Genetic Epidemiology, Endophenotypes, and Eating Disorder Classification

Cynthia M. Bulik, PhD1,2,*
Johannes Hebebrand, MD, PhD3
Anna Keski-Rahkonen, MD, PhD, MPH4
Kelly L. Klump, PhD5
Ted Reichborn-Kjennerud, MD6
Suzanne E. Mazzeo, PhD7,8
Tracey D. Wade, PhD9

ABSTRACT
Objective: To explore how genetic epidemiology has informed the identification of endophenotypes and how endophenotypes may inform future classification of eating disorders.
Method: Literature review and synthesis.
Results: Although a number of endo- and subphenotypes have been suggested for eating disorders, few reach the rigorous definitions developed for candidate endophenotypes.
Conclusion: Further study of endophenotypes and subphenotypes for eating disorders may assist with developing a more homogenous classification system that more closely reflects underlying biological mechanisms, and provides a clearer focus for the development of coherent models and treatments. © 2007 by Wiley Periodicals, Inc.
Keywords: endophenotypes; subphenotypes; genetic epidemiology; eating disorders; anorexia nervosa; bulimia nervosa; binge eating; obsessionality

Introduction
Anorexia nervosa (AN), bulimia nervosa (BN), and eating disorders not otherwise specified (EDNOS) are potentially devastating illnesses. The current tripartite classification system represents a series of cumulative historical accidents which, rather than optimizing and incorporating extant empirical observations, perpetuates clinical opinion and the biases inherent therein. In part, this reflects the uncomfortable truth that sufficient data of the appropriate type do not exist to inform the diagnostic criteria for eating disorders fully, yet certain troubling facts underscore the importance of critically evaluating and revising our diagnostic approach to eating disorders.

We address how genetic (family, twin, and molecular) and related biological research can inform future renditions of the DSM criteria for eating disorders by introducing the concept of endo- and subphenotypes and address how their identification can assist with developing a scaffold upon which to refine and rebuild our diagnostic criteria. We then take a “within disorder” approach to explore how these studies can inform the extant criteria for AN and BN followed by a “cross-disorder” approach to explore what these studies can tell us about endophenotypes that cross diagnostic boundaries that may inform future diagnostic criteria. Finally, we address directions for future research.

Our bias is that refinements of the diagnostic criteria for eating disorders could be more richly informed by biology. Our current diagnostic criteria are heterogeneous—Reichborn et al.1 noted considerable within-diagnosis heterogeneity in symptom origin, with some criteria reflecting observable, measurable, and heritable features and others which are unobservable, difficult to measure, and more influenced by environmental factors which require complicated inferences about intentions and cognitions of the patient. Whereas gene–environment interplay is essential to understand the
development of psychiatric disorders, and environmental main effects cannot be ignored, we argue that core diagnostic criteria should be observable, measurable and, if possible, reflect underlying biological processes.

### Can Endophenotypes Inform Diagnostic Criteria?

The concept of endophenotype was identified in 1973 and has been resurrected with modern genetic approaches. Endophenotypes are measurable components unseen by the unaided eye along the pathway between disease and distal genotype. 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 or not 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 employed 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; the endophenotype of P50 event-related potential suppression.

While the ostensible advantage of endo- and subphenotypes is that they are hypothesized to involve fewer genes that would simplify the detection of contributing genetic loci, the reported genetic effect sizes for endophenotypes have not proven to be unanimously significantly larger than those observed for the phenotypes they underlie. However, several significant advantages emerge from the identification of endophenotypes, including deconstruction of complex disorders that could theoretically assist in developing a more biologically based and homogenous classification system for eating disorders. Refining endophenotypes for eating disorders may assist with identifying core, genetically influenced traits that inform the underlying scaffolding around which the diagnostic criteria for eating disorders should be constructed. Thus, many fields of psychiatry have embraced research on endophenotypes, however, only four references were located in eating disorder field. Table 1 presents candidate endo- and subphenotypes for eating disorders and evaluates them across the definitional dimensions presented above. Although the designation of endo- or subphenotype is not always clear, we have attempted to evaluate each candidate for endophenotype status based on extant data.

### Within Disorder Perspective

#### Anorexia Nervosa

**Criterion A.** The hallmark feature of AN is maintenance of low body weight, yet aside from body weight itself, we have little evidence regarding underlying biological mechanisms that initiate or maintain this symptom. Twin studies have shown that BMI is heritable and hundreds of genes have been reported to influence BMI and/or obesity. Much less is known about the low end of the BMI continuum, and it is unclear whether what we do know about biology of low BMI applies to the low weight seen in AN.

Concerns with the phrasing of Criterion A (i.e., particularly the term “refusal”) and the appropriateness of the 85% weight cutoff have been dealt with extensively elsewhere. We focus on BMI per se. Premorbid weights of individuals with AN span the BMI spectrum, although very high BMIs may be underrepresented. Even after recovery, BMIs are lower than expected, in part due to reduced body fat. Although few adequately designed studies have been conducted, the BMIs of family members of individuals with AN do not appear to be lower than relatives of those without AN. Hebebrand et al. noted that the low weight maintained in AN defies observations about the body’s tendency to defend its set point. This fundamental dysregulation sets AN apart from healthy low weight.

Low weight in AN differs from healthy underweight in many ways. First, in over 400 male and female students with a BMI below 85% average body weight, most individuals were healthy (Hebebrand et al., unpublished data) and tracking...
of BMI in adulthood implies that many lean young adults will remain so over time. These individuals can also expect a longer life span than those with higher body weight. Second, intentional weight loss is not common among students with a BMI \( \leq 85\% \) average body weight, in contrast, \( \sim 25–33\% \) of such underweight individuals repeatedly attempt to gain weight and are unhappy with their thinness (Hebebrand et al., unpublished data). Moreover, the presence of constitutional thinness in women and men has been shown to be associated with decreased rather than increased odds of having disordered eating behaviors and attitudes. Third, the “risk” of thinness was elevated in the relatives of thin individuals (Hebebrand et al., unpublished data). In contrast, two studies have reported relatives of AN probands to be at no greater risk of thinness (Hebebrand et al., unpublished data), while another found cotwins of twins with AN were at significantly higher risk for current low BMI. However, if subthreshold forms of AN are accounted for, cotwins of twins with AN do not appear to differ in BMI from women from the general population. Fourth, serum leptin levels also differentiate between constitutionally lean females and those with AN. Fifth, initially at least, weight loss in AN is usually voluntary, and although intentional weight loss is moderately heritable, the majority of genetic factors affecting BMI are different from those affecting intentional weight loss.

Molecular genetic studies that incorporated relevant covariates into linkage analyses have included the related construct of minimum BMI, a variable that more closely approximates the core phenotype of AN as it indexes the extreme low BMI values reached as the body experiences a complete failure to regulate weight. For minimum BMI achieved during the illness, families showed highly concordant and extreme values rendering the variable appropriate for covariate-based linkage analyses. Incorporation of this variable enabled identification of a suggestive signal for lifetime minimum BMI at 4q13.1 in the AN cohort and one significant [4q21.1] and three suggestive [3p23, 10p13, 5p15.3] signals in the BN cohort. These findings could highlight specific factors that influence the anomalous dysregulation of body weight in AN.

In sum, twin studies have explicated factors associated with intentional weight loss and constitutional thinness, but they have not honed in on the grossly abnormal weight dysregulation associated with the maintenance of unusually low body weight in AN. Serum leptin appears to distinguish between constitutional thinness and AN, and mini-

### TABLE 1. Summary of data addressing whether psychological, physical, and biological traits represent endophenotypes or subphenotypes for eating disorders

<table>
<thead>
<tr>
<th>Trait</th>
<th>Measurable</th>
<th>Heritable</th>
<th>Cosegregates with Illness</th>
<th>State Independent</th>
<th>Observed in Unaffected Family Members</th>
<th>Biologically Plausible Causal Mechanism</th>
<th>ENDO?</th>
<th>SUB?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfectionism</td>
<td>+</td>
<td>Moderate</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>UNKNOWN</td>
<td>UNKNOWN</td>
<td>++</td>
</tr>
<tr>
<td>Obsessivity</td>
<td>+</td>
<td>Moderate</td>
<td>++++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>UNKNOWN</td>
<td>++</td>
</tr>
<tr>
<td>Drive for thinness</td>
<td>+</td>
<td>Moderate</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>UNKNOWN</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>+</td>
<td>Moderate</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>UNKNOWN</td>
<td>++</td>
</tr>
<tr>
<td>Negative emotionality</td>
<td>+</td>
<td>Moderate</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Decreased food intake</td>
<td>+</td>
<td>Moderate-Large</td>
<td>+++</td>
<td>+</td>
<td>UNKNOWN</td>
<td>+++</td>
<td>UNKNOWN</td>
<td>+++</td>
</tr>
<tr>
<td>Low body weight (dysregulation of body weight)</td>
<td>+++++</td>
<td>Moderate-Large</td>
<td>+++</td>
<td>+</td>
<td>UNKNOWN</td>
<td>UNKNOWN</td>
<td>UNKNOWN</td>
<td>+++</td>
</tr>
<tr>
<td>Increased physical activity</td>
<td>+</td>
<td>Moderate-Large</td>
<td>+++</td>
<td>+</td>
<td>UNKNOWN</td>
<td>UNKNOWN</td>
<td>UNKNOWN</td>
<td>+++</td>
</tr>
<tr>
<td>Cognitive set shifting</td>
<td>+</td>
<td>Moderate-Large</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Binge eating</td>
<td>+</td>
<td>Moderate</td>
<td>+++</td>
<td>No</td>
<td>UNKNOWN</td>
<td>+</td>
<td>NO</td>
<td>+++</td>
</tr>
<tr>
<td>Self-induced vomiting</td>
<td>+</td>
<td>Moderate-Large</td>
<td>+++</td>
<td>No</td>
<td>UNKNOWN</td>
<td>NO</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Impulsivity</td>
<td>++</td>
<td>Moderate</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Undue influence of weight or shape</td>
<td>+</td>
<td>Small</td>
<td>+++</td>
<td>+</td>
<td>UNKNOWN</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AN = anorexia nervosa; ANR = restricting type AN; BN = bulimia nervosa; ANBP = binge/purge type AN; ENDO = endophenotype; SUB = subphenotype; UNKNOWN = no studies have examined the issue or existing data are inconclusive. Plus marks (+) denote the strength of data supporting each criterion. For example, for 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). For 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). For the ENDO? and SUB? column, 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.

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mum BMI provides valuable information to hone linkage signals for AN. Although not nearly definitive, these findings collectively support the importance of continuing to refine and explore factors associated with low body weight as core subphenotype for AN.

**Criterion B.** Fear of fatness or fear of weight gain has been considered to be a key feature of AN, yet family, twin and genetic studies have little to say about the underlying biology of the symptom. Hebebrand et al.\(^{18}\) underscore the lack of reliability and validity of this criterion, difficulty with measurement, absence in non-Western cultures,\(^{36,39}\) failure to reflect the biology of AN,\(^{40,41}\) and fluctuations over the course of AN.\(^{42,43}\) Thus, this criterion is best conceptualized as an environmental feature relevant to understanding maintenance factors for AN, for predicting clinical course, and for understanding cultural manifestations,\(^{44}\) but not a candidate endophenotype reflective of a core underlying biological process.

**Criterion C.** This composite criterion clusters three distinct and possibly unrelated processes—all difficult to measure and lacking a plausible biological explanation: disturbance in experiencing one's body weight or shape, denial of the seriousness of the current low body weight, or undue influence of body weight or shape on self-evaluation. Although sometimes confused with body dissatisfaction, undue influence of weight and shape has a specific meaning solely relating to the degree that self-evaluation is influenced by weight or shape relative to other factors in the person's life (e.g., work, specific skills, relationships).

Twin studies have not found consistent genetic contributions to undue influence of weight and shape: in a Norwegian study,\(^1\) this trait was best explained by models incorporating only common and unique environment, without any genetic effects. However, a recent study\(^{15}\) which defined the criterion for undue influence of either weight or shape as a combined phenotype, did find a small contribution of additive genetic variance of 25% (95% CI: 14–36%). Compared with unaffected women, this combined phenotype remained significantly elevated in women recovered from an eating disorder, representing either scarring effects of illness or a predisposing and persistent trait. Thus, the degree to which “undue influence” meets the requirements for an endophenotype is largely unknown.

A second issue with the “undue influence” is the extent to which it reflects a “normative discontent” amongst women in the developed world. It is conceivable that whereas the content of the concerns may be environmentally mediated, the cognitive-affective component of this feature may be heritable. Alternatively, these psychological features may best be considered to reflect the cultural context in which the core biological features of eating disorders emerge. If one adopts the position that gene environment interaction may be operative in eating disorders, then these more culturally embedded features may serve as environmental triggers for underlying genetic predisposition. As such they become less attractive as core subphenotypes for eating disorders and may best be considered as contextual rather than diagnostic features.

**Criterion D.** Although some aspects of menstruation have been studied in the context of twin research (e.g. timing of puberty\(^{45}\)), no family or twin studies have addressed the familiality or heritability of amenorrhea. It is difficult to conceptualize amenorrhea as a unique diagnostic criterion for AN, when on the most basic biological level, the curtailment of energy intake (for any reason) compromises normal reproductive function and results in amenorrhea.\(^{46,47}\) Given that amenorrhea cannot be assessed in males, in pre-menarcheal girls and in females using hormonal contraceptives, one alternative to current criterion is a diagnostic requirement of somatic symptoms indicating adaptation to semi-starvation (e.g., hypothermia, bradycardia, hypotension, lanugo hair and/or amenorrhea). Together with criterion A this would imply that the underweight is of such a degree as to have led to physiological alterations of the organism, thus entailing a clear distinction between healthy leanness and disorder-inherent thinness. This broader novel criterion would be age independent, applicable to both sexes,\(^{18}\) and likely to be heritable to some degree.

**Bulimia Nervosa**

**Criterion A.** The symptom of binge-eating has received considerable support as a subphenotype of BN. Dismantling BN into its component behaviors of objective binge eating and self-induced vomiting, Sullivan et al.\(^{48}\) estimated the heritability of binge eating to be 49% (95% CI: 32–63%), which concurred with other reported estimates (41%\(^{49}\) to 82%\(^{50}\) controlling measurement error). Genetic risk factors for binge eating and BN may be largely similar, whereas nonshared environment may be important in influencing the risk for developing BN once binge eating is initiated.\(^{51}\) In sum, binge-eating represents a heritable, somewhat measurable candidate behavioral subphenotype for BN.
Criterion B. This criterion lumps several compensatory behaviors: self-induced vomiting; use of laxatives, diuretics, enemas, or other medications; excessive exercise, and fasting. Whether these behaviors share an underlying mechanism is unclear. Intriguingly Sullivan et al. \(^{48}\) revealed substantial genetic effects on self-induced vomiting (\(\alpha^2 = 72; \; 95\% \; CI: 55–88\)) suggesting that it is strongly heritable and perhaps more reliably measured than binge eating which has shown at best moderate reliability, \(^{52}\) perhaps due to the lack of clarity of the “out of control” sub-criterion. In the absence of clear data on other forms of purging and physical activity in BN, it is premature to determine whether these behaviors meaningfully cluster as one criterion.

Criterion C. To determine whether the twice per week threshold is meaningful for binge eating and whether a meaningful threshold exists for self-induced vomiting in a genetically informative sample, Sullivan et al. \(^{48}\) chose the a priori principal validator of risk to cotwin. For the different thresholds of binge eating, the risk ratio peaked at four binges per month or once per week. For vomiting thresholds, the risk ratio increased with greater thresholds—as vomiting increased so did risk to the co-twin. Their results did not support the current thresholds for binge eating which, as in AN, could reflect hypoleptinemia. In food restricted rats, exogenous leptin suppresses the development of semi-starvation induced hyperactivity \(^{57}\); in AN patients leptin levels are inversely correlated with motor restlessness. \(^{58}\) The optional inclusion of symptoms of elevated activity would allow reference to a biologically based phenomenon, which appears rather specific to AN. Less is known about hyperactivity in BN and EDNOS. This feature may mainly be found in those BN patients with low body weight (or low body fat) which, as in AN, could reflect hypoleptinemia.

Cross-Disorder Perspective

In addition to exploring what we know about the extant criteria, we must also consider whether genetic research supports the inclusion of additional optional or obligatory symptoms into future diagnostic schemes. To achieve this, we take a “cross-disorder” approach and explore what endophenotypes might exist that cross the boundaries between currently conceptualized disorders. This approach is consistent with some observations including a latent profile analysis that suggested, from a general population perspective, there is no meaningful differentiation between clinically significant eating disorders, including EDNOS \(^{35}\) and with unpublished data which show AN and BN spectrum disorders share 50% of their genetic risk factors (Wade, Treloar, Heath, Martin, unpublished manuscript). It is also noteworthy that this approach may identify trans-diagnostic endophenotypes that may identify meaningful biological bridges between entire classes of psychiatric illnesses (e.g. anorexia nervosa and autism spectrum disorders \(^{35}\)). Within this framework, four areas emerge as worthy of further investigation as possible cross-diagnostic endophenotypes, outlined in Table 1. These include increased physical activity, dimensions of temperament (obsessionality, impulsivity and negative emotionality), dimensions reflecting weight concern (including drive for thinness), and impaired set shifting. As well as meeting the criteria for an endophenotype, the utility of each must be further judged with respect to whether they are unique to eating disorders as opposed to other psychiatric disorders.

Physical Activity

Increased physical activity observed in a subgroup of individuals with eating disorders (primarily AN) during the course of the illness raises the question of whether subtyping on the basis of hyperactivity is meaningful. Animal models of “anorexia based activity” exist \(^{54}\) and both rodent and human studies indicate that hypoleptinemia is associated with hyperactivity and motor restlessness. \(^{55,56}\) In food restricted rats, exogenous leptin suppresses the development of semi-starvation induced hyperactivity \(^{57}\); in AN patients leptin levels are inversely correlated with motor restlessness. \(^{58}\) The optional inclusion of symptoms of elevated activity would allow reference to a biologically based phenomenon, which appears rather specific to AN. Less is known about hyperactivity in BN and EDNOS. This feature may mainly be found in those BN patients with low body weight (or low body fat) which, as in AN, could reflect hypoleptinemia.

Temperament

Temperament and personality indicators, whilst heritable and cosegregating with illness, may share some problems with non-behavioral measures including being influenced by many genes rather than few. A number of temperaments are worthy of consideration as inclusions in future diagnostic criteria, including those that have been shown to remain elevated after recovery, or elevated in unaffected family members, namely high harm avoidance, low self-directedness and cooperativeness, \(^{59}\) obsessive-compulsive personality disorder (OCPD) and obsessive compulsive spectrum disorders, \(^{60,61}\) perfectionism and ineffectiveness, and lower levels of interoceptive awareness \(^{62}\) and self-directedness. \(^{63,64}\)
Negative emotionality should also be considered given longitudinal evidence that this temperament- 
mal trait prospectively predicts disordered eating 
symptoms, and exhibits shared genetic variance with 
these characteristics. Anxiety or depression 
precede the onset of bulimic symptoms, and par-
teral depression also predicts development of an 
eating disorder in children. Family studies sug-
gest that these heritable disorders are important in 
increasing risk for eating disorders. There is 
evidence for shared genetic vulnerability between 
AN and depression and anxiety. Further, such 
shared genetic vulnerability exists between BN and 
depression, as well as BN and a range of anxiety 
disorders including phobia, panic disorder, and 
GAD. Cluster B personality disorders are 
elevated among BN probands, and Wade et al. found that risk for BN in one sibling was associated 
with risk for higher levels of novelty seeking and 
psychoactive substance use (a possible behavioral 
marker for novelty seeking) in the other sibling 
when the other sibling was male.

In sum, obsessionality and forms of anxiety show 
promise as diagnostically meaningful endopheno-
types for both AN and BN. Perfectionism may show 
diagnostic utility due to showing some degree of 
genetic risk factors with obsessionality. Impulsiv-
ity or indicators of novelty seeking may be a useful 
diagnostic endophenotype for eating disorders that 
are characterized by binge eating. Negative emo-
tionality, whilst not a diagnostic endophenotype 
specific to eating disorders, may be a necessary but 
not sufficient inclusion to diagnostic criteria, espe-
ially as an indicator of the clinical severity of eat-
ing disorders. Clearly, additional research using 
family designs and robust outcome variables is 
required to understand the relation between per-
sonality and eating disorders.

**Cognitive Features**

Various cognitive features predict the onset of 
disordered eating, including weight concern and 
drive for thinness, composite measures of dietary 
restraint, body dissatisfaction, feeling fat, impor-
tance of weight and fear of weight gain. A com-
posite measure of weight concern was elevated in 
women with AN compared to controls, as was 
their restraint for women who had either lifetime 
AN or BN. Consistent with evidence supporting 
this variable as an endophenotype, a follow-up 
study of 108 infants at 8 years of age showed that 
maternal restraint predicted worries about being 
too fat in girls but not boys. However, the compo-
site measure of weight concern has been found to be 
influenced by environmental variance only, while 
other studies suggest that measures of body dissatis-
faction, weight preoccupation and drive for thinness 
are influenced by genetic factors in older adolescent 
female twins. Interestingly, shared genetic var-
iance between negative emotionality and both body 
dissatisfaction and weight preoccupation were 
limited. Drive for thinness is associated with poten-
tially biologically plausible mechanisms, where 
elevated levels are associated with carriers of the 
deletion polymorphism of the serotonin transporter 
promoter 5-HTTLPR and has been a valuable cova-
riate in linkage analyses. In women recovered from 
bulimia-type AN, [18F]altanserin binding potential 
and drive for thinness were negatively correlated in 
several cortical regions, suggesting that altered 5-HT 
neuronal system activity persisted.

Given that different measures have been used to 
capture these cognitive features, further work is 
required to increase the reliability and validity of 
these measures before conclusions can be drawn 
about their potential status as an eating disorder 
endophenotype, including the degree to which they 
are influenced by genetic factors.

In sum, measures of weight concern have shown 
promise in predicting onset and persistence of 
cross-diagnostic eating disorder behaviors. How-
ever, twin studies suggest that these measures suf-
fer from some degree of inconsistency in relation 
to genetic risk factors. Drive for thinness, a con-
struct that captures the composite nature of weight 
care concerns including body dissatisfaction, dieting, 
and importance of weight, does show promise as a 
biologically plausible endophenotype across eating 

disorders.

**Set-Shifting**

Of particular intuitive appeal as a candidate for an 
endophenotype are tests of cognitive processes, given 
their measurable nature. Of interest in relation to eat-
ing disorders are measures of executive functioning, 
responsible for the supervision of such cognitive 
processes as setting goals, planning and organizing. 
One indication of executive functioning is set-shifting 
ability, which has been examined specifically with respect to 
AN. Set shifting involves the ability to move back and 
forth between tasks, operations or sets, and impaired 
ability in this area is postulated to contribute to rigid 
and obsessional behavior. It is moderately herit-
able. Deficits are present in women with AN and 
BN, and are observed in both women with AN 
and women with high levels of obsessionality who 
have no eating disorder history compared to con-

In addition, sisters of

women with AN exhibit significantly impaired set shifting compared to controls, comparable to that of their siblings with AN. Further appeal with respect to this measure of cognitive function as a potential endophenotype is its association with the dopaminergic system.96

In sum, whilst measures of cognitive function show much promise as endophenotypes for eating disorders, much remains unknown, especially with respect to functioning in BN. Of consideration is the degree to which set shifting is specific to eating disorders, as such impairment has also been noted in bipolar disorder and schizophrenia. Other measures of cognitive function may provide some degree of specificity for eating disorders, and further research is required to discover and validate endophenotypes in this area of executive function. Constructs of theoretical interest to eating disorders and which show some degree of heritability include response inhibition (Willcutt et al., unpublished data) and contingencies (Willcutt et al., unpublished data).99

Where To From Here?

Our review indicates that the pursuit of clarification of endophenotypes and subphenotypes for eating disorders may be a fruitful approach for clarifying diagnostic criteria that more closely reflect underlying biological mechanisms. The eating disorders field has fallen somewhat behind in psychiatry in these pursuits and would be served well by a concerted research effort in this area. Our hope is that this paper will represent a “call to arms” for twin and genetic researchers to utilize our powerful methodology to better identify endophenotypes that may assist with refining core DSM criteria for eating disorders. Over thirty years ago, Robins and Guze100 cited family aggregation as one of the criteria for validation of diagnostic criteria. Genetic and biological data were viewed on equal footing with the phenomenology, course, and outcome data needed to establish a disorder as an independent diagnostic entity. Acknowledging that familial aggregation has limitations as a validator of psychiatric illness, and recognizing the importance of nature-nurture interplay in the final phenotypic expression of disease, we believe that in order to “carve nature at its joints,” we must put the “nature” back into our diagnostic conceptualizations of eating disorders.

This research was supported by the National Institutes of Health Grants (MH66117; PI: Devlin). Johannes Hebebrand receives funding from the German National Genome Research Net.

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