social functioning, the utility of rodent models in the study of human social dysfunction has been called into question (99). Conceding that certain aspects of human social functioning, such as agency and alexithymia, are impossible to test in mice, several tasks may be useful for assessing the neurobiological basis of impaired social functioning patients with EDs. The social interaction test, a measure of direct physical interaction, is a simple and high-throughput task in which social deficits manifest as a decreased preference for a social target versus inanimate object (100). More complex tasks also can be employed to tease out more subtle behavioral differences (101–103). Mother-infant attachment can be assessed with the homing test, in which the researcher measures the preference of an isolated pup for home cage bedding versus bedding from another cage (49,104). Infant ultrasonic vocalizations have been used as a measure of communication and attachment because pups vocalize on isolation from the mother (49,98). Different versions of the social preference test can assess aspects of social interest (preference of social target over nonsocial target) and social novelty (preference of unfamiliar social target over familiar target). The resident-intruder paradigm was used to assess social dominance and subordination in mice (100,104), although the task was not well suited for the study of female rodents, which would be of primary interest to the study of EDs. Finally, given the temporal association that anxiety and social deficits often precede the onset of ED symptoms, it might be of interest to induce social anxiety experimentally in rodents and examine the impact on food intake.

AROUSAL AND REGULATORY SYSTEMS

Given the central role of feeding in multiple physiologic processes, patients with EDs frequently exhibit dysregulation of functions within this domain. In particular, disruptions in sleep and circadian rhythms are common clinical manifestations of EDs. However, given the importance of food intake to regulation of circadian activity and sleep, it can often be difficult to disentangle if the disturbance contributes to the development of the ED or is an epiphenomenon.

Clinical Evidence

Increased locomotor activity is one of the most prominent features of AN (105). This increased activity is also associated with features including increased arousal and decreased sensing of fatigue that are unique to patients with EDs and not typically associated with semistarvation.
It is hoped that advances in human genetics, such as the recent identification of mutations within the estrogen-related receptor alpha, histone deacetylase 4, and epoxide hydrolase 2 genes (117,118) that predispose to the development of EDs, coupled with neuro-psychology, functional imaging, and basic science studies in model systems will accelerate our understanding of the neuro-biological basis of EDs.

ACKNOWLEDGMENTS AND DISCLOSURES

The authors report no biomedical financial interests or potential conflicts of interest. This work was supported by the Dylan Tauber Researcher Award from the Brain and Behavior Foundation (ML) and the Klarman Family Foundation Grants Program in Eating Disorder Research (ML).

REFERENCES


Table 1. Proposed Battery of Animal Tests

<table>
<thead>
<tr>
<th>Domain</th>
<th>Construct</th>
<th>Initial Tasks</th>
<th>Additional Tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Valence</td>
<td>Potential threat</td>
<td>Elevated plus maze</td>
<td>Light-dark box, open field</td>
</tr>
<tr>
<td>Positive Valence</td>
<td>Willingness to work</td>
<td>Operant responding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preference-based decision making</td>
<td>Diet preference test</td>
<td>Food conditioned place preference</td>
</tr>
<tr>
<td></td>
<td>Initial response to reward</td>
<td>Binge-eating model</td>
<td>Tongue protrusion</td>
</tr>
<tr>
<td></td>
<td>Reward learning/habit</td>
<td>Acquisition of operant responding</td>
<td>Compulsive grooming</td>
</tr>
<tr>
<td>Cognitive Systems</td>
<td>Attention/impulsivity</td>
<td>Go/no-go</td>
<td>Delayed discounting, stop task, 5-choice serial reaction time task</td>
</tr>
<tr>
<td></td>
<td>Executive function</td>
<td>Reversal learning</td>
<td>Attentional set-shifting task</td>
</tr>
<tr>
<td>Systems for Social Processes</td>
<td>Attachment/affiliation</td>
<td>Social interaction, homing test</td>
<td>Ultrasonic vocalizations, social interest test, social novelty test</td>
</tr>
<tr>
<td></td>
<td>Social dominance</td>
<td>Resident-intruder paradigm</td>
<td></td>
</tr>
<tr>
<td>Arousal and Regulatory Systems</td>
<td>Arousal</td>
<td>Activity-based anorexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Circadian rhythms</td>
<td>Wheeling running rhythms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep</td>
<td>EEG</td>
<td></td>
</tr>
</tbody>
</table>

EEG, electroencephalography.

(105). These features led to the development of a concept termed “drive for activity” that was proposed as a core pathologic feature of AN (106). Multiple studies analyzed the circadian expression patterns of hormones in the periphery. Investigations of melatonin, the most studied circadian hormone, yielded mixed results. Most studies reported a normal nocturnal peak but were inconsistent with regard to an overall increase, decrease, or no change in total melatonin levels (107–109). These studies were complicated by the fact that melatonin levels are affected by acute nutritional state, hemococoncentration, and comorbid depression among other factors (108,109). A separate study of multiple hormones with nocturnal peaks found a blunting of growth hormone, luteinizing hormone, follicle-stimulating hormone, and prolactin levels in patients with AN with elevations reported in insulin and cortisol levels (110). Finally, sleep studies in patients with EDs most frequently found an overall fragmentation of sleep and decrease in slow wave sleep in underweight patients with AN that improved with weight restoration (111,112).

RDoC Correlates with Animal Behavior

Studies of regulatory systems are among the best conserved and robust experimental rodent models. The activity-based anorexia model is a particularly well-studied task within the field of ED research (113–115). In this model, rodents are given access to a running wheel paired with either ad libitum access to food or a restricted feeding schedule. The combination of restricted feeding and access to the running wheel drives hyperactivity and weight loss with face and predictive validity to the “drive for activity” observed in AN. Finally, methods for studying sleep are also well established (116).

CONCLUSIONS

The clinical focus in patients with EDs is often on the dramatic disruptions in eating patterns observed. However, dysfunctions across multiple domains with the RDoC matrix have been reported allowing for a comprehensive battery of tests for use in translational neuroscience studies. One potential battery of tests is presented in Table 1. It is hoped that advances in human genetics, such as the recent identification of mutations within the estrogen-related receptor alpha, histone deacetylase 4, and epoxide hydrolase 2 genes (117,118) that predispose to the development of EDs, coupled with neuro-psychology, functional imaging, and basic science studies in model systems will accelerate our understanding of the neuro-biological basis of EDs.


Animal Models of Eating Disorders


