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EATING DISORDERS (C GRILO, SECTION EDITOR)

Recent Advances in Neuroimaging to Model Eating Disorder Neurobiology

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Abstract The eating disorders (EDs) anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) are severe psychiatric disorders with high mortality. There are many symptoms, such as food restriction, episodic binge eating, purging, or excessive exercise that are either overlapping or lie on opposite ends of a scale or spectrum across those disorders. Identifying how specific ED behaviors are linked to particular neurobiological mechanisms could help better categorize ED subgroups and develop specific treatments. This review provides support from recent brain imaging research that brain structure and function measures can be linked to disorder-specific biological or behavioral variables, which may help distinguish ED subgroups, or find commonalities between them. Brain structure and function may therefore be suitable research targets to further study the relationship between dimensions of behavior and brain function relevant to EDs and beyond the categorical AN, BN, and BED distinctions.

Keywords Eating disorder · Anorexia nervosa · RDoC · Dimensional · Imaging · Neurobiology

Introduction

The eating disorders (EDs) anorexia nervosa (AN) and bulimia nervosa (BN) are severe psychiatric disorders of unknown etiology. EDs usually begin during adolescence and occur most commonly in females [1]. The diagnostic criteria for AN include restriction of energy intake relative to requirements leading to significantly low body weight, intense fear of gaining weight, and a disturbance in the way in which one's body weight or shape is experienced. The previous criterion of loss of menses was dropped in the new edition of the diagnostic and statistical manual for mental disorders (DSM-5). A restricting type, marked by food restriction and commonly over-exercising, has been distinguished from a binge eating/purging type, where afflicted individuals regularly eat large amounts of food in a relatively short period of time ("binge eating"), or engage in behaviors to counteract weight gain, such as self-induced vomiting or use of laxatives or diuretics ("purging"). BN individuals are usually at normal weight, and engage in recurrent binge eating and purging behavior at least once a week for at least 3 months. Individuals with ED symptoms who did not meet full criteria for AN or BN were in the past classified as ED not otherwise specified (NOS). A large part of individuals with ED NOS would now be diagnosed with "binge eating disorder" (BED), which is part of the ED diagnostic categories in DSM-5. In DSM-5, patients who do not meet the full AN, BN, or BED criteria could be diagnosed with "other specified or unspecified feeding or eating disorder." Importantly, research has shown that subthreshold EDs are a "way station" between full ED syndromes and stages of recovery [2]. It is therefore possible that (a) state of illness and severity of ED symptoms are associated with degrees of alterations of brain function [3], and (b) different ED characteristics could be related to distinct neurobiological abnormalities that contribute to overlap in symptoms across EDs. This has not been specifically explored before. Dimensional research in ED populations based on specific ED behaviors across traditional diagnostic categories could significantly advance our ability to connect specific ED behaviors with brain mechanisms and develop new treatments based on this improved

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neurobiological understanding. The complex interactions between state and possibly trait psychosocial and neurobiological abnormalities in EDs have further limited the development of neuroscience-based models of disease and treatments [3, 4], and models are needed that include all those factors to better describe ED subgroups and underlying psychopathology.

Here, I will review studies from the recent past that support the notion that a dimensional research approach across EDs may be beneficial to identify specific neurobiological targets that characterize ED individuals; in addition, the article will emphasize that state dependent factors will need to be taken more into account to be able to acquire more consistent and ED-relevant brain imaging results. Lastly, the review will highlight the need for building complex models of disease to better understand the prognosis and potentially therapeutic needs of ED patients depending on the state of illness.

Research on Brain Volume

Recent advances in the field of brain research using neuroscience-based imaging paradigms have made great progress with respect to linking brain regions and circuits to emotional and cognitive processes that may be altered in psychiatric illness including eating disorders, for instance, pathways that are involved in processing of fear including fast activation of the amygdala in response to potentially dangerous stimuli followed by conscious appraisal in the frontal cortex [5]. Furthermore, a circuitry between the ventrolateral prefrontal and cingulate cortex and hippocampus and amygdala has been identified in emotion processing and emotion regulation relevant to the study of mood disorders [6, 7]. The insula as primary taste cortex receives afferent taste stimulation and stimulates the ventral striatum to modulate food approach, which is further aided by or "fine tuned" by input from the orbitofrontal cortex that computes quality and value of reward stimuli including food [8–10]. Cognitive flexibility is largely processed in the frontal cortical regions [11].

A recent systematic review of structural studies in EDs [12••] suggested variably reduced gray matter volume in anorexia nervosa in the insula, frontal operculum, occipital, medial temporal, or cingulate cortex, while one recent study found *increased* gray matter volume in the dorsolateral prefrontal cortex [13–16]. Others found global reductions in gray matter volume across the cerebellum, temporal, frontal, and occipital lobes, including a study suggesting that this measure may correlate with illness duration [17]. A recent study in AN and BN indicated less gray matter in AN compared to both healthy controls and BN in the cerebellum, temporal, frontal, and occipital cortex, but reduced caudate volume in BN compared to AN and controls; furthermore, that study also found bilaterally *increased* somatosensory cortex volume in AN and BN groups [18]. One study in BN suggested *increased* localized gray matter volume in the orbitofrontal cortex and striatum [12••]. A new study that investigated cortical thickness in BN found widespread brain surface volume *reductions* in the frontal and temporo-parietal areas [19].

Those studies did not find a common theme with respect to functionally important regions that could specifically drive ED behavior [12••], although it appears that the underweight and malnourished state of AN is associated with smaller gray and white matter volume. Only some studies corrected for age or overall brain volumes, some studies distinguished restricting from binge eating/purging anorexia nervosa while others did not, and the effects of comorbid diagnoses or medication were often not taken into account [12••]. Furthermore, the effects of acute dehydration and starvation [20] as well as excessive exercise [21] most likely have significant confounding effects that may not be directly related to the underlying ED-specific pathophysiology. Importantly, the global effects of malnutrition may obscure particularly in studies that showed widespread alterations across large cortical regions brain pathology that drives ED behavior.

To avoid such confounds, we recently studied a sample of currently ill ED individuals in a nutritionally highly controlled environment. In addition, we controlled for age, depression, anxiety, medication use, and brain volume. In that study, brain gray matter volume could identify shared abnormalities among ED groups but also distinguish AN from BN individuals [22•]. The sample consisted of individuals with restricting type currently ill (n=19) or recovered AN (n=24), ill BN (n=19) and healthy control women (n=24) showed in the three ED groups increased gray matter volume of the medial orbitofrontal cortex gyrus rectus compared to controls. In addition, ill and recovered AN had increased right, while BN individuals had increased left insula gray matter volumes compared to controls, while dorsal striatum volumes were reduced in BN and recovered AN, and predicted sensitivity to reward in all ED groups. In a follow up study in *adolescents* with AN (n=19) and controls (n=22), with similar methods, AN adolescents showed increased left orbitofrontal and right insular gray matter volumes similarly to AN adults and compared to controls [23••]. In contrast, in adults with *obesity*, a condition typically associated with ongoing excessive food intake without significant periods of food restriction or compensatory behaviors to prevent weight gain, we found *reduced* orbitofrontal cortex gyrus rectus volume [24] using the same methods as in the studies described above in AN and BN.

There are several important new insights that can be gained from those studies. First, altered orbitofrontal cortex could contribute to food avoidance in EDs [25]. The orbitofrontal cortex processes how much food of a certain kind we have eaten and when to stop that type of food, while still being interested in other types of food (for instance not being interested in more meat after having eaten a steak, yet still being interested in a desert) [26]. Thus, larger orbitofrontal cortex

volume in AN and BN could send a satiety signal earlier than maybe physiologically needed and contribute to food restriction in those disorders. In obesity, a smaller volume could send such satiety signals too late or maybe with too little intensity, and thus insufficiently control food intake after a physiological need is satisfied. Binge eating/purging behaviors of BN individuals compared to the restricting type AN group in this sample could be driven by insula differences between the two disorders [27, 28]. The left insula receives information on gastric distention [29] and self-reported fullness [30], and it is possible that a disturbed processing of this gastric input could "enable" excessive eating during binges. On the other hand, the *right* anterior insula has been associated with self-recognition, the "abstract representation of oneself" [31] and interoceptive awareness [32], and a fixed perception of being fat while severely underweight in especially restricting type AN [33] could thus be related to increased right-sided anterior insula volume, maybe resulting in faulty information processing from the body's somatic perceptual input. Second, these studies suggest that when studying currently ill ED individuals, it is most likely imperative to control for nutritional state as well as comorbidity and medication use in order to be able to get more consistent results. This will help identify brain alterations that are important for relevant ED behavior as opposed to results that could be mostly related to quickly changing effects of starvation. And third, it is possible that increased orbitofrontal cortex volume is a neurobiological disease marker for AN and BN, while smaller orbitofrontal cortex volume is such a marker for obesity. Thus, orbitofrontal cortex volume could be a target for research along dimensions of body mass or chronic food intake patterns. Whether such alterations are premorbid traits that become functionally important in the context of other factors such as anxiety, food restriction, or overeating remains to be seen. Alternatively, they could be results from the extremes of eating behavior. However, this may be less likely, especially in the AN groups, as the increased orbitofrontal and insula volumes were already seen in adolescent AN who had a much lower illness duration compared to the adult sample.

A direction that we are now pursuing is to study brain structure of relatives of individuals with EDs to test whether we can identify any biological traits. The results of that study will help us identify whether the alterations we have found are potential biomarkers for EDs.

Brain Function and Taste-Reward Processing

There is a complex interplay between cognitive, emotional, and energy homeostasis maintaining mechanisms between brain and body that drives food intake [34]. A cognitive or cephalic phase that involves desire or craving, as well as a consummatory phase involving the hedonic experience have been distinguished. The neurotransmitter dopamine has been associated with "wanting" or the drive to approach a reward, while the opioid system processes "liking" or the hedonic experience during food consumption [35, 36]. Those processes are regulated by the brain reward system, integrating more basic metabolic hunger signals with higher-order processing of taste and cognitive-emotional factors that drive whether we approach or not approach food stimuli [37]. A network of brain regions regulates those processes. The insula is the primary taste cortex and central gateway to the dopaminergic basal ganglia and midbrain; to higher-order brain centers including the prefrontal and cingulate cortices that integrate cognition and emotions; the orbitofrontal cortex, which determines when to stop eating a type of food; and the amygdala that associate stimuli with emotional experience and that are thought to modulate dopamine circuitry in the midbrain and striatum [38–40].

The majority of functional studies that tested brain response to food stimuli used visual food cues. Several studies found lower activity in the parietal cortex, orbitofrontal cortex, and lateral prefrontal cortex compared to controls, while the medial prefrontal cortex tended to show increased activation [41]. The underlying mechanisms for those responses are uncertain but it was hypothesized that anxiety may trigger heightened medial prefrontal activation. Interestingly, one group found that serum oxytocin predicted lower brain response including the insula and orbitofrontal cortex in AN [42]. A few studies exist in BN that indicated reduced activation compared to controls in the temporal, parietal, and occipital lobe, but higher response compared to controls in the insula and lateral prefrontal cortex [41]. The literature on food cue stimulation and binge eating disorder is small. For instance, one study found increased medial prefrontal cortex activation in that group compared to controls [43], and another suggested that the activation pattern in the striatum could distinguish BED subjects from individuals with BN [44]. And a study that exposed individuals with high BMI to visual food cues indicated a positive correlation between BMI and brain response and binge eating symptoms [45], suggesting that potentially overweight or binge eating frequency alter brain function, although the opposite could also be true. Quite interestingly, a pilot investigation using a monetary incentive task suggested that ventral striatum activity during reward cue anticipation, and activation in the medial prefrontal cortex during reward outcome predicted inversely binge eating abstinence after treatment [46]. However, it is uncertain yet whether monetary reward and food reward stimuli elicit similar responses in ED groups.

Taste reward using actual taste stimuli has been studied in a variety of studies in EDs. Some studies used basic taste stimuli such as sugars; others used more complex tastes such as milkshakes with added flavors. The less complex and less appetitive stimuli may be more suited to identify more basic

taste processing while the more complex and "real food" stimuli may activate also strongly cognitive and emotional response. In paradigms that applied sugars or aversive taste stimuli, individuals recovered from AN had reduced brain response to *repeated* but increased response to *randomly* applied taste stimuli [47•, 48•, 49]. In those studies, the insula, striatum, or orbitofrontal cortex response distinguished the groups. Importantly, those results in opposite directions suggest that unpredictable and predictable stimulus presentation activate differently circuits or neurotransmitter systems, when studying AN.

Application of the more complex stimulus chocolate milk one study found in restricting type AN in the right amygdala and left medial temporal gyrus greater activation compared to controls when hungry contrasted against the satiety state [50], which could indicate heightened vigilance and anxiety in that group as having the chocolate milk breaks the fasting and promotes weight gain. Another study that applied chocolate milkshake found that women with BN had a positive correlation between negative affect and activity in the putamen, caudate, and pallidum during milkshake anticipation [51]. It was hypothesized that negative affect may increase the reward value of food in BN but it may be more likely that negative affect became a conditioned response to palatable food as it is associated with weight gain. Those approaches could be further tested across the spectrum of EDs and tried to separate the more subconscious taste reward aspects from anxiety and conditioned emotional response.

From a pharmacological standpoint, the treatment development goal is to identify molecular targets that are associated with illness behavior and for which a medication can be used to improve that behavior. Such targets could be for instance serotonin or dopamine receptors that could be blocked or stimulated [52••]. The dopamine neurotransmitter system is of particular interest for ED research as it is involved in food reward processing [53]. Past research in AN when ill and after recovery indicated dopamine alterations [54–57], but we know little how such alterations may be clinically important.

The brain dopamine system has been well studied, and dopamine neuron activity can be modeled based on environmental stimuli and learning [53]. Dopamine neurons exhibit a phasic burst of activation in response to presentation of an unexpected rewarding stimulus (the primary, unconditioned reward stimulus US). After repeated presentation of an additional arbitrary conditioned stimulus (CS) preceding the US, the phasic activation of dopamine neurons transfers in time to the presentation of the CS. Thus, the CS elicits a conditioned dopamine response. This conditioned response is thought to reflect a *prediction* regarding *upcoming* rewards. As it is thought to be a prediction, such a prediction can be violated. If the CS (and therefore the conditioned dopamine response) is not followed by the expected reward (US), then there is a violation of the prediction, and as a consequence at the time of expected but omitted reward, there is a dip in dopamine tone. This relationship between CS and US is termed "prediction error," the difference between the value of the reward stimulus received and that predicted [58]. This model also takes into account experience from previous trials and includes an individual's learning rate.

The prediction error model was first validated in rodents [59] and later adapted for human brain imaging [60, 61], and a significant amount of research has focused on how this brain response can be related to internal perception and behavior. Studies found that those circuits are critically associated with providing signals regarding the presence and amplitude of rewards [53, 62]. Such signals facilitate reinforcement learning [63], and code the value of stimuli [64, 65], maybe even including metabolic values of food [66], which could be disturbed in ED individuals. The prediction error model provides a computational theoretical framework for reward learning that is based on brain dopamine response in the ventral tegmental area and anteroventral striatum and allows making inferences on in vivo brain dopamine function [67]. This dopamine signal is functionally important to learn from past experience and to drive approach rewards, including food based on prior exposure to reward stimuli [36]. In light of the suspected dopamine alterations in EDs and the relevance of dopamine to drive eating, this model could be a valuable tool to study dopamine function in EDs. Also important is that the dopamine system can be modulated by extremes of eating patterns. Food restriction has been associated with heightened brain reward activation [68–70], while overeating appears to downregulate those pathways [71, 72]. This suggested that disordered eating may be associated with abnormal brain reward and dopamine function, which could be trait abnormalities or a lasting effect from a particular eating behavior.

We applied the above-described prediction error task in 21 underweight, restricting-type AN (age M 22.5, SD 5.8 years), 19 obese without BED (age M 27.1, SD 6.7 years), and 23 healthy control women (age M 24.8, SD 5.6 years), using blood oxygen level-dependent (BOLD), functional magnetic resonance brain imaging (fMRI) [73•]. Subjects learned to associate different visual stimuli with sweet taste or receiving no taste stimulus. At times, this prediction was violated, that is after seeing the sugar solution predicting stimulus no taste followed, or the conditioned cue that predicting no taste stimulus the sweet taste was delivered. Results were controlled for medication use and comorbidity, and subjects were studied under tight nutritional control as described above. The dopamine prediction error model reward-learning signal

distinguished groups in the anteroventral striatum, insula, and prefrontal cortex with brain responses that were greater in the AN group, but lesser in the obese group, compared with controls. These results suggest that brain reward circuits are more responsive to food stimuli in AN, but less responsive in obese women, supporting in humans the possibility of altered prediction error response in the context of under- or overeating. We conducted a similar study in adults with BN [28]. In that group, we found reduced prediction error response in the insula, anteroventral striatum, and frontal cortex. In addition, higher binge/purge frequency predicted lower prediction error response, supporting that this construct may play a role in BN. BN has been associated with addiction disorders [74] due to the episodic and often compulsive binging on palatable foods. The same neural pathways that reinforce motivation to approach food are also activated in response to addictive drugs [75]. This has lead to the hypothesis that prone individuals could get "addicted" to food, including increased tolerance as well as reduction of dysphoria, and such behaviors could be related to altered reward processing [76, 77]. A possible underpinning of the reduced prediction error response could be that repeated binge eating downregulates dopamine neuron activity somewhat similar as in obesity, but not to the same degree.

In summary, prediction error brain response is on opposite ends between AN, BN, and obese groups and promises to be an excellent construct to model brain reward function in EDs in a dimensional approach. This could capture brain response on a trajectory dependent on type or severity of ED-related behavior. Aside from BMI, food restriction, and frequency of binge/purge episodes, behaviors such as sensitivity to punishment and reward [28, 78] as well as emotion regulation [79, 80] are altered in EDs and are promising targets for investigation to test whether they relate to biological correlates in the brain [81–84]. Also very much needed are studies that include individuals with BED, as we have almost no information on brain function in this population. A hypothesis could be that their prediction error response is even lower compared to obese without BED.

With respect to clinical utility, we are still not able to use those techniques as tools in treatment [85]; however, we are currently exploring the predictive value of brain function on treatment outcome. At this point, it seems as if reward prediction error response predicts early weight gain in treatment but this needs further study (unpublished data).

Dimensional Research and Complex Model Building

Most groundbreaking pharmacological discoveries have been made by serendipity, which may be due to the fact that the brain is more complex than other organs in the human body [86]. As Insel and others pointed out, "the field needs to focus on clinically meaningful differences between relevant clinical populations, rather than hypothesis-rejection versus normal controls," which is an important underpinning of NIMH's Research Domain Criteria Project (RDoC) [87••]. The goal of RDoC is to define basic dimensions of functioning that have been validated in basic research (such as fear circuitry, valence systems), relate those to psychiatric disease, and then study those dimension across multiple "units of analysis," such as behavior, physiology, brain circuits, molecules, and genes [88]. Identifying such underlying biological constructs that drive pathologic behavior would help identify biological markers that could be common across or distinguish disorders [89]. In those models, there can be so called bridge symptoms identified that go across diagnostic boundaries and that could help identify biological or genetic overlap between disorders [90]. Figure 1 describes how research in EDs might be able to apply those concepts.

There are five domains in the RDoC matrix: Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal/Regulatory Systems [88]. This matrix contains columns that specify *Units of Analysis* used to study the Constructs, and include genes, molecules, cells, circuits, physiology (e.g., heart rate or event-related potentials), behavior, and self-reports. The matrix also has a separate column to specify well-validated paradigms used in studying each construct [88]. Using the RDoC constructs, we may identify psychobiological dimensions relevant to EDs, such as reward- or anxiety-related circuits. The next step would then be to identify or develop behavioral tasks relevant to EDs that (a) measure those dimensions of behavior in humans, and (b) that are solidly associated with certain biological functions based on basic science research. The application of those tasks could then be used to tests specific hypotheses on neurotransmitter function in EDs. This would take us a step further from higher or lower activation strength in most of our functional studies, toward identifying molecular targets that could be altered in EDs in relation to specific behavior. Lastly, when such a target is identified, one could test whether a pharmacologic intervention can ameliorate the biological alteration as well as ED behavior. The above-described prediction error paradigm is one of the RDoC identified concepts and paradigms to test motivation to approach rewards as well as reward learning [88]. Our above-described functional data suggest individuals with AN have a heightened while BN and OB have a reduced response. Dopamine and serotonin receptors have been identified as molecular targets to study in the reward approach and learning constructs. In fact, a significant amount of brain imaging has identified altered dopamine and serotonin receptor alterations across EDs. Studies in EDs suggested lower cerebrospinal fluid (CSF), serotonin (5-HT), and dopamine (DA) metabolite levels, neurotransmitters involved in the regulation of eating, mood, and anxiety among other functions, but

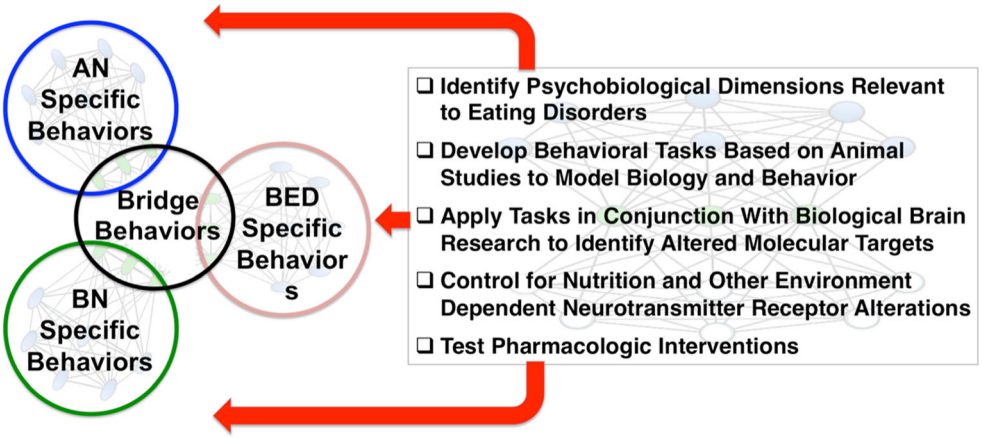

Fig. 1 A model on how to approach dimensional research in eating disorders. Such a strategy may help better characterize biologically subgroups of eating disorders as well as promote development of pharmacological strategies

higher 5-HT metabolite levels after recovery suggested that this could be a trait alteration [91]. More recent research in EDs using brain imaging implicated neurotransmitter receptors such as the 5-HT_{1A} receptor, 5-HT_{2A} receptor, and 5-HT transporter or DA D2/3 receptors, which predicted high anxiety and harm avoidance [92]. Other "units of investigation" in the context of reward anticipation and learning are brain circuits involving the orbitofrontal cortex and ventral striatum as described above in our prediction error studies, indicating that those regions indeed could be related to ED phenotype. Genes and cells have not been well described in relation to ED pathology and reward processing. However, studies have found elevated sensitivity to reward and punishment in EDs [28, 78]. In summary, there is a picture emerging of possibly heightened responsiveness in AN and low activation in BN and obesity in tasks that test the prediction error construct but this will need replication in larger samples. The receptor imaging studies are promising to provide molecular correlates but multimodal imaging studies that combine the various technologies are yet missing.

Another approach to further gain insight into ED pathophysiology and most importantly potential treatment options is to develop complex models of the disorders. This will help better define subtypes of EDs, and can also be used to model specific neurobiological alterations in an effort to inform pharmacological treatment decisions. Typically, research has used methods such as latent class analysis to model disorder subtypes, growth mixture analyses to study course of illness over time or factor analysis to model symptom dimensions [93]. The future of disease modeling though may be the development of more complex multidimensional models where all this information is collected into one model. Such models will also include state-related factors and comorbidity. For instance, the nutritional state has significant impact on brain neurobiology and neurotransmitters, including dopamine [68, 70, 71] and serotonin [94, 95] receptors, and this information will then go into the model to refine disorder-specific neurobiology. Those models that take into account also the state-dependent variations will better reflect real-world conditions and avoid type II errors, when studying neurobiological mechanisms underlying psychiatric disorders including EDs. Also potentially fruitful is to learn from addiction models for building models of brain pathology in ED research as obesity and BN have been associated with addictive disorders [96, 97], and there could be a neurobiological overlap between eating and addictive disorders and neurotransmitter function [98].

Conclusion

The neurobiology of the brain is still too complex and unexplored to be able to reliably use biological tests for making psychiatric, including ED-related, diagnoses; determine disorder severity; or identify novel molecular targets empirically to develop disorder-specific and more effective treatments [85, 87••, 99]. However, moving away from contrasting ill groups with controls toward a dimensional approach that identifies neurobiological underpinnings of psychiatric disease based on specific behavioral constructs may help eventually develop more accurate models of EDs and identify empirically more specific and effective biological treatments. This review described how research on brain structure as well as function, may help better model EDs. Importantly, careful subject assessment and accounting for comorbidity, medication use as well as acute nutritional status is critical to improve the consistency of results. In the future, with the additional integration of psychosocial factors and course descriptors of the various disorders, we hopefully will be able to model subtypes of EDs and develop disorder-specific biological interventions.

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Compliance with Ethics Guidelines

Conflict of Interest Guido K.W. Frank declares that he has no conflict of interest.

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