Animal Models of Eating Disorder Traits

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Contents

Abstract Eating disorders, such as anorexia and bulimia nervosa, are psychiatric disorders that are likely determined by a complex interaction between genetic variations, developmental processes, and certain life events. Cross-species analysis of traits related to eating disorders may provide a way to functionally and systematically study neurobiological mechanisms underlying these disorders. Interspecies trait genetics may offer opportunities to identify common neurobiological mechanisms underlying eating disorder characteristics relevant to the initiation, progression, and/or maintenance of the disease, such as cognitive rigidity, increased anxiety levels, and behavioral hyperactivity. These can subsequently be tested directly by studying allelic variation in mice and human subjects and by applying methods that can modify gene expression levels in rodent models. Increasing our knowledge about these traits and their underlying neurobiological mechanisms will be relevant to develop new therapies for patients within the heterogeneous eating disorder populations. Novel mouse genetic and phenotyping tools offer a way to study these neurobehavioral traits under controlled environmental and genetic background conditions.

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1 Why Studying Eating Disorder Traits?

The human population with eating disorders is highly diverse revealing many different phenotypes both between and within eating disorders. Anorexia nervosa, for example, is a serious psychiatric disorder characterized by severe and selective restriction of food intake. This eating disorder, with a high prevalence among young adolescent females (15–19 years), results in extreme body weight loss and has a mortality rate of up to 15% (Hoek 2006). Anorexia nervosa patients also show other symptoms that are not observed consistently throughout the anorexia nervosa patient population. For example, behavioral hyperactivity is considered an important phenotype of the disease (Bergh and Sodersten 1996; Brewerton et al. 1995b; Davis et al. 1997; Hebebrand et al. 2003), since it leads to accelerated body weight loss and is observed in a large proportion (40–80%) of the anorexia nervosa population. In addition, a large group of anorexia patients suffers an anxiety disorder that is already present pre-morbidly and that can vary greatly between patients [e.g., a general anxiety disorder, social phobia, or panic disorder (Brewerton et al. 1995a; Bulik et al. 1997; Godart et al. 2002; Toner et al. 1988)]. Furthermore, lifetime compulsion and obsession phenotypes occur in a large sample of the anorexia nervosa population (Halmi et al. 2003). Thus, the expression of an eating disorder is not uniform and is characterized by different phenotypes that are variable within the patient population.

Phenotypic heterogeneity within the eating disorder population complicates identification of disease genes and may also reflect differences in the etiology of these disorders. The current diagnostic criteria are not sensitive enough to differentiate between subgroups of anorexia nervosa patients. Further understanding these differences is highly relevant for finding the disease genes as well as in view of developing effective treatment programs that may be directed toward specific pathophysiological features of the disease. Indeed, current treatment possibilities only cure a small proportion of the eating disorder patients [for review, see (Fairburn and Harrison 2003; Treasure et al. 2010)], and high relapse rates are documented (Herzog et al. 1999; Carter et al. 2004). Furthermore, genetic studies have, thus far, not revealed many replicated candidate genes for neither anorexia nervosa nor bulimia nervosa [for review, see (Hinney et al. 2000; Kas et al. 2003b; Klump and Gobrogge 2005; Mazzeo et al. 2006; Bulik et al. 2007b)], suggesting that either different subgroups within the population may relate to differences in affected genetic pathways or major susceptibility genes have not been found. For those reasons, dissecting phenotypic variation across the patient population and targeting those behavioral deficits that are leading to the initiation, progression, and/or maintenance of the disease would be an alternative strategy in the battle against these dramatic disorders.

2 Eating Disorder Traits

Several studies have focused on the identification of heritable phenotypes that are present in the eating disorder population (Keski-Rahkonen et al. 2005; Bulik et al. 2007a; Mazzeo et al. 2009). Recently, Gottesman and Gould (2003) put forward the psychiatric endophenotype concept to facilitate the identification of genes relevant for neuropsychiatric disorders. Endophenotypes, which are expected to have lower genetic heterogeneity than clinical diagnoses, may represent simpler clues to genetic underpinnings than the disease syndrome itself. Furthermore, endophenotypes may not be specific to one psychiatric disorder but have overarching effects impacting on several different diagnoses. This promotes the view that psychiatric diagnoses can be deconstructed to facilitate more straightforward and successful genetic analysis.

As described earlier in a paper by Bulik et al. (2007a), "an endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature. Endophenotypes are heritable, cosegregate with a psychiatric illness in the general population, are state independent, (i.e., manifest in the individual whether illness is active), and are found in nonaffected family members at a higher rate than in the general population. Other enhancements of the definition of endophenotype include being linked to the causal process, involved in plausible biological mechanisms, predictive of the disorder probabilistically, and lying closer to the site of the primary causative agent. The term subphenotype has also been used to identify more homogeneous subgroups of complex syndromes (e.g., early onset depression or BN with self-induced vomiting). Although not as clearly defined as endophenotypes, they are commonly used as a means to reduce the heterogeneity inherent in sampling based on a diagnostic category or syndrome. An example of the hierarchy would be: the phenotype of schizophrenia; the subphenotype of individuals with schizophrenia who report auditory hallucinations; and the endophenotype of P50 event-related potential suppression." Based on these definitions, Bulik et al. (2007a) have generated an overview on potential traits for eating disorders (Table 1).

By making use of neuroimaging techniques, new insights into neurobiological mechanisms of eating disorders have been obtained. As with psychological and behavioral eating disorder traits, neurocircuit wiring and their related functioning may also provide novel ways to classify subgroups within the eating disorder population. In a recent review, Kaye et al. (2009) described how altered brain activity in the insula could explain interoceptive dysfunction in anorexia nervosa. Furthermore, altered striatal brain activity may be related to differences in reward signaling in eating disorder patients (Kaye et al. 2009). Behavioral changes seen in the development of anorexia nervosa may be related and maintained by (permanent) brain circuit alterations due to developmental (e.g., puberty) and/or environmental factors (e.g., stressful life events). For those reasons, neuroimaging characteristics may provide a way complementary to behavioral traits to closer study neurobiological circuits underlying eating disorders.

Table 1 Summary of data addressing whether psychological, physical, and biological traits represent endophenotypes or subphenotypes for eating disorders (from Bulik et al. 2007a, b)

Trait	Endophenotype criteria						Endo?	Sub?
	Measurable	Heritable	Cosegregates with illness	State independent	Observed in unaffected family members	Biologically plausible causal mechanism		
Perfectionism	+	Moderate	++	+++	+	Unknown	Unknown	++
Obsessionality	+	Moderate	+++	+++	+	+	+	
Drive for thinness	+	Moderate	+++	++	+?	+	Unknown	+++
Anxiety	+	Moderate	+++	++	+	+	+	
Negative emotionality	+	Moderate	+++	++	+	+	+	
Decreased food intake	+	Moderate-large	+++	+	Unknown	+++	Unknown	+++
Low body weight (dysregulation of body weight)	+++	Moderate-large	+++	+	Unknown	Unknown	Unknown	+++
Increased physical activity	+	Moderate-large	+++	+	Unknown	Unknown	Unknown	+++
Cognitive set-shifting	++	Moderate-large	++	+	+	+++	++	
Binge eating	+	Moderate	+++	No	Unknown	+	No	+++
Self-induced vomiting	+	Moderate-large	+++	No	Unknown	Unknown	No	+++
Impulsivity	+	Moderate-large	++	++	+	+	+	
Undue influence of weight or shape	+	Small	+++	++	Unknown	No		

AN anorexia nervosa, *ANR* restricting type AN, *BN* bulimia nervosa, *ANBP* binge/purge type AN, *Endo* endophenotype, *Sub* subphenotype, *Unknown* no studies have examined that the issue or existing data are incondusive. Plus marks (+) denote the strength of data supporting each criterion. For example, in the "measurable" column, a single plus (+) denotes that only self-report measures were used to assess the trait. A double plus mark (++) indicates that observer ratings or neuropsychological data were used to assess the trait. A triple plus mark (+++) indicates that the trait can be measured objectively by an outside observer (e.g., body weight) or can be assessed with a biological assay or marker (e.g., 5HT transporter activity). In the remaining criteria columns, the plus marks indicate the strength of the data supporting the criterion in terms of the number of studies reporting positive findings (i.e., + = few studies; ++ = more studies; +++ = many studies). In the Endo? and Sub? columns, the plus marks indicate the extent to which the trait satisfies the criteria for an endophenotype or subphenotype (+ = some evidence that criteria are supported; ++ = moderate evidence; +++ = strong evidence). Traits exhibiting the strongest evidence in support of their categorization as endophenotypes are noted in bolded and outlined text

In view of these behavioral and neuro-anatomical characteristics, some considerations should also be taken into account. For instance, some of the core characteristics identified may be highly dependent on each other and/or may reflect the same pathophysiological process. For example, do neurocircuits that underlie disturbed set-shifting in anorexia nervosa (partially) overlap with those of compulsive behavior and/or of perfectionism observed in these patients, or are these truly separate components of the disease? In addition, recent studies have indicated that behavioral hyperactivity seen in anorexia nervosa is related to the levels of anxiety and food restriction (Holtkamp et al. 2004), indicating that some behavioral characteristics are highly dependent on others. This requires practical considerations about study design to assess these potentially related eating disorder characteristics properly. Once we understand better the mechanisms underlying the traits that contribute to the development and maintenance of an eating disorder, new horizons arise for novel treatments. Future research is necessary to study the relation between these eating disorder characteristics, and the genetic pathways and neural circuits underlying the pathophysiological neuroprocesses that drive these behavioral characteristics.

3 Rational for Animal Models of Eating Disorders

Understanding the biology of behavioral disorders, including eating disorders, requires identifying and functionally testing biological substrates in relation to these disorders. Interference with, for example, pharmacological agents or genetic manipulations is a standard tool in animal research to test their involvement in physiological processes. Animal studies allow systematic studies in which environmental and genetic factors can largely be controlled for. The challenge is, of course, how to develop an animal model for eating disorders, such as anorexia nervosa. Indeed, validity of translational animal models is widely accepted for common physiological processes (such as blood pressure regulation); however, cross-species comparison for psychiatric disorders offers a challenging opportunity for biomedical research (Dennis 2005).

Recently, a proof of concept of the confluence between mouse and human for psychiatric traits was presented by Chen (Chen et al. 2006). A common genetic variant of the brain-derived neurotrophic factor (BDNF) gene in humans is associated with alterations in brain anatomy, memory and has been associated with psychiatric disorders, such as eating disorders, depression, and schizophrenia (Egan et al. 2003; Ribases et al. 2004; Lang et al. 2005; Lohoff et al. 2005; Neves-Pereira et al. 2005; Ribases et al. 2005; Schumacher et al. 2005). BDNF has an important function in neuronal survival, differentiation, and synaptic plasticity. Chen and co-workers showed that when the human Val66Met variant is genetically introduced in mice, it exhibits phenotypic characteristics in humans with the variant allele, including anxiety-related behaviors. This finding illustrates the potential of comparative neurobehavioral genetic studies between mouse and human.

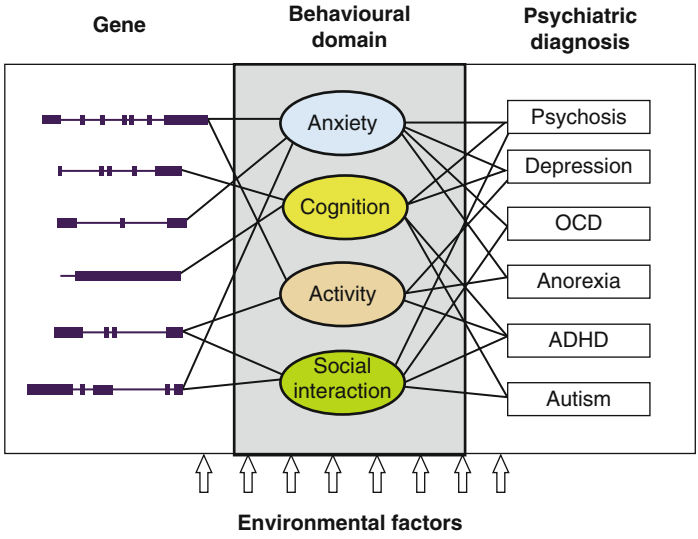

Fig. 1 The behavioral domain concept across psychiatric diagnosis. The relationship of behavioral domains to susceptibility genes will be more direct than the relationship with clinical diagnosis, since the disease will be a more heterogeneous composite of behavioral traits, which are modulated by protective and adverse life events. The contribution of these life events can also be modeled in mouse where environment can be controlled and manipulated. Note that this schematic diagram is intended to be illustrative of a behavioral domain concept, rather than demonstrate associations, which are proven by genetic epidemiology (from Kas et al. 2007)

Interestingly, certain behavioral domains that are affected in eating disorders may be relevant across the psychiatric spectrum. For example, set-shifting difficulties are observed in anorexia and bulimia nervosa (Tchanturia et al. 2004; Holliday et al. 2005), but are also observed in obsessive–compulsive disorders, suggesting that there may be common neurobiological mechanisms underlying certain aspects across diagnosis. Moreover, certain behavioral domains, such as intra- and extra-dimensional set-shifting can be studied in animals as well (Birrell and Brown 2000; Brigman et al. 2005; Bissonette et al. 2008). These behavioral domains may provide a good starting point for understanding the neurobiological mechanisms underlying these behavioral disorders (Fig. 1).

4 How These Traits Are Mimicked in Animals

As indicated with the Val66Met variant in the BDNF gene, studying gene function in relation to behavioral deficits across species may be one way to go in view of translational research for psychiatric disorders. In addition, novel gene identification methodologies for behavioral traits are another option and have been largely

developed. For instance, with the current availability of a large variety of inbred mouse strains and their known genome sequences (Frazer et al. 2007; Yang et al. 2007), mouse genetics offer a challenging way to study complex neurobehavioral traits. In contrast to patient populations, mouse strains can be used to control for phenotypic and genetic heterogeneity as well as for studies aiming at understanding complex gene–environment interactions. With the recent generation of genetic reference populations, such as recombinant inbred strains (RIS) (Plomin et al. 1991) and chromosome substitution strains (CSS) (Singer et al. 2004), quantitative trait loci (QTL) analysis can be performed for complex neurobiological traits in mice. Additional approaches for mice, such as haplotype mapping (Grupe et al. 2001; Wade et al. 2002; Wade and Daly 2005), genome-wide gene expression (Sandberg et al. 2000; Jansen and Nap 2001; Fernandes et al. 2004; Letwin et al. 2006; Hovatta et al. 2007), and quantitative complementation studies (Yalcin et al. 2004) provide a complementary technological platform for gene identification. With the technology in place, the true challenge for this translational approach is the development of appropriate animal models for eating disorders and exposure of genetically defined mice to these models.

The activity-based anorexia (ABA) or semi-starvation-induced hyperactivity model is, among others (Siegfried et al. 2003), a known animal model to study pathophysiological processes in anorexia nervosa. The ABA model is around since the 1960s (Routtenberg and Kuznesof 1967) and ABA is induced in rodents with voluntary access to running wheels and that are exposed to daily scheduled restricted food availability. Reminiscent of anorexia nervosa, certain rat and mouse inbred strains exposed to this daily scheduled feeding paradigm exhibit a paradoxical behavioral hyperactivity with reduced food availability and a subsequent accelerated body weight loss (Kas et al. 2003a; Gelegen et al. 2007). Excessive behavioral hyperactivity may be a core trait of anorexia nervosa (Brewerton et al. 1995b; Bergh and Sodersten 1996; Davis et al. 1997, 1999; Hebebrand et al. 2003). In addition, it has been shown that Olanzapine, an antipsychotic drug, can suppress behavioral hyperactivity in both anorexia nervosa patients and rodents exposed to the ABA model (Hillebrand et al. 2005b). Furthermore, plasma leptin levels are correlated with physical activity levels in anorexia nervosa patients during the acute phase of the illness (Holtkamp et al. 2003; van Elburg et al. 2007), and chronic leptin infusion suppresses behavioral activity in rats exposed to the ABA model (Exner et al. 2000; Hillebrand et al. 2005a). Moreover, reminiscent of the high incidence of anorexia nervosa in young females (in the age of 15–19 years) (Hoek 2006), young adolescent rodents are more susceptible to ABA than older rodents (Barbarich-Marsteller et al. 2007). Taken together, these findings provide some face- and predictive validity of the model for pathophysiological processes observed in anorexia nervosa.

By screening a panel of CSS in the ABA model, we have recently found that different behavioral characteristics of the model can be genetically dissociated. In a CSS panel, each of the 21 mouse substrains has a C57BL/6J genetic background with a single A/J chromosome being substituted (e.g., CSS 1 carries A/J chromosome 1 in a C57BL/6J genetic background). This allows studying

the contribution of single A/J chromosomes to phenotypes and providing a starting point for genetically fine mapping loci on those chromosomes that contribute to the phenotype of interest. When this particular CSS panel was tested in the ABA model, some substrains showed disorganized behavioral hyperactivity with accelerated body weight loss (Gelegen et al. 2010), while other substrains exhibited behavioral hyperactivity during the hours of limited food access (Kas et al. 2010). Some of the substrains did not contribute to ABA phenotypes. Together, these data showed that behavioral components within the ABA model can be dissociated using these CSS and that the dissected components are regulated by mechanisms of different genetic origin. Interestingly, these dissociable ABA phenotypes affect different aspects relevant to the progression and maintenance of eating disorder characteristics. For example, the disorganized behavioral hyperactivity phenotype observed in certain CSS led to accelerated body weight loss (Gelegen et al. 2010), whereas the high levels of running during the daily hours that food is present directly interferes with the eating behavior itself (Kas et al. 2010).

At the genetic level, these findings using CSS may contribute to identify novel mechanisms underlying these eating disorder traits. For example, genomic regions on A/J chromosomes that contributed to disorganized behavioral hyperactivity and subsequent accelerated body way loss display homology with regions on human chromosomes linked with genetic linkage regions in anorexia nervosa cohorts. For example, a region on human chromosome 1 (1p34.2) has been linked to the restricting subtype of AN (characterized by a severe limitation in food intake) (Grice et al. 2002), and this region shows complete overlap with a long region of mouse chromosome 4 that was identified in our genetic screen (Gelegen et al. 2010). For the other dissociable phenotype, behavioral hyperactivity during food access (Kas et al. 2010), the identified mouse chromosomes overlap with two previously observed human OCD chromosomal regions 7p and 15q (Shugart et al. 2006), suggesting that there may be overlap in compulsive wheel running during food access (while being food restricted) and compulsivity in OCD. In this way, our data open new roads for interspecies genetic studies for these neurobehavioral traits that may be relevant to anorexia nervosa and OCD.

In addition to studies that focus on behavioral traits within animal models for eating disorders, such as behavioral hyperactivity in the ABA model, one could also consider modeling susceptibility traits of eating disorders. As described above, anxiety disorders are highly comorbid with eating disorders (Fornari et al. 1999; Godart et al. 2006). Anxiety disorders, such as social phobia, may represent risk factors for eating disorders and could share common mechanisms that are relevant to the development of anorexia and bulimia nervosa. Animal models for these susceptibility traits may reveal new insights into the mechanisms underlying eating disorder development. Table 2 presents a list of characteristics that are relevant to eating disorders and approaches to their measurement in humans together with potential analogous rodent models and their measurement approaches (from Kas et al. 2009).

Table 2 Examples of how eating disorder characteristics may be modeled/tested in rodents and measured in humans (from Kas et al. 2009)

Domain	Characteristic	Human	Rodents
Anxiety and anxiety disorders	Generalized anxiety	Clinical interview	Light-dark box
	Social phobia	Laboratory measures of anxiety and arousal	Open field test
		State Trait Anxiety Inventory	Elevated plus maze
		Social Phobia and Anxiety Inventory	Novelty-suppressed feeding
	Social threat perception	Internet-based programs to assess social threat perception	Social approach behavior
Depression	Dysphoria	Clinical interview	Cocaine withdrawal
	Anhedonia	Beck Depression Inventory	Sucrose preference test
			Anticipatory activity
Weight	Weight dysregulation low	Low BMI	Strains that do not gain weight even with increased consumption
	Weight dysregulation high	High BMI	Strains that gain weight in the absence of increased caloric intake
Motor activity	Behavioral activity	Actiwatch	Activity-based anorexia model
		Observation Questionnaires	Home cage activity monitoring
			Open field testing
Cognition	Set-shifting	Trail Making Test (TMT)	Multidimensional visual stimuli task
		Wisconsin Card Sort Test (WCST)	
		Brixton task	
		Haptic Illusion CatBat task	
		Set-shifting subset of the Cambridge Neuropsychological Test Automated Battery (CANTAB)	
Obsessionality and compulsivity	OCD traits	Yale-Brown Obsessive-Compulsive Scale	Quinpirole-induced compulsive checking
	Symmetry and exactness	EatAte Life	Barbering
	Flaw detection	Internet delivered tasks	Drug seeking behavior
Hormonal	Amenorrhea in response to food deprivation/low BMI	Plasma hormone levels	Plasma hormone levels
			Vaginal cytology

(*continued*)

Table 2 (continued)

Domain	Characteristic	Human	Rodents
Eating behavior	Binge eating	Self-report/laboratory observation In response to short term food deprivation (disinhibition)	Restriction/refeeding and stress-induced eating Intermittent access to palatable foods Deprivation-induced binge eating Novelty-suppressed feeding
Impulsivity	Impulsive behavior	Barratt Impulsivity Scale (BIS) Go/No-go task	Go/No-go task
Brain activity	D2/D3 receptor activity in striatum	SPECT, fMRI, PET	SPECT, fMRI, PET Gene expression analysis
Physiology	Body temperature	Hypothermia	Hypothermia
Perfectionism	Concern over mistakes	Multidimensional Perfectionism Scale (MPS)	?
Drive for thinness	Dieting Fear of weight gain	Eating disorder inventory (EDI)	?
Body image distortion	Body dissatisfaction	Various self-report or IT-delivered measures	?

While animal models cannot mimic all eating disorder traits, such as perfectionism, body dissatisfaction, or drive for thinness, behavioral scientists have been working for decades on animal models for other behavioral characteristics relevant to anorexia and bulimia nervosa, such as, e.g., depressive symptoms [for review, see (Redei et al. 2001; Nestler et al. 2002; Cryan and Mombereau 2004; Cryan and Holmes 2005; Dranovsky and Hen 2006)], for compulsive behavior [for review, see (Joel 2006; Korff and Harvey 2006)], for impulsivity [for review, see (Evenden 1999; Jentsch and Taylor 1999; Lesch and Merschdorf 2000)], for set-shifting (Brigman et al. 2005; Brooks et al. 2006), and for body weight regulation [for review, see (Rohner-Jeanrenaud and Jeanrenaud 1997; Barsh et al. 2000; Mercer and Tups 2003; Adan et al. 2006; Buettner et al. 2007)]. Insights into mechanisms underlying these separate components may contribute to understanding the development of heterogeneity within eating disorder populations. Nevertheless, novel advances to refine assessments of these behavioral components in rodents are needed to optimize animal research for eating disorder traits.

As indicated above, there is substantial comorbidity of eating disorders and anxiety disorders [for review, see (Swinbourne and Touyz 2007)]. Studies have consistently shown that a significant number of patients with anorexia nervosa or bulimia nervosa experience one or more anxiety disorders (Kaye et al. 2004). Lifetime prevalence of at least one anxiety disorder in individuals with eating disorders varies from 25% (Keck et al. 1990) to 75% (Schwalberg et al. 1992) in bulimia nervosa and from 23% (Laessle et al. 1991) to 75% (Deep et al. 1995) in anorexia nervosa. Several studies have shown that anxiety disorders are premorbid to the development of an eating disorder (Schwalberg et al. 1992; Brewerton et al. 1995b; Deep et al. 1995; Bulik 2002; Godart et al. 2003; Brewerton et al. 1995a), indicating that studies unveiling mechanisms underlying anxiety disorders may provide insights into susceptibility factors for eating disorders.

In rodents, considerable information exists on the determination of anxiety levels. Standard laboratory tests, such as the open field, elevated plus maze, and the light–dark box test, are generally used to measure novelty-induced anxiety levels in rodents. In general, rodent species have an innate preference for sheltered places that have lower light intensities than the outside world and that provide a sense of safety via body contact with the shelter area surface (thigmotaxis). The open field test was one of the first behavioral tests developed for emotionality and that was based on the assessment of these behavioral expressions (Hall 1936). These relatively brief tests provide insights in novelty-responsiveness of the animal, but are confounded by strain differences in locomotor activity and do not provide baseline measures of anxiety levels. For these reasons, the field will benefit from novel measures that assess baseline anxiety levels and control for strain differences in locomotor activity (Kas and Van Ree 2004; Kas et al. 2008). By means of interspecies genetic analysis, we have recently found an association at the genetic level between increased baseline sheltering preference (using longitudinal automated home cage observations) and a human mood disorder (de Mooij-van Malsen et al. 2009). Furthermore, in addition to measures of anxiety levels in relation to novel environments with a nonsocial context, animal models for social

phobia have also been introduced and may be relevant to eating disorder development. For instance, behavioral tests have been developed in which rodents can be tested for their preference for social approach or avoidance (Nadler et al. 2004; Moy et al. 2007). These refinements in rodent behavioral testing paradigms will contribute to face, predictive, and construct validity of animal models for eating disorder traits.

In addition to the development of behavioral testing paradigms to assess eating disorder characteristics in both mouse and human, neuroimaging approaches have recently been initiated across species to picture brain activities in relation to eating disorder development. For example, a recent study (Wagner et al. 2007) showed that individuals who have recovered from restricting-type anorexia nervosa had altered patterns of response in the ventral and dorsal striatum to positive and negative feedback. That is, an anterior ventral striatum response that distinguished between winning and losing was seen in the comparison women but not in the anorexia nervosa group. These findings suggest that individuals with anorexia nervosa may have difficulty discriminating between positive and negative feedback, relative to healthy comparison subjects. Similarly, in a study using a startle reflex paradigm (Friederich et al. 2006), a generalized failure to activate the appetitive motivational system was observed in individuals with anorexia nervosa. Interestingly, Barbarich-Marsteller et al. (2005) found changes in the striatum, hippocampus, and thalamus in rodents exposed to the ABA model. Similarly, van Kuyck et al. (2007) found altered activity in the ventral striatum, insula, thalamus, and ventral pontine nuclei, as well as a positive correlation between body weight loss and metabolism in the anterior cingulate and related regions in ABA rodents. When considered together, these human and rodent studies suggest the possibility of involvement of common pathways, but differences in imaging techniques and the effects of nutritional status make direct comparisons problematic.

Integration of genetic, behavioral, and neuroimaging findings may, in the end, provide more complete insight into the mechanisms underlying complex disorders. For example, increased anterior ventral striatum dopamine D2/D3 receptor binding in recovered anorexia nervosa patients could be contributing to the above-mentioned alteration in anterior ventral striatum function (Frank et al. 2005). Disturbed dopamine D2 receptor binding observed by these brain imaging techniques would be consistent with recently observed genetic linkage with the dopamine D2 receptor and anorexia nervosa (Nisoli et al. 2007; Bergen et al. 2005). Furthermore, recent animal studies have shown that mice with high susceptibility to develop ABA have increased striatal dopamine D2 receptor mRNA levels when compared to mice that do not develop behavioral hyperactivity in this animal model (Gelegen et al. 2008). In view of the relation between dopamine D2 receptor regulation and eating disorders and reward seeking in humans (Blum et al. 1995), it is interesting to note that mice with a genetic deletion of this receptor have deficits in reward processes (Maldonado et al. 1997; Cunningham et al. 2000; Elmer et al. 2002; Tran et al. 2002; Drew et al. 2007) that may also translate to certain aspects observed in eating disorders (Bergh and Sodersten 1996).

5 Future Directions

Eating disorders are multifactorial psychiatric disorders with unknown etiology and (at this point) relatively low success rate with current treatment programs. Understanding the complex interactions of genetic background and environmental factors will become crucial in unraveling the biology of this disease. More and more, the role of the environment, gender, and critical time periods during development have raised awareness in the development of this disease. Hand-in-hand with upcoming genetic findings, systematic and controlled animal studies will, therefore, play an important role to study their relationship in the development of eating disorders.

Extensive human genetic studies are underway and will provide novel candidate genes for eating disorders, such as anorexia nervosa. To unravel the contribution of these candidate genes in a neurobiological mechanism underlying eating disorders, translational research will be needed. Gene knockout technology in mice has provided a tremendous contribution to gene function research in all biomedical disciplines. This has evolved in novel and refined applications, such as conditional knockout technology, vector-directed gene expression, and short-hairpin interference methodologies to study gene function relationships over time [e.g., genetic deletion during development or adulthood (Gross et al. 2002) and in a tissue-specific manner]. Thus, sufficient gene manipulation technology is available to functionally test human candidate genes for anorexia nervosa. Furthermore, novel mouse genetic mapping panels allow the identification of genomic regions for mouse phenotypes that are homologous with human genomic regions identified for eating disorder characteristics (Gelegen et al. 2010; Kas et al. 2010). Together, in combination with relevant animal paradigms at the behavioral and neuroanatomical level for eating disorder traits, these methods will contribute to unravel gene functions in neurobiological mechanisms underlying the pathophysiology of self-starvation. Better understanding of the pathophysiology of eating disorders will pave new roads for directed treatment development.

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