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Genetics and Neurobiology of Eating Disorders

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Abstract

Eating disorders (anorexia nervosa, bulimia nervosa, and binge-eating disorder) are a heterogeneous class of complex illnesses marked by weight and appetite dysregulation coupled with distinctive behavioral and psychological features. Our understanding of their genetics and neurobiology is evolving thanks to global cooperation on genome-wide association studies (GWAS), neuroimaging, and animal models. Until now, however, these approaches have advanced the field in parallel, with inadequate crosstalk. This review covers overlapping advances in these

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key domains and encourages greater integration of hypotheses and findings to create a more unified science of eating disorders. We highlight ongoing and future work designed to identify implicated biological pathways that will inform staging models based on biology as well as targeted prevention and tailored intervention and galvanize interest in developing pharmacologic agents that target the core biology of the illnesses for which we currently have few effective pharmacotherapeutics.

Keywords

eating disorders; genomic; GWAS; metabolic; psychiatric

Eating disorders are severe psychiatric disorders that, for many, evolve into chronic or fluctuating conditions with serious adverse outcomes[1]. Among adolescents and young adults, the disability-adjusted life years (DALYs) for anorexia nervosa (AN) and bulimia nervosa (BN) are among the highest of all psychiatric disorders[2]. Binge-eating disorder (BED) and other specified feeding and eating disorders have yet to be included in estimates, but are projected to account for the majority of global disease burden of eating disorders[3]. Although the disorders occur in pure forms, although diagnostic crossover across the course of illness is common[4]. For a brief definition of the symptoms and epidemiology of the three primary eating disorders, see Box 1.

Biological effects within eating disorders range from the subcellular (genetic variants and their effects on gene expression and structure), through the cellular (signaling) and intercellular (neurons and neuronal circuits), to organismal effects (eating disorders and disorder-related behaviors)[5]. These levels of biology are interconnected, but are investigated using different scientific approaches, with limited crosstalk to date. Integrating results from different approaches is vital. A hierarchically connected research approach, reflecting the biological interconnectivity, will provide a more complete understanding of the biology of eating disorders, providing the foundations for developing much-needed novel treatments. In this review, we describe the state of the science across biological levels and approaches and conclude by discussing progress towards this more integrated understanding.

Human Genetics of Eating Disorders

Twin-based heritability.

Large-scale twin studies yield heritability estimates ranging from 0.28 to 0.74 for AN[6], with imprecision reflecting varying definitions of illness and sample size, with more severe definitions associated with higher heritabilities[7]. Heritability estimates range from 0.55 to 0.62[6] for BN and 0.39 to 0.45 for BED[6].

GWAS.

Candidate gene and linkage literature in eating disorders was rife with unreplicated small-sample studies and was minimally informative beyond signaling the likely complexity of their genetics[6]. We take as a starting point the most recent genome-wide association study (GWAS) of AN performed by the Eating Disorders Working Group of the Psychiatric

Genomics Consortium (PGC-ED)[8]. Combining existing samples[9] with the Anorexia Nervosa Genetics Initiative (ANGI)[10] yielded a European ancestry dataset including 16,992 AN cases and 55,525 controls, from 17 countries, and identified 8 genome-wide significant loci, including 4 single-gene loci: *CADM1*, *MGMT*, *FOXP1* and *PTBP2*[8]. Analysis of tissue enrichment for AN-associated genes revealed a significant association with the central nervous system, and comparison to single-cell gene expression datasets from mice revealed significant associations with hippocampal pyramidal neurons and striatal medium spiny neurons. Song et al.[11] further identified that AN-associated genes were enriched in the prefrontal cortex.

Genetic correlations implicate psychiatric, education, and metabolic factors in AN.

Genetic correlations (SNP-r_g) between AN and psychiatric disorders such as obsessive-compulsive disorder (OCD), major depressive disorder (MDD), anxiety, and substance-related disorders [8,12] correspond with clinical observations of comorbidity[13] and twin studies[14-16]. Building on this work, AN and OCD risk genes pinpointed through GWAS showed similar prefrontal cortex expression alterations meaning that these disorders may have similar functional pathways[11]. A novel positive SNP-r_g with objectively measured physical activity was found in the PGC-ED GWAS[8] and may relate to the driven exercise seen in AN. Significant positive SNP-r_g with educational attainment was not seen for IQ (Figure 1).

Earlier results hinted at a significant negative genetic correlation between AN and body mass index (BMI)[9,17]. The PGC-ED GWAS revealed significant genetic correlations with metabolic, lipid, and anthropometric traits, suggesting that metabolic mechanisms may drive physiological resistance to healthy body weight in AN[8]. The observed correlations were not confounded by the genetics of BMI—a concern given that BMI is a component of the AN diagnosis[8]. Likewise, exploratory Mendelian randomization (MR) analyses in the PGC-EDs GWAS indicated a bidirectional causal relationship between AN and low BMI. The authors concluded that both metabolic and psychological factors may need to be considered to fully understand AN and that doing so may hasten the development of more effective treatments. Based on the strong associations with psychiatric traits, physical activity, educational attainment, and metabolic traits, multivariate GWAS analyses (e.g., genomic structural equation modeling) could offer novel opportunities to disentangle common and specific genetic effects and help boost power for discovery.

Polygenic scores.

Polygenic scores (PGS) summarize genome-wide data into a single variable of genetic liability to the phenotype—as a sum of the number of risk alleles present in the individual weighted by the SNP effects from GWAS. Higher PGS for AN derived from the 2019 PGC-ED GWAS were associated with increased odds of AN, and equally in females and males[8]. Further, PGS of age of onset of AN predicted age at onset in independent cohorts[18]. A rich body of literature applying PGS is emerging, with multiple studies reporting that BMI and psychiatric PGS influence childhood and adolescent disordered eating behaviors[19-21]. PGS for other phenotypes may also differentiate among AN, BN, and BED on the genomic level. UK Biobank analyses revealed strong positive associations between binge-

type eating disorders (BN and BED) and anthropometric PGS (e.g., overweight and waist circumference), suggesting that binge eating may share genomic variants with overweight and obesity. In contrast, in AN, the direction of these associations was reversed[22].

We anticipate increasing evidence that PGS will predict developmental phenotypic manifestations of illness (i.e., premorbid behavioral traits, course of illness) and gene-environment associations, and ultimately inform risk assessment and clinical applications. Presently, clinical utility is limited[23,24].

Cross-disorder GWAS.

A cross-disorder GWAS of eight psychiatric disorders (AN, ADHD, autism spectrum disorder, bipolar disorder, MDD, OCD, schizophrenia, and Tourette's syndrome) revealed 109 pleiotropic loci (i.e., signals for at least two disorders), of which eight had signals for AN[25]. The top locus (18q21.2) was associated with all disorders, has previously been implicated in MDD and neuroticism, and encodes the netrin 1 receptor gene (*DCC*) that regulates axon outgrowth. A joint genomic structural equation model showed that AN loaded onto a factor with OCD and Tourette's syndrome[26]. These findings suggest overlapping genetic risk across disorders and that work needs to be done to separate specific from non-specific susceptibility variants, and the association of specific variants with cellular gene expression datasets to generate testable hypotheses for their ultimate impact on brain circuit function. Other cross-disorder GWAS on AN/OCD have yielded promising insights but require larger samples to pinpoint risk loci (i.e.,[27]).

Mendelian randomization (MR).

MR studies treat genetic variants as unconfounded proxies of an exposure of interest to evaluate the causal effect of an exposure on a phenotypic outcome. However, MR analyses investigating the causal effects of AN on other traits are presently limited in power. As stated earlier, a bidirectional causal association between AN and low BMI was found in the PGC-ED GWAS[8]. An MR study on the ALSPAC cohort (n = 4,473) suggested possible causal effects of genetically predicted childhood BMI on binge eating and weight and shape concern, and of binge eating and overeating on BMI[28]. In another study, adiponectin, a fat-tissue derived hormone, showed evidence consistent with a causal effect on eating disinhibition but not eating restraint[29]. Adams et al.[30] found evidence consistent with a protective effect of fasting insulin level (n = 108,557) on AN (n = 72,515) (OR = 0.48, 95% CI: 0.33, 0.71), but not for fasting glucose or glycated hemoglobin (HbA1c) on AN. Future MR studies will help to disentangle the nature of pleiotropy and shed light on causal exposure-outcome effects.

Rare mutations and copy number variants.

No Mendelian forms of eating disorders have been identified and efforts to find rare genetic variants have not yet been successful. In an exome-chip based GWAS in 2,158 AN cases and 15,327 controls[31], 16 independent variants were taken forward for *in silico* and *de novo* replication. No findings reached genome-wide significance. Scott-Van Zeeland et al.[32] conducted a series of targeted sequencing and genotyping studies focusing on 152 candidate genes in 1,205 AN cases and 1,948 controls, implicating variants in the estrogen receptor-b

(*ESR2*) and epoxide hydrolase 2 (*EPHX2*) genes. A smaller exome sequencing study of 93 AN cases reported an enrichment of rare variants in neuropeptide/neurotrophic pathways[33]. Combined linkage and sequencing of densely affected families with multiple AN or BN cases has been reported[34,35]. Results of these studies are tentative as sufficient sample sizes to identify rare point mutations have yet to be attained.

The situation is similar for genome-wide analyses of copy number variants (CNVs). Wang et al.[36] found no evidence of CNV enrichment in AN cases compared to controls. Yilmaz et al.[37] analyzed 1,983 female AN cases[38] seeing no occurrence of well-established pathogenic CNVs for neurodevelopmental disorders (1q21.1; 2p16.3; 3q29; 7q36.3; 13q12; 15q11.2; 15q13.3; 16p11.2(1); 16p11.2(2); 17q12; or 22q11.21). Chang et al.[39] reported association of a 15q11.2 microduplication with AN, but cautioned that the results require validation. Currently, there is no credible evidence that novel or known large effect size CNVs influence AN. Much larger sample sizes may be required before we can exclude a role for CNVs carrying moderate effect sizes.

Limitations of human genetic studies.

Several limitations in the field should be considered. First, to our knowledge, no GWAS of bulimia nervosa, binge-eating disorder, purging disorder, atypical AN, avoidant/restrictive food intake disorder (ARFID), pica, or rumination disorder have been published. Second, for AN, genome-wide signals presently account for a low proportion of phenotypic variance (1.7%), while gene mapping and gene expression results presently rely on limited Hi-C, eQTL, and brain cell data. Larger sample sizes are required to improve statistical power and detect more susceptibility loci. Large, systematic sequencing studies are required to assess the role of rare variants and to complement common variant GWAS. Finally, although eating disorders are likely under-detected in males, the gender ratio is definitely tipped in the direction of females. Accruing larger samples sizes of afflicted males is essential for identifying genetic sex differences and is a priority for future research.

Integration.

Genomic discovery in eating disorders is underway and early discoveries highlight new directions for deepening our understanding of some of the more perplexing facets of AN (e.g., extreme weight dysregulation, the frequent re-loss of therapeutically restored weight, compulsive exercise). The PGC is expanding genomic samples of AN, BN, and BED with efforts such as the Eating Disorders Genetics Initiative (EDGI)[40]. Novel biological discoveries are anticipated to accelerate therapeutic opportunities in drug discovery, the repositioning of current drugs, and our understanding of pleiotropy including opposing effects that may mitigate unintended off-target effects. The availability of biobanks with genetic and electronic health record data offer opportunities for extending genetic associations to other medical phenotypes not currently available. As with many illnesses, global cooperation and harmonization of methods boost sample sizes and accelerate science. Clearly, collaboration with researchers in other fields will increase the utility of GWAS results and integrate them into a unified science of eating disorders. This unification can be achieved through targeting dimensional phenotypes and symptoms and generating hypotheses for testing the causal impact of genomic variants on neural circuit function.

Eating disorders GWAS have focused primarily on diagnoses; however, exploring relevant dimensions or core symptoms may enhance translation to approximate phenotypes in animal models. Fine-mapping approaches are required to delve deeper into trait-associated regions to identify specific variants or genes that causally influence the target trait. Clearly describing the strength of evidence for the functional involvement of specific genes and variants in eating disorders will provide strong targets for causal validation and neurobiological exploration.

Neurobiology of genes implicated in AN GWAS.

Although too recent to have influenced neurobiological studies directly, several genes implicated by the latest AN GWAS have been studied in relation to other traits and show neurobiological relevance to eating disorders. For example, FOXP1 haploinsufficiency is a rare form of intellectual disability, related to autism spectrum disorder[41]. Haploinsufficiency of *FOXP1* is associated with neurodevelopmental impairments, but also with feeding difficulties and gastrointestinal disturbance in humans and in mice, supporting *FOXP1* in AN[41]. Conditional Foxp1 knockout studies in the mouse brain implicate neurogenesis and neural migration, particularly the development and functioning of medium spiny neurons and pyramidal neurons. Both cell types have been implicated as relevant neuronal cell types by systems biological analyses of the AN GWAS[41].

As well as being implicated in AN, *CADM1* and *PTBP2* have also been implicated in GWAS of BMI[42]. *PTBP2* encodes a neuron-specific RNA binding protein that organizes axonogenesis in the developing cortex, relevant across psychiatric disorders[43]. By comparison, *CADM1* has not been associated with psychological or behavioral traits except BMI and AN (although family member *CADM2* has been implicated in numerous traits related to impulsive behavior)[44]. *CADM1* encodes a synaptic cell adhesion molecule. The BMI-associated variants appear to increase the expression of CADM1 in the human hypothalamus and cerebellum, and parallel experiments in mice suggest this increased expression contributes to weight gain, potentially through CADM1-positive innervation of POMC neurons[45]. CADM1 is also involved in the neural control of first estrous in mice, which is of particular interest given amenorrhea in AN[1]. *MGMT*, which encodes a DNA alkyltransferase, is the most well-studied of the genes implicated in the AN GWAS, as it is involved in DNA repair and protection against cancer[46]. The biological pathways linking DNA repair dysfunction to AN is unclear, although recent research suggests that postmitotic neurons require recurrent DNA repair that is relevant to neuronal dysfunction[47,48]. Assuming future GWASs support *MGMT* as a causal gene for AN, its role is worthy of future investigation.

Identifying conserved, eating disorder-relevant genes is currently limited by underpowered phenotype-driven analyses in humans and rodents. Neuroscience typically focuses on a different level of the biological hierarchy than statistical genetics. As such, deeper insight may be gained through examining the neuronal circuitry implicated directly through neuroscientific approaches and indirectly through GWAS-based approaches. GWAS-based approaches use information on cell-type specific genome biology, such as epigenetic markers[49] or gene expression[50]. These methods show that genes associated with AN are

on average specifically expressed in brain tissues, especially in medium spiny neurons and CA1 hippocampal pyramidal neurons[8]. Results from these methods implicate the same cell types in other psychiatric disorders and are supported by functional studies in rodents. Differential vulnerability to ABA in female C57BL/6J mice was associated with GABAergic inhibition of hippocampal CA1 pyramidal cells[51]. Prolonged binge-like consumption of sucrose has been shown to alter the morphology of medium spiny neurons in the nucleus accumbens of rats[52]. However, beyond broad support for brain tissues in general, most circuits implicated in neurobiological studies of mice and of humans are poorly supported by these GWAS-based approaches, most likely due to limitations of power and insufficient data from appropriate tissues. For example, in contrast to the neurobiological evidence supporting a role for DA circuitry in AN, there is no such evidence from AN GWAS[8]. However, evidence for genetic variants affecting the DA system in eating disorders may emerge as the power of eating disorder GWAS increases. Both of these limitations are being overcome through increasing GWAS sample sizes and via collaborative brain mapping initiatives like the PsychENCODE project[53].

Human Neuroimaging in Eating Disorders

Neuroimaging research in eating disorders has been motivated by (1) prior work in animal models which study microcircuitry involved in homeostatic and hedonic eating pathways and (2) genetic/GWAS studies that have identified shared functional networks that exhibit overlapping phenotypes (cortico-striatal-thalamo-cortical pathways) (Figure 2).

Hedonic reward pathways - Mesocorticolimbic and mesolimbic networks.

The brain reward system is well-defined and plays a central role in the drive to eat. Mesocorticolimbic and mesolimbic pathways project from the ventral tegmental area (VTA) to the cerebral cortex (frontal, cingulate, and entorhinal cortex) and limbic structures (ventral striatum, hippocampus, and amygdala), respectively. Importantly, these systems are largely intertwined and overlapping[54], and assigning specific brain regions to one clinical phenotype (e.g., restriction) or characteristic (e.g., cognitive control) is unhelpful as they act in unison. Collectively, mesocorticolimbic and mesolimbic pathways are responsible for cognitive functions, reward, emotion, and motivation, which may represent transdiagnostic factors underlying AN, BN, and BED[55,56].

Early studies focusing on understanding the neurobiology of eating disorders suggested that there were pathological alterations in monoamine neurotransmitter systems, specifically DA and 5-HT[56]. These align with other works that have strongly implicated the reward system in pathological changes in hedonic eating and decision making. The VTA comprises a cluster of dopamine (DA) producing neurons that play a key role in positive and negative reinforcement, decision making, working memory, incentive salience, and aversion. Dopaminergic VTA neurons innervate corticolimbic regions via the mesocortical pathway, forming the mesocorticolimbic reward network. A subpopulation of midbrain DA neurons projecting to the striatum co-release glutamate and GABA onto their target neural substrates[57]. Understanding the structural and functional connectivity of these reward

circuits in eating disorders has been a central focus for neuroimaging investigations highlighted below.

Functional neuroimaging studies suggest altered processing of rewarding and aversive food stimuli in acute and recovered AN[58,59]. In binge-type eating disorders (BN, BED), functional neuroimaging findings are less consistent[60,61]. Positron emission tomography (PET) data in individuals recovered from AN show *increased* striatal dopamine receptor (D2/D3) binding, which was also related to striatal responses during monetary choices and self-reported trait anxiety[62]. Although, two PET studies focusing on individuals with acute[63] and weight restored AN[64] compared to healthy controls, found no difference in DA receptor binding. PET studies in individuals with BN have identified *decreased* striatal dopamine transporter availability[65]. In patients with BN, increases in glutamate signaling receptors (metabotropic glutamate receptor subtype 5; mGlu5) were higher in the anterior cingulate cortex (ACC), subgenual prefrontal cortex, and straight gyrus compared with controls[66]. Structural neuroimaging studies in AN and BN reveal volumetric abnormalities in the insula[67]. Further, lower white matter measures of axonal integrity (measured via fractional anisotropy) and increased structural white matter connectivity between the insula and orbital frontal cortex suggest that altered processing of taste perception may be present across eating disorders. The insular cortex extends beyond taste function and is a center of body awareness, integrating autonomic, cognitive, and affective processing[68] of the homeostatic state of the body. Both structural and functional neuroimaging studies highlight deficits in the insula and abnormal interoceptive activity in AN[69,70] and BN[71].

Cognitive control and habitual responding—cortico-striatal-thalamo-cortical pathways.

The cortico-striatal-thalamo-cortical (CTSC) pathway is a brain circuit that controls movement execution, habit formation, and reward, all of which have been hypothesized to be relevant to eating disorders. Hyperactivity throughout the CTSC circuits is believed to underlie OCD[72], increasingly relevant given the strong positive genetic correlation between OCD and AN[8]. Overlapping CTSC loops, including lateral PFC, ACC, dorsal striatum, the presupplementary motor area, insula, and parietal regions, are involved in these processes.

In patients with BN, there are limited neuroimaging data to suggest that functional and structural alterations in control circuits occur early in the course of BN and may contribute to the disorder's persistence over time[73,74]. In patients with AN, maladaptive excessive self-control is commonly described although the differences in underlying neurobiological correlates (i.e., structures) involving cognitive control are inconsistent in imaging studies[75,76]. Both AN and BN patients show reduced gray matter volume in caudate nucleus, ACC, and insula[77]; however, these results may normalize in AN and BN following successful treatment[78].

Limitations.

Deficits in cognitive control, executive functioning, reward and affective processing are commonly reported across multiple psychiatric disorders, with similar neurobiological correlates reported in the dorsal lateral prefrontal cortex, insula, and dorsal anterior cingulate cortex[79-81]. A limited number of studies compare neuroimaging across psychiatric

disorders (e.g.,[82,83]) or use meta-analytic techniques to do so (e.g.,[79,80]). Those that have been conducted have not included eating disorder patients despite evidence of psychiatric multimorbidity (including mood, substance use, and anxiety disorders)[84]. Eating disorder exclusion may occur because of state-specific neurobiological alterations due to malnourishment or dehydration stemming from key eating disorder specific behaviors (e.g., caloric restriction, purging, excessive exercise). Failure to account for state-specific effects has stymied human neuroimaging research in eating disorders. Eating disorder specific recommendations from experts in the fields of eating disorders and neuroimaging[85] have been proposed to account for malnutrition effects. Importantly, novel experimental designs are essential to disaggregate the extent to which any observed neurobiological alterations in AN are truly related to disease etiology or more accurately attributed to the impact of prolonged malnutrition/starvation. Accordingly, re-evaluation of prior eating disorder neuroimaging findings accounting for effects of malnourishment (e.g., white-matter alterations in AN[86] and BN[87]) has led to improved understanding of state vs. trait effects in the brain.

Integrating human genetics and neuroimaging.

Imaging and genetics target distant levels of the biological hierarchy, and so integration is challenging. Genetically informed models of eating disorders hold the potential to generate construct-valid neurobiological disease models. Direct examination of the effect of genetic variation on brain structure and function is underway through the ENIGMA consortium[88]. Further insights could be obtained by examining intermediate levels of the biological hierarchy. Cellular-level data can be inferred from eating disorder GWAS—this has implicated hippocampal pyramidal neurons and striatal medium spiny neurons as the cell types that express identified genes in AN[8]. However, this approach remains in its infancy—larger sample sizes for GWAS and for gene expression datasets in neuronal and non-neuronal cells (e.g., microglia, oligodendrocytes) are needed to provide sufficient power for the parallel implication of brain circuits from neuroimaging and from GWAS.

Animal Models for Eating Disorders

As eating disorders GWAS become larger and more robust, their ability to interconnect with animal models will increase. Animal models offer speed in achieving power, control over allele frequency and genetic background, environmental exposure, and recording and collection of the appropriate cell types and tissues at appropriate time points to study the dynamic genetic architecture and genomic adaptations across eating disorder progression and recovery. Two popular animal models for eating disorder are the activity-based anorexia (ABA) model and the binge-like eating (BLE) model (see Box 2). Genes, variants, and circuit mechanisms gleaned from animal studies can be discovered and validated first within the same species and genetic background and then in humans. Likewise, identified genes from human GWAS and proposed circuitry from human neuroimaging studies can also be tested for causality and function in animal models, potentially on multiple genetic backgrounds (Figure 3).

Phenotype-driven genetics of ABA.

Various mouse strains exhibit differential susceptibility to ABA. Specifically, DBA/2J female mice show greater wheel running activity, greater weight loss, less food intake, and severe hypoleptinemia compared to C57BL/6J[89]. C57BL/6J showed greater ABA than A/J and multiple chromosome substitution strains[90]. A genetic correlation between baseline physical activity (wheel running, locomotor) and ABA across inbred strains[91] identified physical activity as a potential premorbid trait that predicts the development of ABA. Despite inbred strain differences in ABA, causal genetic factors have yet to be found.

Phenotype-driven genetics of BLE.

Phenotypic differences in BLE between inbred rodent strains implicate underlying causal genes[92,93]. In an intermittent, limited access paradigm for BLE of sweetened PF, cytoplasmic FMR-interacting protein 2(*Cyfip2*) was mapped and validated in a cross between C57BL/6 substrains. *Cyfip2*+/− mice showed a decrease in compulsive BLE of PF but not chow[94]. *Cyfip1*+/− mice also showed modulation of BLE, depending on parent-of-origin, genetic background, and sex[95]. *CYFIP1* CNV is implicated in autism, ADHD, psychosis[96], and, possibly, AN although lab validation of the CNV calling failed[39]. The study of BLE with increased genetic diversity, additional diets (high fat diet), and environmental variables will increase gene identification. In support, a recent study involving a cross between the BLE-prone DBA/2J strain with the BLE-resistant C57BL/6J strain[92] identified multiple QTLs influencing eating behavior and body weight, including a sex-combined QTL containing the candidate gene Lcorl that influences initial consumption of palatable food, a female-selective locus containing the candidate gene Zeb1 underlying changes in body weight during BLE, and a male-selective locus for escalation in palatable food intake that contains the candidate genes Adipor2 and Plxnd1[97].

Given the diverse array of mouse crosses and populations that are now available to accelerate gene mapping, forward genetic studies of ABA and BLE in rodents provide the opportunity for novel gene/pathway identification. Such studies are sorely lacking. Nonetheless, *CYFIP1* and *CYFIP2* have homologs to study in humans. Although neither of these genes has yet been associated with AN through GWAS[8], ongoing GWAS of BED and BN will be more relevant for assessing the association between CYFIP genes and binge eating in humans.

Omic studies of ABA.

Omics analysis has been applied to both brain tissue and gut microbiota to improve our understanding of molecular adaptations associated with ABA and BLE. Proteomic studies in ABA models have identified hypothalamic mitochondrial and autophagy processes[98], deficits in energy metabolism in colonic mucosa[99], and an increase in ATP-producing glycolytic enzymes in gut microbiota[100]. These results implicate an adaptive energy source in the gut that could influence brain function and feeding behavior in AN. Opposing changes in energy utilization between the hypothalamus and gut mucosa during ABA suggest that restoration of energy homeostasis between the CNS and periphery could improve treatment of AN in humans.

Animal models can be used to longitudinally measure the impact of early life factors like stress, diet, or genetics on eating disorders. In a mouse model involving chronic, variable mild stress in pregnant dams, prenatal stress (PNS) induced transcriptomic indices of hypothalamic HPA and metabolic dysfunction associated with obesity and protected against ABA in adolescent female mice. PNS protection was associated with increased DNA methylation and placental miR-340 downregulation and upregulation of miR-340 targets[101]. Low miR-340 and ABA resistance were also associated with increased expression of SLC nutrient transporters (amino acids, glucose), and growth factors that are potentially regulated by miR-340 targets. Placental overexpression of miR-340 recapitulated fetal and adolescent hypothalamic and circadian dysfunction[101], supporting a role for placental miR-340 in regulating nutrient availability that could influence eating disorder susceptibility.

Omics of BLE.

Transcriptome analysis of the striatum found a BLE-induced downregulation of myelination genes[94], supporting reports of decreased white matter integrity with increased BE in individuals with BN[102]. Gut microbiota from male rat feces following intermittent access to energy-rich “cafeteria” showed changes in microbial flavonoid, bile acid, d-arginine, d-ornithine, fatty acid, and geraniol biosynthetic pathways that correlated with body weight, adipose tissue, glucose, leptin, and insulin[103]. Although similar studies are needed in humans, these data suggest that microbial pathways could be targeted to normalize eating and metabolic function in BE.

To summarize, omics analysis of relevant tissues at appropriate time points in animal models for eating disorders offer distinct, complementary advantages to human studies and will continue providing unique insights into the hedonic and homeostatic adaptations that could inform therapeutics. Furthermore, combining omics with phenotype-driven forward genetic studies can further inform mechanisms of gene dysfunction and the consequent genomic adaptations that drive and sustain disordered eating. Expanding these latter approaches would provide valuable triangulation of omics studies in humans.

Viral overexpression and neural circuit studies of ABA.

Contemporary circuit approaches to understand feeding suppression and stimulation have been reviewed elsewhere (e.g.,[104-106]). Here, we distinguish our discussion from the physiology of homeostatic meal termination—adaptive anorexigenic responses—and focus on related studies involving ABA that more holistically model AN pathology and behavioral phenotypes. These studies provide more direct evidence as to the associative and causal neurobiological factors of AN. Viral overexpression of the D2 dopamine receptor in D2-containing mouse neurons of the NAc core induced hyperactivity, increased food intake, and enhanced ABA-induced wheel running and weight loss in females[107]. Only females showed severe weight loss during scheduled fasting alone, even without a change in food intake or hyperactivity. More recently, chemogenetic activation inhibition of the projection from medial PFC to NAc shell decreased cognitive flexibility and increased ABA whereas inhibition prevented ABA weight loss and increased cognitive flexibility[108]. Zhang and Dulawa propose that projections from the NAc shell to the lateral hypothalamus (LH)

and in turn, from the LH to the VTA, could link ABA-induced mesocorticolimbic reward dysfunction with ABA-induced changes in metabolism[109] (Figure 4).

The NAc receives strong input from VTA dopamine-producing neurons, and specific chemogenetic activation of NAc-projecting VTA DA neurons increases food intake, food anticipatory activity, and survival in the ABA model[110]. These results implicate female-specific metabolic dysfunction induced by NAc D2 overexpression[107] and suggest that NAc D2 receptor density and signaling could affect risk for AN and predispose individuals toward excessive exercise, potentially as a means to alleviate underlying reward deficiency —although further studies are needed to support this hypothesis. Combined with genetic studies implicating striatal neurons that express either D1 or D2 and human imaging studies, we propose that striatal circuits are a biological risk hub that warrant further investigation.

Moreover, animal, clinical, and genetic findings implicate leptin in the risk and maintenance of AN. Hyperactivity, eating restraint, and earlier weight loss after inpatient refeeding are correlated with lower leptin in AN patients[111], implicating a loss of leptin signaling in VTA underlies ABA hyperactivity. In ABA rats, leptin treatment reduced hyperactivity via the VTA region[112], implicating a loss of leptin signaling in VTA underlies ABA hyperactivity. GWAS-based genetic correlations suggest an overlap in the biological regulation of AN, leptin, and physical activity[8]. A case report suggested that leptin treatment may reduce hyperactivity and eating disorder-related cognitions in AN[113]. Although it has not been studied in AN, human neuroimaging studies in healthy individuals demonstrate that leptin regulates mesolimbic dopamine systems under stress[114]. Accordingly, leptin is an important hormone in linking genetics with alterations in the DA reward system.

Optogenetic and chemogenetic analysis of BLE.

Optogenetic and chemogenetic approaches seek to identify and manipulate specific cell types and fibers to test proposed circuitry in feeding[115], see reviews (e.g., [104]). *Here, we focus on studies employing BLE paradigms directly or indirectly associated with the mesolimbic reward pathway.*

Several studies have identified that activation of inputs to VTA dopamine (DA) neurons from the lateral hypothalamus, bed nucleus of the stria terminalis, or the dorsal raphe nucleus produces positive valence, appetitive behavior, and can increase compulsive-like food or liquid reward consumption[104]. Broadly, these studies support a physiological role for these brain circuits in shaping motivation and food consumption by transient phasic activation of VTA DA neurons. Conversely, persistent activation of VTA DA neurons using chemogenetics or via the 5HT2C receptor agonist lorcaserin resulted in a reduction in binge eating[116]. Of note, direct stimulation of VTA DA neurons does not stimulate eating per se[117]. These data suggest that the observed contribution of VTA DA neurons to BLE is complex and sensitive to the time scales of experimental manipulations. These findings also underscore the critical need to understand how VTA DA neuron activity is altered across multiple binge eating episodes. Finally, the incorporation of pathological BLE models that pair food consumption with aversive consequences (e.g., footshock) will be useful in distinguishing between patterns of VTA neuron activity that accompany adaptive hedonic

food consumption versus repetitive compulsive-like BLE that is insensitive to negative reinforcement.

Studies of BLE have also revealed important changes in neural circuits **receiving** robust dopamine inputs and how dopamine receptors modulate neural activity in these sites. The VTA and substantia nigra pars compacta DA neurons project to the ventral (NAc) and dorsal striatum. Released DA then shapes ongoing neural activity in medium spiny neurons primarily via modulation of downstream PKA-dependent signaling cascades. In the NAc, a multiday course of binge eating increase delta band oscillations of local field potentials (LFPs) and single unit activity in anticipation of palatable food intake[118]. Palatable food consumption was specifically disrupted via targeted stimulation during anticipatory periods, a phenomenon that may require activation of D2 receptors[119]. Interestingly, delta band oscillations in the ventral striatum were observed in humans[118]. Anticipatory activity, or ramps, are also visible in the dorsal striatum at the level of single neurons or bulk calcium transients during food approach [120]. These ramps rapidly terminate during food consumption and their functional requirement to binge eating is unknown.

Modulation of the dorsal and ventral striatum also occurs from prefrontal and insular cortex (IC) inputs. The IC integrates taste, interoception, and motivation to regulate feeding, and food-predictive cues reliably activate IC neurons[121,122]. Chemogenetic activation of the anterior IC as a whole decreases palatable food intake and cue reactivity in a rat model of binge eating[123], and optogenetic activation of the right anterior IC in mice similarly reduces food intake[124]. Conversely, in a model of compulsive binge eating in rats, pathway-specific inhibition of the insula cortex (IC) to NAc decreased appetitive behavior to receive palatable food intermittently paired with foot shock[125]. These studies indicate a complex role of the insula in reinforcement and compulsive BLE. In the prefrontal cortex (PFC), activation of NAc shell projecting neurons reduced food intake in a binge-eating model in rats predisposed to high impulsivity, a trait observed in a previous study[126]. Optogenetic activation of inhibitory VIP-expressing interneurons of infralimbic and prelimbic mPFC in male mice decreased BLE of a high caloric diet[127]. These findings implicate reduced function of the PFC->NAc circuit in impulsivity and BLE. Further study of these circuits across the acquisition of BLE behavior (first episode vs last) is necessary to investigate the dynamics and link to pathology more precisely. Nonetheless, these findings demonstrate that BLE can be inhibited in real time through neural circuit manipulations demonstrating that ongoing activity of specific cortical and limbic circuits is required for BLE.

Animal Model Limitations.

One of the primary limitations in the use of animal models is their inability to capture complex psychological constructs important to the etiology of eating disorders like a drive for thinness, body dysmorphia, or intense fear of weight gain in the case of AN and a loss of control for BLE. However, emerging technologies in markerless pose estimation and deep learning provide basic scientists the opportunity to extract novel behavioral phenotypes that may be associated with these constructs[128]. The other major limitation of animal models is that, to date, animal models have not yet been used to test the causal nature of a sum of polygenic risk-associated common variants from an eating disorder group. This is an

important technical and conceptual factor to consider as we move closer to testing causality of disease-associated variants.

Integration.

Circuit approaches in animal models provide increasing specificity with regard to cell types and their connections underlying ABA and BLE. Convergent evidence across studies suggests that longitudinal assessment of neuronal function in mesolimbic and nigrostriatal circuits, combined with single cell omics will advance our understanding of the central neuronal adaptations as well as peripheral cell type-specific adaptations that drive maladaptive feeding. These assessments should incorporate hypotheses informed by emergent GWAS and human imaging data and can in turn contextualize and inform studies in humans.

Genetic, neuroimaging, and animal model research in eating disorders have largely represented independent disciplines. These sciences of eating disorders have now matured adequately that cross-communication is both possible and essential in order to strengthen causal inferences and translate observations into biological understanding and novel therapeutics.

Conclusions and Future Directions.

As human GWAS and neuroimaging studies grow and diversify and novel animal models are developed, efforts to bridge disciplines must expand. Ongoing GWAS of BED and BN will give context to findings from mouse BLE models. Gene-driven approaches in neurobiology and behavior should increasingly incorporate evidence for association of target genes from human GWAS. Interdisciplinary efforts will benefit studies investigating the main effects of genes and variants, as well as gene-gene and gene-environment interactions. Exquisite control over environmental factors in animal models will allow rigorous testing of putative interactions from genome-wide observational epidemiology in eating disorders. Finally, eating disorder research must be proactive in embracing other disciplines. For example, the utility and diversity of induced pluripotent stem cell models has increased rapidly, and the application of these models to eating disorder research could yield valuable new insights[129]. Our hope is to accelerate target identification by applying robust statistical genetic and pathway analysis methods, large-scale brain and neurodevelopmental systems biology approaches, and innovative chemoinformatics[130]. In order to do this, eating disorders should seek to communicate across disciplines, including establishing meetings dedicated to translational eating disorders research. Ultimately, the goal is to translate genetic and neuroscience findings directly into the clinic to enable biologically informed tailored treatment selection and delivery and to eliminate morbidity and mortality from these debilitating illnesses.

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Box 1:

Overview of Eating Disorder Phenotypes

Anorexia nervosa.

The hallmark symptom of AN is low body weight, accompanied by persistent restriction of energy intake and/or increased energy expenditure, intense fear of gaining weight or persistent behavior preventing weight gain, and distorted body image[1]. Both a restricting and a binge-eating/purging subtype exist. The lifetime prevalence is 1.4% (0.1-3.6) for women and 0.2% (0-0.3%) for men%)[131]. The standardized mortality ratio of AN is >5 [132] with deaths primarily attributable to illness effects and suicide[133]. Treatment outcome in adults is poor with only 30% achieving full recovery[134]. Family-based treatment for youth is recommended; multidisciplinary interventions are recommended for adults although the evidence base remains particularly weak[135]. No medications exist that successfully treat the disorder or are approved by the FDA[135].

Bulimia nervosa.

The core symptoms of BN include binge eating (eating an unusually large amount of food in a circumscribed period of time accompanied by a sense of loss of control) and inappropriate compensatory behaviors (e.g., self-induced vomiting, abuse of laxatives, diuretics, fasting, excessive exercise), with self-evaluation being strongly influenced by shape and weight[1]. BN can occur at all body weights, but is diagnosed as AN binge-eating/purging subtype in the presence of AN. The lifetime prevalence is 1.9% (0.3-4.6%) for women and 0.6% (0.1-1.3%) for men[131], and onset is typically in late adolescence or early adulthood. Cognitive-behavioral therapy (CBT) is the leading evidence-based treatment and fluoxetine, whose efficacy was established in placebo-controlled clinical trials in the early 1990s, is the only FDA approved medication[135] BN recovery rates are ~50% at 5-10 years follow-up[136].

Binge-eating disorder.

BED is marked by recurrent binge eating that causes distress, the absence of regular compensatory behaviors, and behavioral and emotional features such as eating rapidly or when not hungry, and feeling embarrassed or disgusted by one's behavior[1]. The lifetime prevalence is 2.8% (0.6-5.8%) for women and 1.0% (0.3-2.0%) for men[131]. Onset is typically early adulthood but can be at any time and in individuals spanning the normal to obese weight ranges[1]. Evidence-based treatments for BED include CBT, second-generation antidepressants, and since 2015, lisdexamfetamine an FDA approved stimulant originally prescribed for the treatment of attention deficit hyperactivity disorder[137]. Preclinical, clinical, genetic studies (of binge eating), and neuroimaging data converged on dysfunction in systems regulating eating behavior and reward (i.e., dopaminergic and noradrenergic), and support the repositioning of lisdexamfetamine in BED[138].

Box 2:

Animal Models for Eating Disorders

Activity-based anorexia (ABA).

AN has some characteristics that cannot be modeled in rodents (drive for thinness, body image distortion, intense fear of weight gain). However, key behavioral components of AN as well as traits commonly comorbid with AN can be modeled in mice (high physical activity, anxiety, depression, social anxiety, obsessive-compulsive-like behavior). Perhaps most well-known is the activity-based anorexia (ABA) model that starts with daily unlimited chow availability but for only 2h per day or less followed by introduction of a running wheel which leads to compulsive-like running, appetite suppression, voluntary restriction of food intake, decreased anxiety-like behavior, severe weight loss, and death without intervention[139]. ABA induces other AN-like effects on physiology, including hypothermia, loss of estrus, increased HPA axis activity, anhedonia, ulcers, and humoral, CNS, cardiovascular, and GI dysfunction[140]—a credible model for the behavioral and physiological components of AN.

Binge-like eating (BLE).

Binge eating shares several features with substance use disorders—tolerance, withdrawal, relapse, loss of control, and compulsive intake. Binge-like eating (BLE) has been studied in animals[141], defined by increased intake of palatable food (PF; high caloric) versus chow and escalation of intake over time[142]. Compulsive-like eating refers to habitual, often increased effortful intake despite potential harm (aversive stimulus) that can relieve negative affect during withdrawal[143]. Home cage chow restriction, stress exposure, and limited, intermittent access to PF can all promote BLE[144]. Intermittent BLE models induce the most robust binge-like eating, yet do not typically induce obesity, as rodents voluntarily restrict chow intake in anticipation of PF which in turn, increases PF reinforcing efficacy[145,146]. BLE is a reasonable animal approximation of the behavioral components of dysregulated eating characteristic of human binge eating.

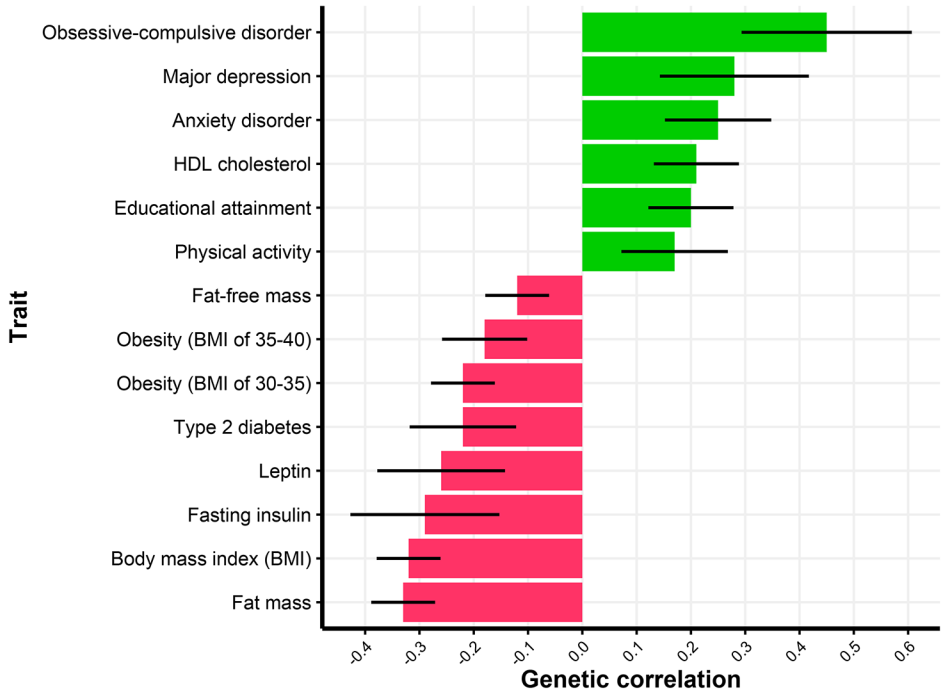

Figure 1. Genetic correlations between anorexia nervosa and selected top traits.
The error bar represents the 95% confidence interval. Values retrieved from[8].

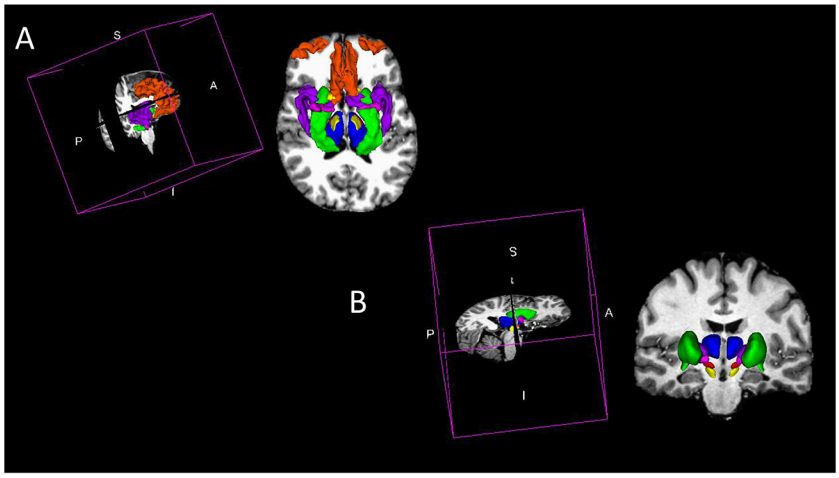

Figure 2.

Human neuroimaging circuitry involved in eating disorders. (A) Represents the structures comprising two major dopaminergic pathways, mesolimbic and mesocortical pathways, supported by prior work in animal models. Both originate in the ventral tegmental area (red); mesolimbic pathways project to the nucleus accumbens, and is part of the complex circuit involving the amygdala (pink), hippocampus (green), and the bed nucleus of the stria terminalis (yellow). The mesocortical pathway projects primarily to the prefrontal cortex (orange) and insula (purple). (B) Represents sub-structures involved in the cortico-striatal-thalamo-cortical (CSTC) pathway that are supported by recent genetic/GWAS studies with shared functional networks that exhibit overlapping phenotypes. The CSTC pathway is a multi-synaptic neuronal circuit that connects the cortex with the striatum and thalamus. The striatum (green) receives glutamatergic input from the cortex and the thalamus (blue) sends out GABAergic inputs to the sub-thalamic nucleus (pink, purple, red).

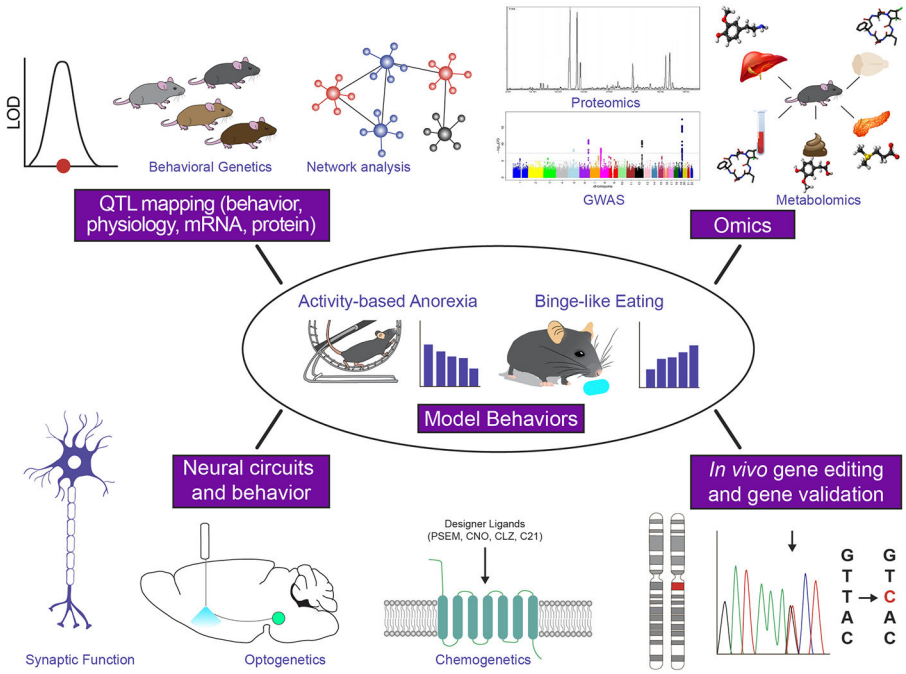

Figure 3.

Forward and backward translation of eating disorder-relevant traits at different levels of biological hierarchy. Activity-based anorexia (ABA) and binge-like eating (BLE) are behavioral models for restrictive eating in AN and for binge eating in BN and BED. Within the use of animal models, there are four primary approaches that seek to elucidate the fundamental biology of eating disorders: QTL mapping, Omics, neural circuit manipulations, and in vivo gene editing. QTL mapping is used to discover genetic loci and ultimately candidate causal genes and variants that regulate phenotypic traits at the molecular, cellular, or behavioral level. QT mapping capitalizes on natural variation across different strains or substrains of laboratory models like mice. Omics investigations are carried out at the genomic, transcriptomic(not shown), proteomic, microbiomic, or metabolomic levels and can reveal novel biological pathways that regulate feeding and/or metabolism. In vivo gene editing research can be used to establish causality for candidate genomic variants identified from rodent QTL/GWAS or in silico studies. Neural circuit approaches are also used to establish causal molecular, cellular, or circuit elements that drive eating behavior and metabolism. They span the range of observing neural activity and synaptic function, manipulating those circuits in real time (e.g., via optogenetic. chemogenetic, or pharmacological approaches), and layering these experiments with pathological models.

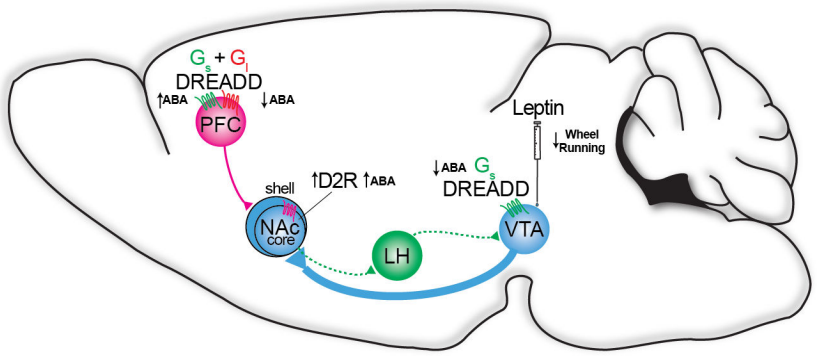

Figure 4. Mesocorticolimbic reward dysfunction in activity-based anorexia.

VTA: ventral tegmental area; NAC: nucleus accumbens; LH: lateral hypothalamus; mPFC: medial prefrontal cortex; DREADD = designer receptor exclusively activated by designer drugs; Gi = G inhibitory DREADDS; Gs = G stimulatory DREADDS; D2 = D2 dopamine receptor overexpression. Green indicates excitation of cell type and pathway. Red indicates inhibition of pathway. Purple indicates overexpression. Overexpression of D2 dopamine receptors in medium spiny neurons of NAc core increased ABA phenotypes and combined with scheduled fasting alone (no wheel running), was sufficient to induce weight loss and glucose intolerance in females without affecting food intake[107]. Chemogenetic activation of the mPFC->NAc shell pathway decreased cognitive flexibility and increased ABA; inhibition had the opposite effect[108]. Chemogenetic activation of VTA neurons decreased ABA and increased survival[110]. Leptin injections into the VTA decreased wheel running[112]. Blue arrows indicate pathway proposed by Zhang and Dulawa[109] to mediate mesocorticolimbic reward modulation of energy expenditure and metabolism in ABA. Additional work is necessary to delineate the circuits, neurotransmitters, and hormones that link ABA reward dysfunction with increased energy expenditure.

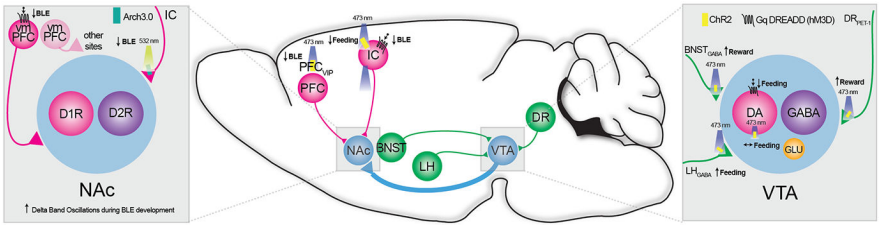

Figure 5. Mesolimbic-centered neural circuits that modulate binge-like eating (BLE).

Converging on the VTA to NAc dopaminergic circuit, behavioral neuroscientists have used circuit-level techniques like chemogenetics and optogenetics to study BLE, normal feeding, and reward-like behavior. Inputs to the VTA from the DR, BNST, and LH modulate reward and food consumption as shown by pathway-specific optogenetics. Within the VTA, chemogenetic activation of VTA DA neuron reduces BLE and direct optogenetic activation has no impact on feeding. Within the NAc, pathway specific optogenetic inhibition of the inputs from the insular cortex reduces BLE. Similarly, chemogenetic activation of the NAc-projecting input cells from the vmPFC or VIP-expressing neurons in the prelimbic and infralimbic PFC also reduces BLE. Abbreviations: BLE – binge-like eating; BNST – bed nucleus of the stria terminalis; ChR2 – Channelrhodopsin2; DA – dopamine; D1R – dopamine D1 receptor; D2R – dopamine D2 receptor; DR – dorsal raphe; GABA – gamma aminobutyric acid; GLU – glutamate; IC – insular cortex; LH – lateral hypothalamus; NAc – nucleus accumbens; PET-1 - PC12 ETS Domain-Containing Transcription Factor; PFC – prefrontal cortex; VIP – vasoactive intestinal polypeptide; vmPFC – ventromedial prefrontal cortex; VTA – Ventral tegmental area.