Open Access

OBM Neurobiology

Review

Dopaminergic Activity and Exercise Behavior in Anorexia Nervosa

Sasha Gorrell [1], Anne G.E. Collins [2], Daniel Le Grange [1, 3], Tony T. Yang [1]

1. Department of Psychiatry, UCSF Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, USA; E-Mails: sasha.gorrell@ucsf.edu; daniel.legrange@ucsf.edu; tony.yang@ucsf.edu
2. Department of Psychology and Helen Wills Neuroscience Institute, University of California, Berkeley, CA, USA; E-Mail: annecollins@berkeley.edu
3. Department of Psychiatry & Behavioral Neuroscience, The University of Chicago, Chicago, IL, USA (Emeritus)

* **Correspondence:** Sasha Gorrell; E-Mail: sasha.gorrell@ucsf.edu

Academic Editors: Sarah Maguire and Bart Ellenbroek

Special Issue: Neurobiological Underpinnings of Anorexia Nervosa

OBM Neurobiology
2020, volume 4, issue 1
doi:10.21926/obm.neurobiol.2001053

Received: December 03, 2019
Accepted: March 19, 2020
Published: March 23, 2020

Abstract

Driven exercise (i.e., the tendency to exercise in excess to influence weight/shape or regulate emotion) is difficult to manage in the context of anorexia nervosa, and is associated with poorer treatment outcomes, and psychological and medical severity. Driven exercise is observed in a considerable number of those diagnosed with anorexia nervosa; however, to date, this hallmark symptom remains poorly understood. Dopamine signaling is implicated in motivating and maintaining appetitive behavior among patients with eating disorders; but, much less is known about the role of dopamine signaling specific to the symptom of driven exercise. An improved understanding of this biobehavioral mechanism may inform the etiology of driven exercise in anorexia nervosa, with the potential to impact future research and treatment efforts. This review describes the role that dopamine serves in maintaining symptoms in the context of anorexia nervosa, and synthesizes current relevant evidence on

exercise in anorexia nervosa and related dopaminergic activity. Throughout, theoretical implications are discussed, along with critical directions for future research.

Keywords
Dopamine; anorexia nervosa; exercise; physical activity; eating disorders

1. Introduction

Anorexia nervosa (AN) is a deadly psychiatric disorder associated with significant medical morbidity and mortality [1]), marked distress and impairment [2], and considerable treatment costs [3]. Given these concerns, as well as the significant global health burden associated with AN [4], efforts have increasingly been made to better understand key biobehavioral mechanisms that influence the pathogenesis and maintenance of AN, including dopamine (DA) signaling [5]. DA has been studied extensively for its role in behavioral motivation processes across psychiatric disorders, including eating disorders (EDs) (e.g., [6, 7]). In the last four decades, increasing attention has been paid to the role of DA in impacting appetitive behavior in EDs (e.g., [8-10]). However, much less is known about the role that DA may play in specifically impacting onset and maintenance of *driven exercise*, a serious and understudied symptom of AN. In the following review, we begin by highlighting current theories of exercise behavior in AN. We then summarize the role that DA broadly serves in maintaining AN symptoms, including discussion of several possible theoretical and biological mechanisms of action. Finally, we synthesize current relevant research evidence specific to DA-related reward processes and driven exercise in AN. Throughout, theoretical implications are discussed, along with critical directions for future research.

2. Exercise Behavior in Anorexia Nervosa

Exercise has many benefits, but in the context of EDs, some individuals exercise in a driven manner to control weight or shape and/or to regulate affect [11, 12]. Up to 80% of those diagnosed with AN report such pathological exercise behaviors [13, 14] and, in the context of AN, driven exercise is associated with poorer treatment outcome [13], worse disorder prognosis [15], and suicidal behavior [16]. Driven exercise is also associated with elevations in obsessive-compulsive symptoms [11, 14], anxiety [17], and anhedonia [18]. Despite these concerning sequelae, this pernicious symptom in the context of EDs remains poorly understood.

Recent systematic review suggests that evaluation of physical activity in the context of EDs has largely focused on AN, with studies that have relied on self-report measures, or a combination of self- and objective report assessment [19, 20]. Of note, a recent study of outpatients found that adults with AN accurately self-report their high or moderate intensity activity, but underreport lighter activity (as measured by accelerometer) [21]. Many possible origins for physical activity in the context of AN have been proposed across the literature, including a conscious motivation to engage in physical activity for the purposes of optimizing weight loss (see [19] for review). Terms used to qualify this motivated and problematic exercise behavior have historically included “obligatory [22],” “overcommitted [23],” and “addictive [24],” among many others.

Another hypothesis for the origin of physical activity in the context of AN derives from a need to

stay warm when consistently at a low weight [25, 26], suggesting that exercise may not be under voluntary cognitive control of the patient [19]. Based upon rodent research, this view posits that physical activity is thermoregulatory in nature [27]. In rodent studies, the introduction of heat or increased ambient temperature has been shown to decrease activity, and either decrease weight loss [28], or facilitate weight gain [29]; preliminary evidence also suggests that ambient heat may decrease physical activity in human AN [25]. Despite suggestions that a translational approach between rodent and human models of AN should be emphasized [30, 31], expert clinical knowledge continues to center on potential psychosocial models of physical activity in human AN [32].

While several psychosocial models of driven exercise in EDs have been proposed [33], one leading model contends that driven exercise is reinforced by reward response to physical activity; this model defines the symptom as *exercise dependence* [34-39]. Conceptualizing driven exercise as exercise dependence likens it to other forms of behavioral addiction (e.g., substance misuse, gambling), which are robustly supported by literature confirming the role of DA in the maintenance of these behavior patterns [40]. Another leading model of driven exercise in EDs refers to this symptom as *compulsive exercise*, whereby repetitive behaviors may serve to reduce anxiety and are therefore reinforced by reductions in negative affect [11-13, 33]. Exercise dependence and compulsive exercise represent competing theoretical models for the maintenance of exercise behaviors in EDs, whereby these behaviors are either positively reinforced by rewarding experiences or negatively reinforced by way of reduction in negative affect, respectively. In both of these models, exercise behavior may become entrenched and habitual, despite adverse consequences (e.g., extreme weight loss; cardiac risk). While habit-related behavior is typically considered less DA-mediated, in both models, learning occurs via either positive or negative reinforcement, in behavioral reward processes that intricately involve DA signaling [41].

3. Dopamine: Mechanisms of Action in Anorexia Nervosa

Basic animal and human research supports the notion that physical activity is influenced by neurochemical pathways associated with reward [42, 43]. Specifically, ventral tegmental area (VTA) DA neurons serve a central role in motivated behavior and reward processing [44-47]. DA is thought to operate primarily through projections from the midbrain VTA through the mesolimbic pathway into the ventral striatum of the basal ganglia in the forebrain (i.e., nucleus accumbens [NAc]), as well as the mesocortical pathway to the prefrontal cortex. These dual pathways provide the initial groundwork for generating conditioned responses [48, 49], both in reinforcing tendencies to approach stimuli that are associated with primary rewards (e.g., food), and for maintaining habit strength once behaviors have been learned [46].

The role of DA in behavioral stimulus-reward associations includes two hypotheses relating to its mechanism of action: DA mediates (1) the pursuit of a reward based on attribution of incentive salience (i.e., a cognitive process that confers a *wanting* attribute), and (2) the 'stamping in' of anticipated future rewards (i.e., *learning/habit formation*) [44, 47, 50-52]. Of note, DA was historically thought to also mediate the hedonic impact of a reward (i.e., *liking*) [53], but the hypothesis that DA directly impacts the experience of pleasure is currently less well-supported [54]. In contrast, hypotheses related to incentive salience (i.e., *wanting*) and *learning/habit formation* are well-supported and differentiated in experimental testing [47]; however combined

research findings suggest that the actions of DA are neither necessary, nor sufficient to independently and fully explain *learning/habit formation* [5]. Instead, evidence suggests that habit formation may be less DA-dependent whereas DA *is* necessary for *wanting*, and sufficient to support incentive salience [55, 56]. Of note, and particularly when discussing exercise behavior, it is possible to want something in the absence of liking it. Further, for an individual who experiences reward value from driven exercise, an interaction likely occurs between these related processes (i.e., *wanting, learning/habit formation*); however, most evidence suggests that DA is exerting its influence through incentive salience attribution that leads associated rewards to become *wanted* [50].

Individuals with AN typically report wanting an alteration in their body weight or shape, or wanting to remain at their current weight, for fear of weight gain [57]. Other hallmark symptoms of AN include wanting to engage in dietary restriction, or behaviors that are compensatory for caloric intake (e.g., self-induced vomiting; exercise) [57]. Of note, wanted behaviors reported among those with AN reflect similarities with the compulsive nature of behavior in obsessive-compulsive disorder, as well as the dependent nature of behavior in substance use disorder [58]. In the context of AN, it can be difficult to determine whether the conferral of *wanting* is either a state- or trait-dysregulation, as changes in DA signaling among those who are acutely ill with AN may be normative responses to starvation [59]. Specifically, mesolimbic DA neurons have been implicated in the motivational aspects of feeding behavior [60], and physiologic factors resulting from sustained weight loss stimulate food intake [61]; however, this foraging impetus is in direct conflict with a high drive for thinness and body dissatisfaction in individuals with AN [8,62]. This conflict is made more complex by midbrain DA activity which may also serve to initially reward dieting [59].

To further explore the question of state- versus trait-level dysregulation in the DA system, some work examining patients with AN during and following treatment suggests that aberrations in DA signaling may contribute to the etiology of the disorder [9, 63]. For example, one study of adolescent females found that when acutely ill, reward response was elevated for unexpected reward receipt and omission, and prediction error in those with AN, relative to healthy controls [64]. Of note, prediction error and unexpected reward omission normalized with weight gain, but unexpected reward receipt remained significantly elevated, suggesting this may be a premorbid trait level difference specific to those who develop AN. There is consistent evidence that homovanilic acid, a major metabolite of DA, is decreased in the central nervous system among those with AN who are underweight and in the acute phase of illness [9, 65]. Further, a negative correlation has been demonstrated between striatal D2 receptor availability and body mass [66], and there is evidence that polymorphism of DA D2 receptor genes may be a susceptibility factor in the development of AN [67]. Another study found that individuals with AN who were weight restored showed increased D2/D3 receptor binding in the ventral striatum; these findings suggest that either upregulated D2/D3 receptor activity or decreased intrasynaptic DA concentration – or both, might exist even post-recovery [63]. While distinguishing changes that are due to trait from those that are related to state among those with AN has been a considerable confound in the research of this disorder [68], aberrations in the DA system following weight restoration suggest a trait level contribution to characteristic symptoms of AN.

3.1 DA Signaling and Neural Circuity

Accounting for differences in reward response, the ventral regions of the basal ganglia, including the VTA, play a pivotal role in reward and reinforcement, as well as in the development of addictive behaviors and habit formation [69]. Despite what is generally known about DA, the mesolimbic reward system, and projections to the NAc, a considerable gap in knowledge remains, specifically in understanding the precise circuitry that supports differential responding to appetitive versus aversive stimuli [70]. Recent work with a rodent model suggests that the encoding of either reward or aversion in the NAc is closely associated with a cell's anatomical location, supporting the notion that a 'hedonic hotspot' (i.e., area most responsible for pleasure associated with intrinsic rewards) is site-specific within the limbic area [54, 71, 72]. Specifically, DA in the ventromedial NAc was found to encode *salience* of a cue, whereas DA in the dorsal medial NAc and dorsal lateral NAc was found to encode the *value* signal. Further, DA signaling in the ventrolateral and central ventromedial NAc seemed to encode both value and salience [71]. These preliminary findings support a prior study where DA terminals in the ventromedial NAc were activated by aversive cues, whereas DA signaling to reward-predictive cues were associated with lateral subregions of the NAc [70]. To date, no studies have specifically examined these processes on a neurocircuit level, among patients with AN, arguably an important line of future inquiry.

3.2 Homeostatic Hormones and DA Signaling

In the context of appetitive behavior, hormones that regulate our homeostatic system can interact with, and override, DA signaling [60]. Specifically, leptin inhibits DA neurons whereas ghrelin activates them; the interaction of these hormones with DA signaling may contribute to disturbances in food-related cognitive processing evidenced among those with AN [73]. There is also some evidence that α-melanocyte-stimulating hormone, a hormone associated with appetite control, may modulate an exaggerated DA release in the lateral hypothalamus (LHA) during food anticipation and consumption [74]. Among rodents, elevation in LHA DA levels was inversely related to sucrose intake, suggesting that this DA release surrounding feeding behavior may be associated with hedonic satiety, and decrease motivation to obtain food [74].

As a general consequence of caloric restriction in AN, reduced leptin signaling in the VTA is posited to increase DA signaling, and drive increased physical activity [75]. This phenomenon has been demonstrated in an animal model, whereby leptin injections in the lateral ventricle and VTA of rodents under caloric restriction led to suppressed running wheel activity [75]. Ghrelin has also been shown to mediate the link between reward and physical activity in a rodent model. Specifically, local administration of ghrelin into the VTA increased both intracellular DA levels in the NAc, as well as greater locomotor activity; a similar effect was found with administration of ghrelin into the lateral dorsal tegmental area [76].

Among human patients with AN who report driven exercise, a negative correlation has been shown between increased activity and leptin levels [77, 78]. Notably, low leptin levels are characteristic of acute AN [79], which may be further reduced in the context of high activity [78]. Further investigation of associations between physical activity (i.e., daily step counts) with specific biological markers determined that ghrelin [80] and urinary cortisol [81] are positively associated with physical activity in inpatients with AN. Recent systematic review of differences in cortisol concentrations in adolescents with EDs, and specifically AN, determined that cortisol levels were

higher among those with AN compared to healthy controls, and a reduction in cortisol levels occurred after nutritional recovery [82]. Given that hypercortisolemia seems to be correlated with both self-reported compulsivity in exercise behavior and actual activity level among inpatients with AN [81], cortisol may be directly implicated in problematic exercise behavior. Taken together, via human and animal models, both food-related cognitive processing and also driven exercise behavior in AN may be affected by homeostatic biomarkers like ghrelin, leptin and cortisol, via their dynamic effects on the DA system [73].

3.3 Activity Based Anorexia (ABA)

Efforts to better understand the etiology of AN and the role of DA within it have included a widely used rodent model mimicking features of human AN: the activity-based anorexia (ABA) model [83]. The ABA model demonstrates that when rats are fed one meal a day and allowed to run on an activity wheel, they stop eating, run excessively, and expire due to starvation [84]. While the behavior of these animals is functionally similar to humans who self-starve, the ABA model cannot account for psychosocial components of ED (e.g., anxiety), that motivate driven exercise among humans. However, this rodent model includes aberrant reward response [85], anhedonia [86], and hippocampal processes that modulate anxiety [87], all of which align with psychosocial human models of compulsive exercise [12]. Both in the ABA model, as well as in research with patients diagnosed with AN, considerable attention has been devoted to the role that DA may play in the etiology and maintenance of this disorder [6].

Notably, while certain aspects of rodent models are difficult to reconcile in human experience, a recent comprehensive review of research on the ABA model determined that DA signaling and dysregulation in related reward circuitry was similar in rodents as in humans with AN [88]. Rodents with typical signs of ABA show elevations in D2 receptor expression in the caudate putamen [89]; while no research to date has specifically examined D2 receptors in patients with AN who report driven exercise, as noted above, dysregulated D2 receptor function has been generally recognized in patients with AN [67]. Treating rodents with olanzapine (i.e., an atypical antipsychotic that blocks DA and serotonin receptors) in an ABA study paradigm reduces wheel running activity [90]; another study reported that olanzapine, but not fluoxetine (i.e., selective serotonin reuptake inhibitor) was effective in reducing ABA among mice [91]. Together, these studies suggest that reducing activity via olanzapine treatment is likely due to its mechanism of action in altering DA, rather than serotonin signaling. Several ABA studies demonstrate that DA alteration, and specifically D2/D3 receptor antagonism, seem to have beneficial effects in rodents via increasing food intake and body weight, and reducing wheel running activity [90, 92, 93]. In adult human AN, the use of olanzapine in a clinical trial demonstrated modest weight gain, but no change in psychological symptoms; in particular, with regards to driven exercise behavior, in this trial there was no mitigation of obsessional symptoms or overconcern with gaining weight [94]. Retrospective chart review of adolescents with AN who were treated in a specialized ED program also found modest increases in weight among those who received aripiprazole, a partial D2 agonist, compared to those who had not; this study did not specifically include assessment of compulsivity, other psychological symptoms, or activity [95]. In summary, given preliminary findings that suggest olanzapine may not mitigate psychological aspects of AN but may assist in weight gain, studies that antagonize D2/D3 receptors warrant further substantiation in humans with AN [92], and particularly among those who report driven exercise.

4. Neurobiological Models of Symptom Maintenance in Anorexia Nervosa

To more broadly explain the mechanisms of action related to DA and the maintenance of AN symptoms, two neurobiologically informed theories involving striatal function have been proposed: a reward deficit model [96, 97], and a habit-related model [98, 99]. Described below, each of these models implicates DA activity, and together reflect a continuum in connectivity from reward- to habit-related brain regions that may help to explain how AN symptoms arise, and become maintained.

4.1 Reward-Deficit Model

The reward-deficit model (Figure 1) posits that there are broad deficits in the ventral frontostriatal network in AN [96,97], which may be evidenced in *under-response* to stimuli that typically yield a primary reward response (e.g., highly palatable food) [100], and *increased* response to disorder-salient cues (e.g., thinness) [101]. In the reward-deficit model of AN, altered DA functioning is thought to affect the reward valuation of stimuli, resulting in reduced response to disorder-*nonspecific* reward stimuli and increased response to disorder-*specific* stimuli.

When considering driven exercise behavior as a symptom of AN, relative to the reward-deficit model, an individual might endorse increased experience of positive affect in response to any form of exercise. In particular, they might report elation in anticipation of, or in response to, intense cardiovascular exercise. In turn, they may also report decreased enjoyment, irritability and discontent when asked to participate in a sedentary activity that others without driven exercise symptomology find rewarding (e.g., watching a movie in a preferred genre).

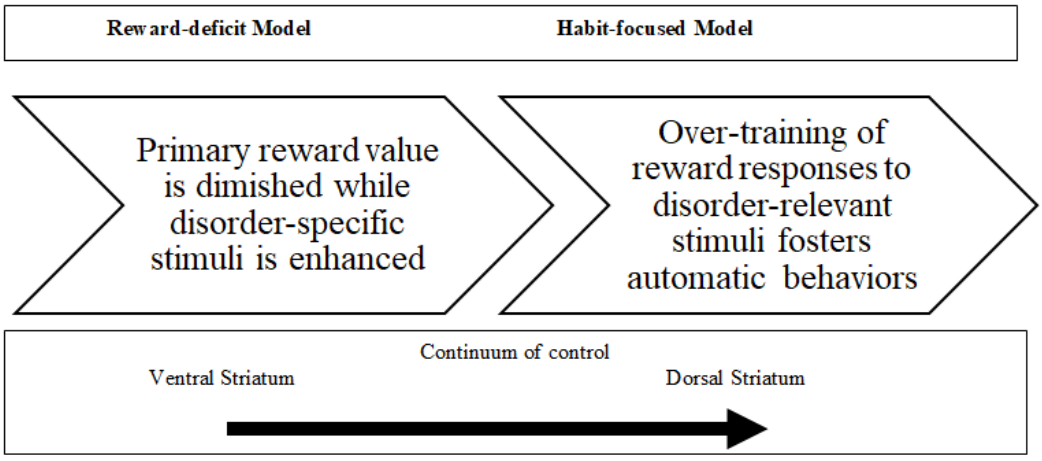

Figure 1 Reward-deficit and Habit-focused models of anorexia nervosa.

4.2 Habit-Centered Model

The habit-centered model (Figure 1) view initially aligns with the reward-deficit model in positing that by way of dysfunction in the ventral striatum, a symptom may be at first goal-directed, and motivated by incentive salience, particularly to disorder- specific cues (e.g., by *wanting* weight loss). However, this theory diverges from the reward-deficit model in postulating that over time, an AN symptom may shift to a stimulus-control response (i.e., habitual pattern),

and be maintained, despite negative consequences [102]. Over-training of reward responses to disorder-relevant stimuli is thought to eventually foster a compulsive reliance on rigid and automatic ED behaviors, independent of momentary DA responding [103]. On the neural level, this shift from behavior that is flexible to that which is relatively automatic might represent a transition from prefrontal to striatal control of behavior [104]. The habit-centered model thus posits that once an individual has fully developed AN (i.e., after initial stages of illness, when symptoms first develop), dysfunctions in the dorsal frontostriatal network may supercede those in more ventral, reward-oriented brain regions [99, 105].

When considering driven exercise behavior as a symptom of AN, relative to the habit-centered model, an individual might report that early on in their disorder, they participated in occasional runs, a few per week, which initially had felt pleasurable and in line with their desire to lose weight. Over time, the amount of running they report feeling obligated to perform on a daily basis may become regimented and obligatory, such that even when the weather is inclement and running outside is objectively miserable, completing a certain number of miles is considered non-negotiable.

In summary, the reward-deficit model suggests a lack of reward response *to non-disorder specific cues,* with no deficit noted when registering reward response to *disorder-relevant* cues. The habit-centered model essentially extends the reward-deficit model, reflecting what might transpire when intact reward responses (to disorder-relevant cues) become over-rehearsed and entrenched. In the context of AN, behaviors that result in instantaneous or expedient weight loss may be particularly rewarding when initially implemented. For example, when considered on a behavioral level, the reward-deficit model would support an explanation for how exercise may be initially rewarding for those with AN. At first, weight loss is tangibly witnessed soon after initiation of increased cardiovascular activity. Over time, negative consequences will likely arise from regular excessive exercise (e.g., injury; exercising at the sacrifice of other necessary or meaningful activities), and engagement in this behavior will be less rewarding (i.e., necessitating larger doses for the same effect; feeling compelled to exercise even in inclement weather). The habit-centered model would support why an individual might continue exercise over time, perhaps fearing that cessation of this learned 'habit' may lead to even worse perceived negative consequences, i.e., weight gain.

In efforts to better understand the synchrony of these two neural networks (i.e., reward and habit), recent work compared resting-state functional connectivity patterns between patients with AN and healthy controls [106]. Findings suggested that compared with healthy controls, those with AN demonstrated widespread dysconnectivity in areas implicated in habit learning, as well as poor functional coordination between key areas associated with reward processing; together, these findings lend credence to both the habit-centered and reward-deficit models of AN [106].

5. Biological Study of Exercise and Reward

5.1 Acutely Ill with Anorexia Nervosa

The limited research that has investigated neurobiological correlates of exercise in AN has identified differences in brain structure, including larger hippocampal volumes among females with AN who reported pretreatment excessive exercise [107].

Turning from structure to connectivity and function, study of reward and related learning in

human AN has focused on disorder-specific cues (e.g., food) and presumed rewards (e.g., money), with very little attention specifically paid to exercise behavior. In neuroimaging studies that have employed food-related image cues (i.e., provoking core AN symptoms), findings support an increase in medial pre-frontal cortex (PFC) activity [108, 109]. However, when completing tasks that challenge cognitive control, restrained eaters such as those with AN demonstrated reduced PFC activity, as compared to healthy controls [110]. In one study using functional magnetic resonance imaging (fMRI) and two affective go/no go tasks to probe inhibitory control, individuals with AN showed reduced response inhibition for food and non-food images in the putamen, as compared with healthy athlete and non-athlete controls [111]. It is notable that this study found hypoactivation in the putamen of those with AN, independent of stimulus category, particularly given prior work that has identified the implication of increased activity of the putamen in stimulus-response habit learning [112]. In contrast, exercise-specific cues (e.g., an image of an individual doing physical exercise) resulted in an exaggerated response in the PFC and cerebellum in AN patients, which the authors proposed reflects increased response inhibition and reward attributed to exercise-specific cues [111]. These results align with the reward-deficit model described above, which highlights altered DA functioning resulting in increased reward response to disorder-compatible stimuli [96, 97].

Other work probing reward response used eye-tracking to compare visual processing of active and non-active cues (i.e., pictures of individuals exercising or sedentary) among patients with AN, athlete controls, and non-athlete controls [113]. Those with AN and athlete controls demonstrated greater attentional engagement and increased pleasure ratings toward exercise-related stimuli, compared to non-athlete controls. Notably, self-report trait reward sensitivity and attentional orientation toward activity images were only evidenced among those with AN, suggesting that this patient population attributes more reward value to cues associated with exercise than non-clinical controls. A study using computational tasks also demonstrated evidence that relative to controls, those currently ill or recovered from AN were more motivated by rewards associated with exercise [114]. In this study, using a progressive ratio breakpoint task, those with AN were willing to expend more effort for access to a small amount of exercise, as compared to healthy controls. Taken together, both of these studies showed implicit and explicit evidence suggesting that those with AN (including those who are recovered) find exercise-related cues more rewarding. However, it is important to note that task- related activity may not generalize to real-world clinical situations. Further, it is quite possible that neural correlates of both goal-directed (i.e., reward-based) and compulsive (i.e., habit-based) behavior may simultaneously or alternately activate; thus, parsing these processes in the context of AN and exercise behavior is a line of inquiry that warrants future research.

5.2 Recovered from Anorexia Nervosa

In efforts to address the stability of reward attribution outside the context of acute illness, some work has used an acute phenylalanine/ tyrosine depletion (APTD) method to transiently decrease DA signaling among those recovered from AN (i.e., mimicking DA levels during acute illness). For example, one study found that those who were recovered from AN implicitly appraised underweight and exercise cues (as measured via eye-blink startle response to photos of thin and physically active female bodies) as more rewarding than did healthy controls [115]. Notably, these

effects were *not* demonstrated when recovered individuals were DA depleted, suggesting that this reward attribution process may, in part, be DA-dependent. These findings support the reward-deficit model, whereby positive incentive salience (i.e., *wanting*) appears to be mediated by DA processes, which contribute to AN symptom maintenance.

In contrast, in another study that used APTD methodology, among those who were recovered from AN, no differences were evidenced in willingness to work for exercise as a reward during a behavioral task paradigm [116]. Notably, this study found that decreasing DA does not reduce motivation to exercise in those recovered from AN, but does so among healthy controls; these findings suggest that in AN, driven exercise develops largely independent of DA-mediated reward processes and instead, becomes dependent on neurocircuitry that regulates compulsive, habit-informed behavior. These results support the aforementioned habit-focused model, and reflect potential vulnerability to disorder-specific behavioral patterns, even after weight restoration and recovery. While there is no current circuit model that comprehensively explains habit formation across disorders [117], a shift from the reward-deficit model to a habit centered model in AN may reflect the status of DA receptor density and affinity throughout the progression of the disorder. Specifically, intracellular DA deficits, and/or upregulated DA receptor activity resulting from sustained weight loss in AN may facilitate a shift from goal-directed behavior (i.e., reward) to stimulus control (i.e., habit) [98]. Evidence that upregulated D2/D3 receptor binding continues after weight restoration [63] may provide support for why some AN habits remain entrenched, with suspended time required for full recovery from this disorder [98].

Taken together, results from preliminary studies highlighted here that use DA-depletion methods appear to support aspects of both reward-deficit and habit-focused models of reward processing.

6. Discussion

In humans with AN, limited research has specifically attended to the mechanism of action that DA may have in motivating and maintaining the symptom of driven exercise. However, DA is broadly implicated in reward response, and intricately related to both the reward-related and habit-focused models of AN [96, 98]. In addition, study of hyperactivity in rodents has robustly supported the role of DA in impacting ABA, with consistent evidence that disrupting DA signaling can mitigate wheel running activity [90, 92, 93]. Of the studies highlighted in this review that focus specifically on exercise in the context of human AN, some work has compared those with AN with healthy controls, while other studies have downregulated DA function among those who were recovered from AN. In the former, evidence suggests increased neural response to exercise stimuli in the PFC and cerebellum [112], greater visual attention to exercise stimuli [113], and greater willingness to work for an exercise reward among those with AN [114], compared to healthy controls. While these findings broadly suggest that those with AN find exercise more rewarding, it remains uncertain *why* those with AN were more attended to, or willing to work for exercise. For example, rather than attributing more reward value to exercise, willingness to work may instead reflect a desire to avoid negative affect (e.g., low mood associated with current weight; guilt for eating; compulsivity in habitual exercise behavior). If exercise is motivated by avoidance of negative affect, the symptom is negatively reinforced, and akin to escape rather than reward. In either case, the use of an in-laboratory paradigm (i.e., pictures of female bodies exercising) to elicit

reward response may not replicate the lived experience and salience of exercise itself, including physiological responses to activity (e.g., increased heart rate, endocannabinoid release). Future work will benefit from studies of *in vivo* exercise in the context of AN, that can capture both the reward as well as negative reinforcement value of physical activity.

In studies that investigated DA and exercise among those recovered from AN, startle potentiation was elevated in response to exercise stimuli, but not under circumstances where DA was depleted (i.e., DA-state dependent) [115]. In contrast, those recovered from AN were still more motivated to work for exercise than healthy controls, even when DA was depleted (i.e., DA-independent) [116]. Taken together, these studies support the reward-deficit and habit-focused models of AN, respectively, but notably cannot fully explain whether vulnerability to hyperactivity is present before illness onset. Symptoms that are DA-independent may be important indicators of potential susceptibility towards illness-related routines even after recovery.

Given the medical acuity of AN, and the high prevalence of driven exercise in this patient population, it is critical that future work investigate biobehavioral mechanisms like DA function that serve to initiate and maintain this symptom. There are several critical lines of inquiry that may guide future research, including whether reward response specific to exercise stimuli is state (relative to acute illness) or trait (premorbid to the illness) dependent. While behavioral and neurobiological response to exercise cues is very likely a combination of both DA-mediated and other interactive mechanisms, efforts to accurately distinguish whether vulnerability for driven exercise pre-dates AN onset warrants further targeted study of DA receptor antagonism.

Secondly, future research design would ideally distinguish between reward response and negative reinforcement (i.e., escape from or avoidance of negative affect). In the psychosocial models of exercise detailed previously, exercise in the context of AN is posited to reflect either its rewarding properties (i.e., exercise dependence) [39] or alternatively, its anxiolytic properties (i.e., compulsive exercise) [12]. Study of neural response and DA signaling may help to reconcile which one of these models is more accurately reflective of either reward-or negatively-reinforced behavior, at different time points over the course of illness and recovery. Even within one model, i.e., the compulsive exercise model, positive and negative reinforcement may both be implicated. For example, compulsivity may create distress when one is not able to engage in intended exercise; subsequently, exercise may become negatively reinforcing in alleviating this distress. By the same token, compulsive exercise might also be positively reinforced, by factors such as mood improvement, or praise from others in regards to improved fitness. Considered together, the degree to which positive and/or negatively-reinforced behavior is implicated in driven exercise behavior, and the degree to which this learning is DA-dependent, warrants further inquiry.

Finally, the current (albeit minimal) research on reward and exercise in AN, appears to support proposed neurobiological models of human AN (i.e., reward deficit and habit-focused models) [30, 31]. However, while some appetitive AN symptoms are posited to be at first be reward-related and then shift to being more habit-controlled, it remains unclear if this neurocircuitry shift also happens for exercise behavior, and if so, when it may occur during the course of illness. While some parallels between ABA and human AN have drawn criticism, DA signaling and the reward systems are similar across species, with compelling evidence that D2/D3 receptor antagonism may decrease physical activity [92, 93]. These findings suggest that further investigation of DA signaling, and receptor antagonism specifically related to exercise behavior among humans with AN is warranted.

7. Summary and Conclusions

Limited research has specifically attended to the mechanism of action that DA may have in motivating and maintaining the symptom of driven exercise in the context of AN. Preliminary evidence suggests increased reward response to exercise stimuli in laboratory paradigms among those acutely ill with AN, compared to healthy controls. Among those recovered from AN, mixed findings indicate that response to exercise cues are both DA- mediated, potentially DA-independent, as well as premorbid to illness onset. Future research is critical to improving understanding of the biobehavioral mechanisms that maintain exercise behavior in AN, with specific lines of inquiry in DA-related reward processing.

Author Contributions

SG drafted the manuscript. All authors contributed and provided edits to the final manuscript draft.

Funding

Dr. Gorrell is supported by the National Institutes of Health (T32 grant MH0118261-33).

Competing Interests

The authors have declared that no competing interests exist.

References

1. Steinhausen HC. Outcome of eating disorders. Child Adolesc Psychiatr Clin N Am. 2009; 18: 225-242.
2. Swanson SA. Prevalence and correlates of eating disorders in adolescents: Results from the national comorbidity survey replication adolescent supplement. Arch Gen Psychiatry. 2011; 68: 714.
3. Agras WS. The consequences and costs of the eating disorders. Psychiatr Clin North Am. 2001; 24: 371-379.
4. Erskine HE, Whiteford HA, Pike KM. The global burden of eating disorders. Curr Opin Psychiatry. 2016; 29: 346-353.
5. O'Hara CB, Campbell IC, Schmidt U. A reward-centred model of anorexia nervosa: A focussed narrative review of the neurological and psychophysiological literature. Neurosci Biobehav Rev. 2015; 52: 131-152.
6. Kontis D, Theochari E. Dopamine in anorexia nervosa: A systematic review. Behav Pharmacol. 2012; 23: 496-515.
7. Monteleone AM, Castellini G, Volpe U, Ricca V, Lelli L, Monteleone P, et al. Neuroendocrinology and brain imaging of reward in eating disorders: A possible key to the treatment of anorexia nervosa and bulimia nervosa. Prog Neuropsychopharmacol Biol Psychiatry. 2018; 80: 132-142.
8. Frank GKW, DeGuzman MC, Shott ME. Motivation to eat and not to eat – the psycho-biological conflict in anorexia nervosa. Physiol Behav. 2019; 206: 185-190.

9. Kaye W. Altered dopamine activity after recovery from restricting-type anorexia nervosa. Neuropsychopharmacology. 1999; 21: 503-506.
10. Kaye W, Ely AV. Appetitive regulation in anorexia nervosa and bulimia nervosa. Agras WS, Robinson A, editors. Vol. 1. Oxford University Press. 2017 [cited 2019 Oct 16]. Available from: http://oxfordhandbooks.com/view/10.1093/oxfordhb/9780190620998.001.0001/oxfordhb-9780190620998-e-4.
11. Davis C, Kaptein S. Anorexia nervosa with excessive exercise: A phenotype with close links to obsessive-compulsive disorder. Psychiatry Res. 2006; 142: 209-217.
12. Meyer C, Taranis L, Goodwin H, Haycraft E. Compulsive exercise and eating disorders. Eur Eat Disord Rev. 2011; 19: 174-189.
13. Dalle Grave R, Calugi S, Marchesini G. Compulsive exercise to control shape or weight in eating disorders: Prevalence, associated features, and treatment outcome. Compr Psychiatry. 2008; 49: 346-352.
14. Shroff H, Reba L, Thornton LM, Tozzi F, Klump KL, Berrettini WH, et al. Features associated with excessive exercise in women with eating disorders. Int J Eat Disord. 2006; 39: 454-461.
15. Carter JC, Blackmore E, Sutandar-Pinnock K, Woodside DB. Relapse in anorexia nervosa: A survival analysis. Psychol Med. 2004; 34: 671-679.
16. Smith AR, Fink EL, Anestis MD, Ribeiro JD, Gordon KH, Davis H, et al. Exercise caution: Over-exercise is associated with suicidality among individuals with disordered eating. Psychiatry Res. 2013; 206: 246-255.
17. Holtkamp K, Hebebrand J, Herpertz-Dahlmann B. The contribution of anxiety and food restriction on physical activity levels in acute anorexia nervosa. Int J Eat Disord. 2004; 36: 163-171.
18. Davis C, Woodside DB. Sensitivity to the rewarding effects of food and exercise in the eating disorders. Compr Psychiatry. 2002; 43: 189-194.
19. Melissa R, Lama M, Laurence K, Sylvie B, Jeanne D, Odile V, et al. Physical activity in eating disorders: A systematic review. Nutrients. 2020; 12: 183.
20. Gümmer R, Giel KE, Schag K, Resmark G, Junne FP, Becker S, et al. High levels of physical activity in anorexia nervosa: A systematic review. Eur Eat Disord Rev. 2015; 23: 333-344.
21. Bezzina L, Touyz S, Young S, Foroughi N, Clemes S, Meyer C, et al. Accuracy of self-reported physical activity in patients with anorexia nervosa: Links with clinical features. J Eat Disord. 2019; 7: 28.
22. Pritchard ME, Beaver JL. Do exercise motives predict obligatory exercise? Eat Behav. 2012; 13: 139-141.
23. Draeger J, Yates A, Crowell D. The obligatory exerciser: Assessing an overcommitment to exercise. Phys Sportsmed. 2005; 33: 13-23.
24. Adams J, Kirkby RJ. Excessive exercise as an addiction: A review. Addict Res Theory. 2002; 10: 415-437.
25. Carrera O, Adan RAH, Gutierrez E, Danner UN, Hoek HW, van Elburg AA, et al. Hyperactivity in anorexia nervosa: Warming up not just burning-off calories. PloS One. 2012; 7: e41851.
26. Carrera O, Gutiérrez E. Hyperactivity in anorexia nervosa: To warm or not to warm. That is the question (a translational research one). J Eat Disord. 2018; 6: 4.
27. Gutiérrez E, Vázquez R, Boakes RA. Activity-based anorexia: Ambient temperature has been a neglected factor. Psychon Bull Rev. 2002; 9: 239-249.

28. Hillebrand J, Derijke C, Brakkee J, Kas M, Adan R. Voluntary access to a warm plate reduces hyperactivity in activity-based anorexia. Physiol Behav. 2005; 85: 151-157.
29. Cerrato M, Carrera O, Vazquez R, Echevarría E, Gutierrez E. Heat makes a difference in activity-based anorexia: A translational approach to treatment development in anorexia nervosa. Int J Eat Disord. 2012; 45: 26-35.
30. Chowdhury TG, Chen YW, Aoki C. Using the activity-based anorexia rodent model to study the neurobiological basis of anorexia nervosa. J Vis Exp. 2015; 104: 52927.
31. Gutierrez E. A rat in the labyrinth of anorexia nervosa: Contributions of the activity-based anorexia rodent model to the understanding of anorexia nervosa. Int J Eat Disord. 2013; 46: 289-301.
32. Noetel M, Dawson L, Hay P, Touyz S. The assessment and treatment of unhealthy exercise in adolescents with anorexia nervosa: A Delphi study to synthesize clinical knowledge. Int J Eat Disord. 2017; 50: 378-388.
33. Scharmer C, Gorrell S, Schaumberg K, Anderson D. Compulsive exercise or exercise dependence? Clarifying conceptualizations of exercise in the context of eating disorder pathology. Psychol Sport Exerc. 2020; 46: 101586.
34. Adams J. Understanding exercise dependence. J Contemp Psychother. 2009; 39: 231-240.
35. Bamber DJ, Cockerill IM, Rodgers S, Carroll D. Diagnostic criteria for exercise dependence in women. Br J Sports Med. 2003; 37: 393-400.
36. Bratland Sanda S, Martinsen EW, Rosenvinge JH, Rø Ø, Hoffart A, Sundgot Borgen J. Exercise dependence score in patients with longstanding eating disorders and controls: The importance of affect regulation and physical activity intensity. Eur Eat Disord Rev. 2011; 19: 249-255.
37. Cook B, Hausenblas H, Freimuth M. Exercise addiction and compulsive exercising: Relationship to eating disorders, substance use disorders, and addictive disorders. In: Eating disorders, addictions, and substance use disorders. Springer. 2014: 127-144.
38. Davis C, Katzman DK, Kaptein S, Kirsh C, Brewer H, Kalmbach K, et al. The prevalence of high-level exercise in the eating disorders: Etiological implications. Compr Psychiatry. 1997; 38: 321-326.
39. Hausenblas HA, Symons Downs D. Exercise dependence: A systematic review. Psychol Sport Exerc. 2002; 3: 89-123.
40. Potenza MN. Neurobiology of gambling behaviors. Curr Opin Neurobiol. 2013; 23: 660-667.
41. Baron A, Galizio M. Positive and negative reinforcement: Should the distinction be preserved? Behav Anal. 2005; 28: 85-98.
42. Greenwood BN, Foley TE, Le TV, Strong PV, Loughridge AB, Fleshner M. Long-term voluntary wheel running is rewarding and produces plasticity in the mesolimbic reward pathway. Behav Brain Res. 2011; 217: 354-362.
43. Heyman E, Gamelin FX, Goekint M, Piscitelli F, Roelands B, Leclair E, et al. Intense exercise increases circulating endocannabinoid and BDNF levels in humans—possible implications for reward and depression. Psychoneuroendicrinology. 2012; 37: 844-851.
44. Schultz W. Dopamine reward prediction-error signalling: A two-component response. Nat Rev Neurosci. 2016; 17: 183-195.
45. Watabe-Uchida M, Eshel N, Uchida N. Neural circuitry of reward prediction error. Ann Rev Neurosci. 2017; 40: 373-394.

46. Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci. 2004; 5: 483-494.
47. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'Liking', 'wanting', and learning. Curr Opin Pharmacol. 2009; 9: 65-73.
48. Graybiel AM, Grafton ST. The striatum: Where skills and habits meet. Cold Spring Harb Perspect Biol. 2015; 7: a021691.
49. Wise RA. Role of brain dopamine in food reward and reinforcement. Philos Trans R Soc Lond B Biol Sci. 2006; 361: 1149-1158.
50. Berridge KC. The debate over dopamine's role in reward: The case for incentive salience. Psychopharmacology. 2007; 191: 391-431.
51. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature. 2006; 442: 1042-1045.
52. Glimcher PW. Understanding dopamine and reinforcement learning: The dopamine reward prediction error hypothesis. Proc Natl Acad Sci. 2011; 108: 15647-15654.
53. Koob GF, Le Moal M. Drug abuse: Hedonic homeostatic dysregulation. Science. 1997; 278: 52-58.
54. Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. Am Psychol. 2016; 71: 670-679.
55. Flagel SB, Watson SJ, Akil H, Robinson TE. Individual differences in the attribution of incentive salience to a reward-related cue: Influence on cocaine sensitization. Behav Brain Res. 2008; 186: 48-56.
56. Wang GJ, Geliebter A, Volkow ND, Telang FW, Logan J, Jayne MC, et al. Enhanced striatal dopamine release during food stimulation in binge eating disorder. Obesity. 2011; 19: 1601-1608.
57. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, D.C: American psychiatric association. 2013: 947.
58. Godier LR, Park RJ. Does compulsive behavior in anorexia nervosa resemble an addiction? A qualitative investigation. Front Psychol. 2015; 6: 1608.
59. Södersten P, Bergh C, Leon M, Zandian M. Dopamine and anorexia nervosa. Neurosci Biobehav Rev. 2016; 60: 26-30.
60. Palmiter RD. Is dopamine a physiologically relevant mediator of feeding behavior? Trends Neurosci. 2007; 30: 375-381.
61. Rosenbaum M, Hirsch J, Gallagher DA, Leibel RL. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. Am J Clin Nutr. 2008; 88: 906-912.
62. Frank GKW, DeGuzman MC, Shott ME, Laudenslager ML, Rossi B, Pryor T. Association of brain reward learning response with harm avoidance, weight gain, and hypothalamic effective connectivity in adolescent anorexia nervosa. JAMA Psychiatry. 2018; 75: 1071.
63. Frank GK, Bailer UF, Henry SE, Drevets W, Meltzer CC, Price JC, et al. Increased dopamine d2/d3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [11c]raclopride. Biol Psychiatry. 2005; 58: 908-912.
64. DeGuzman M, Shott ME, Yang TT, Riederer J, Frank GKW. Association of elevated reward prediction error response with weight gain in adolescent anorexia nervosa. Am J Psychiatry. 2017; 174: 557-565.

65. Kaye WH. Abnormalities in CNS monoamine metabolism in anorexia nervosa. Arch Gen Psychiatry. 1984; 41: 350.
66. Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. The Lancet. 2001; 357: 354-357.
67. Bergen AW, Yeager M, Welch RA, Haque K, Ganjei JK, van den Bree MBM, et al. Association of multiple DRD2 polymorphisms with anorexia nervosa. Neuropsychopharmacology. 2005; 30: 1703-1710.
68. Kaye WH, Fudge JL, Paulus M. New insights into symptoms and neurocircuit function of anorexia nervosa. Nat Rev Neurosci. 2009; 10: 573-584.
69. Haber SN. Corticostriatal circuitry. Dialogues Clin Neurosci. 2016; 18: 7-21.
70. de Jong JW, Afjei SA, Pollak Dorocic I, Peck JR, Liu C, Kim CK, et al. A neural circuit mechanism for encoding aversive stimuli in the mesolimbic dopamine system. Neuron. 2019; 101: 133-151.e7.
71. Yuan L, Dou YN, Sun YG. Topography of reward and aversion encoding in the mesolimbic dopaminergic system. J Neurosci. 2019; 39: 6472-6481.
72. Berridge KC, Kringelbach ML. Pleasure systems in the brain. Neuron. 2015; 86: 646-664.
73. Adan RAH, Hillebrand JJG, Danner UN, Cano SC, Kas MJH, Verhagen LAW. Neurobiology driving hyperactivity in activity-based anorexia. Curr Top Behav Neurosci. 2010; 6: 229-250.
74. Legrand R, Lucas N, Breton J, Déchelotte P, Fetissov SO. Dopamine release in the lateral hypothalamus is stimulated by α-MSH in both the anticipatory and consummatory phases of feeding. Psychoneuroendocrinology. 2015; 56: 79-87.
75. Verhagen LAW, Luijendijk MCM, Adan RAH. Leptin reduces hyperactivity in an animal model for anorexia nervosa via the ventral tegmental area. Eur Neuropsychopharmacol. 2011; 21: 274-281.
76. Jerlhag E, Egecioglu E, Dickson SL, Douhan A, Svensson L, Engel JA. Ghrelin administration into tegmental areas stimulates locomotor activity and increases extracellular concentration of dopamine in the nucleus accumbens. Addict Biol. 2007; 12: 6-16.
77. Holtkamp K, Herpertz-Dahlmann B, Hebebrand K, Mika C, Kratzsch J, Hebebrand J. Physical activity and restlessness correlate with leptin levels in patients with adolescent anorexia nervosa. Biol Psychiatry. 2006; 60: 311-313.
78. Holtkamp K, Herpertz-Dahlmann B, Mika C, Heer M, Heussen N, Fichter M, et al. Elevated physical activity and low leptin levels co-occur in patients with anorexia nervosa. J Clin Endocrinol Metab. 2003; 88: 5169-5174.
79. Hebebrand J, Muller TD, Holtkamp K, Herpertz-Dahlmann B. The role of leptin in anorexia nervosa: Clinical implications. Mol Psychiatry. 2007; 12: 23-35.
80. Hofmann T, Elbelt U, Haas V, Ahnis A, Klapp BF, Rose M, et al. Plasma kisspeptin and ghrelin levels are independently correlated with physical activity in patients with anorexia nervosa. Appetite. 2017; 108: 141-150.
81. Klein DA, Mayer LES, Schebendach JE, Walsh BT. Physical activity and cortisol in anorexia nervosa. Psychoneuroendocrinology. 2007; 32: 539-547.
82. da Luz Neto LM, de Vasconcelos FMN, da Silva JE, Pinto TCC, Sougey ÉB, Ximenes RCC. Differences in cortisol concentrations in adolescents with eating disorders: A systematic review. J Pediatr Versão Em Port. 2019; 95: 18-26.

83. Epling WF, Pierce WD. Excessive activity and anorexia in rats. In: Pirke KM, Wuttke W, Schweiger U, editors. The menstrual cycle and its disorders. Berlin, Heidelberg: Springer Berlin Heidelberg; 1989: 79-87. Available from: http://link.springer.com/10.1007/978-3-642-74631-4_9.
84. Pérez-Padilla Á, Magalhães P, Pellón R. The effects of food presentation at regular or irregular times on the development of activity-based anorexia in rats. Behav Process. 2010; 84: 541-545.
85. Ho EV, Klenotich SJ, McMurray MS, Dulawa SC. Activity-based anorexia alters the expression of BDNF transcripts in the mesocorticolimbic reward circuit. PLOS ONE. 2016; 11: e0166756.
86. Foldi CJ, Milton LK, Oldfield BJ. The role of mesolimbic reward neurocircuitry in prevention and rescue of the activity-based anorexia (ABA) phenotype in rats. Neuropsychopharmacology. 2017; 42: 2292-2300.
87. Aoki C, Chowdhury TG, Wable GS, Chen YW. Synaptic changes in the hippocampus of adolescent female rodents associated with resilience to anxiety and suppression of food restriction-evoked hyperactivity in an animal model for anorexia nervosa. Brain Res. 2017; 1654: 102-115.
88. Schalla MA, Stengel A. Activity based anorexia as an animal model for anorexia nervosa–a systematic review. Front Nutr. 2019; 6: 69.
89. Gelegen C, van den Heuvel J, Collier DA, Campbell IC, Oppelaar H, Hessel E, et al. Dopaminergic and brain-derived neurotrophic factor signalling in inbred mice exposed to a restricted feeding schedule. Genes Brain Behav. 2008; 7: 552-559.
90. Hillebrand JJG, van Elburg AA, Kas MJH, van Engeland H, Adan RAH. Olanzapine reduces physical activity in rats exposed to activity-based anorexia: Possible implications for treatment of anorexia nervosa? Biol Psychiatry. 2005; 58: 651-657.
91. Klenotich SJ, Seiglie MP, McMurray MS, Roitman JD, Le Grange D, Dugad P, et al. Olanzapine, but not fluoxetine, treatment increases survival in activity-based anorexia in mice. Neuropsychopharmacol. 2012; 37: 1620-1631.
92. Klenotich SJ, Ho EV, McMurray MS, Server CH, Dulawa SC. Dopamine D2/3 receptor antagonism reduces activity-based anorexia. Transl Psychiatry. 2015; 5: e613.
93. Verhagen LAW, Luijendijk MCM, Hillebrand JJG, Adan RAH. Dopamine antagonism inhibits anorectic behavior in an animal model for anorexia nervosa. Eur Neuropsychopharmacol. 2009; 19: 153-160.
94. Attia E, Steinglass JE, Walsh BT, Wang Y, Wu P, Schreyer C, et al. Olanzapine versus placebo in adult outpatients with anorexia nervosa: A randomized clinical trial. Am J Psychiatry. 2019; 176: 449-456.
95. Frank GKW, Shott ME, Hagman JO, Schiel MA, DeGuzman MC, Rossi B. The partial dopamine D2 receptor agonist aripiprazole is associated with weight gain in adolescent anorexia nervosa. Int J Eat Disord. 2017; 50: 447-450.
96. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Bischoff-Grethe A. Nothing tastes as good as skinny feels: The neurobiology of anorexia nervosa. Trends Neurosci. 2013; 36: 110-120.
97. Wierenga CE, Ely A, Bischoff-Grethe A, Bailer UF, Simmons AN, Kaye WH. Are extremes of consumption in eating disorders related to an altered balance between reward and inhibition? Front Behav Neurosci. 2014; 8: 410.

98. Steinglass JE, Walsh BT. Neurobiological model of the persistence of anorexia nervosa. J Eat Disord. 2016; 4: 19.
99. Walsh BT. The enigmatic persistence of anorexia nervosa. Am J Psychiat. 2013; 170: 477-484.
100. Holsen LM, Lawson EA, Blum J, Ko E, Makris N, Fazeli PK, et al. Food motivation circuitry hypoactivation related to hedonic and nonhedonic aspects of hunger and satiety in women with active anorexia nervosa and weight-restored women with anorexia nervosa. J Psychiatry Neurosci JPN. 2012; 37: 322-332.
101. Fladung AK, Grön G, Grammer K, Herrnberger B, Schilly E, Grasteit S, et al. A neural signature of anorexia nervosa in the ventral striatal reward system. Am J Psychiat. 2010; 167: 206-212.
102. Uniacke B, Timothy Walsh B, Foerde K, Steinglass J. The role of habits in anorexia nervosa: Where we are and where to go from here? Curr Psychiatry Rep. 2018; 20: 61.
103. Foerde K, Steinglass JE, Shohamy D, Walsh BT. Neural mechanisms supporting maladaptive food choices in anorexia nervosa. Nat Neurosci. 2015; 18: 1571-1573.
104. Gasbarri A, Pompili A, Packard MG, Tomaz C. Habit learning and memory in mammals: Behavioral and neural characteristics. Neurobiol Learn Mem. 2014; 114: 198-208.
105. Godier LR, Park RJ. Compulsivity in anorexia nervosa: A transdiagnostic concept. Front Psychol. 2014; 5: 778.
106. Haynos AF, Hall LMJ, Lavender JM, Peterson CB, Crow SJ, Klimes-Dougan B, et al. Resting state functional connectivity of networks associated with reward and habit in anorexia nervosa. Hum Brain Mapp. 2019; 40: 652-662.
107. Beadle JN, Paradiso S, Brumm M, Voss M, Halmi K, McCormick LM. Larger hippocampus size in women with anorexia nervosa who exercise excessively than healthy women. Psychiatry Res Neuroimaging. 2015; 232: 193-199.
108. Kim KR, Ku J, Lee JH, Lee H, Jung YC. Functional and effective connectivity of anterior insula in anorexia nervosa and bulimia nervosa. Neurosci Lett. 2012; 521: 152-157.
109. Uher R, Murphy T, Brammer MJ, Dalgleish T, Phillips ML, Ng VW, et al. Medial prefrontal cortex activity associated with symptom provocation in eating disorders. Am J Psychiatry. 2004; 161: 1238-1246.
110. Bartholdy S, Dalton B, O'Daly OG, Campbell IC, Schmidt U. A systematic review of the relationship between eating, weight and inhibitory control using the stop signal task. Neurosci Biobehav Rev. 2016; 64: 35-62.
111. Kullmann S, Giel KE, Hu X, Bischoff SC, Teufel M, Thiel A, et al. Impaired inhibitory control in anorexia nervosa elicited by physical activity stimuli. Soc Cogn Affect Neur. 2014; 9: 917-923.
112. Tricomi E, Balleine BW, O'Doherty JP. A specific role for posterior dorsolateral striatum in human habit learning. Eur J Neurosci. 2009; 29: 2225-2232.
113. Giel KE, Kullmann S, Preißl H, Bischoff SC, Thiel A, Schmidt U, et al. Understanding the reward system functioning in anorexia nervosa: Crucial role of physical activity. Biol Psychol. 2013; 94: 575-581.
114. Klein DA, Schebendach JE, Gershkovich M, Bodell LP, Foltin RW, Walsh BT. Behavioral assessment of the reinforcing effect of exercise in women with anorexia nervosa: Further paradigm development and data. Int J Eat Disord. 2010; 43: 611-618.
115. O'Hara CB, Keyes A, Renwick B, Giel KE, Campbell IC, Schmidt U. Evidence that illness-compatible cues are rewarding in women recovered from anorexia nervosa: A study of the effects of dopamine depletion on eye-blink startle responses. PloS One. 2016; 11: e0165104.

116. O'Hara CB, Keyes A, Renwick B, Leyton M, Campbell IC, Schmidt U. The effects of acute dopamine precursor depletion on the reinforcing value of exercise in anorexia nervosa. PLOS ONE. 2016; 11: e0145894.
117. Lerner TN. Interfacing behavioral and neural circuit models for habit formation. J Neurosci Res. 2020; DOI: 10.1002/jnr.24581.