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Behavioral and Neurodevelopmental Precursors to Binge-Type Eating Disorders: Support for the Role of Negative Valence Systems

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Abstract

Background—Pediatric loss-of-control eating is a robust behavioral precursor to binge-type eating disorders. Elucidating precursors to loss-of-control eating and binge-type eating disorders may refine developmental risk models of eating disorders and inform interventions.

Method—We review evidence within constructs of the Negative Valence Systems (NVS)-domain, as specified by the Research Domain Criteria framework. Based on published studies, we propose an integrated NVS model of binge-type eating disorder risk.

Results—Data implicate altered corticolimbic functioning, neuroendocrine dysregulation, and self-reported negative affect as possible risk-factors. However, neuroimaging and physiological data in children and adolescents are sparse, and most prospective studies are limited to self-report measures.

Conclusions—We discuss a broad NVS framework for conceptualizing early risk for binge-type eating disorders. Future neural and behavioral research on the developmental trajectory of loss-of-control and binge-type eating disorders is required.

Keywords

Eating disorders; binge eating; loss of control eating; development; Research Domain Criteria (RDoC)

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Binge-eating refers to episodes in which uncontrolled eating is experienced during consumption of an objectively large amount of food. DSM-5 includes two eating disorders (EDs) defined by recurrent binge-eating: bulimia nervosa (BN) and binge-eating disorder (BED) (American Psychiatric Association [APA] 2013). BN also involves inappropriate compensatory behaviors intended to prevent weight gain. The lifetime prevalence of BN and BED are approximately 0.9–1.0% and 1.9–2.8%, respectively (Hudson et al. 2007, Swanson et al. 2011). Both involve major impairment (APA 2013), with long-term treatment remissions in the range of 30–50% for BN and 50–70% for BED (Kass et al. 2013). Significant diagnostic crossover between BN and BED (Allen et al. 2008, Stice et al. 2013) suggests shared etiologies. Indeed, BN and BED have similar risk-factors (Hilbert et al. 2014) and onset patterns, with peak incidence in late adolescence (Stice et al. 2009, Swanson et al. 2011, Hilbert et al. 2014). Jointly examining risk-factors for these "binge-type" EDs may inform theory.

Loss-of-control (LOC)-eating (APA 2013), the most salient feature of binge-eating, occurs when individuals perceive an inability to control their eating, regardless of the amount consumed (Wolfe et al. 2009, Tanofsky-Kraff et al. 2011). LOC-eating is a childhood precursor to BED (Tanofsky-Kraff et al. 2011, Hilbert et al. 2013) and BN (Brewerton et al. 2014). High rates of diagnostic progression (Stice et al. 2013) suggest that binge- and LOC-eating patterns may be early manifestations of binge-type EDs.

Elucidating developmental risk models for binge-type EDs requires exploration of biological and behavioral constructs that interact to promote BN, BED, and their precursors. We apply the Research Domain Criteria (RDoC) framework (Insel et al. 2010) to binge-type EDs (Tanofsky-Kraff et al. 2013), using the RDoC Negative Valence Systems (NVS)-domain. Animal models and adult findings are described where pediatric data are absent. A working model is offered and areas for future research are highlighted. Importantly, and in accordance with the RDoC approach (Sanislow et al. 2010), we refer to LOC-eating and binge-type EDs throughout to capture syndromes with similar presentations, as opposed to DSM diagnoses.

Research Domain Criteria (RDoC)

Heterogeneity in binge-type EDs suggests poor concordance between nosology and pathophysiology (Cuthbert and Insel 2013), a motivation for the RDoC framework (Cuthbert and Insel 2013). RDoC focuses on mechanisms that isolate primary behavior components in five fundamental "domains": NVS, positive-valence systems, cognitive-processes, social-processes, and arousal/modulation (Sanislow et al. 2010). Domains are divided into basic neuro-behavioral constructs, dysfunction of which are linked to numerous psychopathologies (Sanislow et al. 2010). Assessment of construct functioning can occur across multiple levels, with assessments targeting constructs varying on a continuum, with mental illnesses representing extremes of these dimensions (Cuthbert 2014). Thus, we focus on LOC-eating patterns rather than diagnostic categories. Development is also crucial in RDoC to map trajectories that differentially lead to variations along these continua (Cuthbert 2014).

Dysfunctions within each RDoC domain likely contribute to binge-type ED symptomatology (Tanofsky-Kraff et al. 2013), but herein we restrict our focus to the NVS-domain, mapping the ways in which NVS parameters relate specifically to LOC-eating. Negative affect is prominent in existing theories, which propose that LOC-eating represents a maladaptive attempt to escape or alleviate negative emotions in response to psychosocial stressors (Hawkins and Clement 1984, Heatherton and Baumeister 1991, Fairburn et al. 2003, Rieger et al. 2010). Yet, to our knowledge there is no biologically-driven conceptual model relating NVS-construct functioning to LOC-eating symptoms. Data on comorbidity between binge-type EDs and depressive or anxiety disorders (Swanson et al. 2011, Aspen et al. 2014) underscores the relevance of NVS to LOC-eating.

The NVS-domain encompasses defensive or avoidance motivational systems, and largely functions to reestablish internal biological stability in response to threats and losses (Sanislow et al. 2010). NVS functioning is defined by reactions to noxious stimuli and situations, including responses to acute-threat, potential harm, sustained-threat, frustrative non-reward, and loss (See Table 1 for construct descriptions; RDoC Working Group 2011). LOC-eating may be one phenotypic outcome of numerous dysfunctional NVS responses. We discuss each NVS construct in relation to risk for LOC-eating and binge-type EDs.

Genetics

Genetic factors influencing negative emotionality temperaments confer vulnerability for LOC-eating (Racine et al. 2013, Koren et al. 2014), suggesting a potential link to molecular genetic mechanisms that impact NVS functioning. Numerous possible mechanisms may include those affecting the signaling of serotonin, glucocorticoids, catecholamines, neuropeptide-Y, and brain-derived neurotrophic factor (BDNF) (McEwen 2007). Most molecular genetic studies of binge-type EDs emphasize candidate genes. The genetic architecture of BN is unclear based on null findings from one, albeit significantly underpowered, genome-wide association study (Boraska et al. 2012). NVS genetic findings in relation to LOC-eating are not well replicated, so inferences based upon existing studies should be considered tentative and taken with caution.

Candidate Gene Association Studies

Candidate gene association studies examined many NVS-related gene variants in relation to LOC-eating (see Supplementary Table 1). Polymorphisms affecting serotonergic and BDNF signaling generally are not directly linked to the presence of binge-type EDs, but are associated with greater negative affect and binge-eating severity in those reporting the behavior (Trace et al. 2013). As such, these genetic predispositions may confer heightened emotional response to NVS stressors that exacerbate LOC-eating tendencies, but may not necessarily determine their initial onset. Adults with binge-eating, BN, or BED are more likely to carry low-function variants of glucocorticoid receptor (GR) polymorphisms (Cellini et al. 2010, Steiger et al. 2011, Steiger et al. 2012). Thus, GR gene variants that promote inhibitory feedback insensitivity of the hypothalamic-pituitary-adrenal (HPA)-axis may predispose individuals to LOC-eating via secondary neurophysiological effects promoting non-homeostatic (e.g., eating due to negative states) feeding.

Gene-Environment Interplay

Limited data suggest that genetic and environmental factors interact to influence binge-type EDs. Among carriers of the 5-HTTLPR *s*-allele, repeated childhood exposure to maltreatment escalates risk for greater binge-eating severity in adolescent girls (Akkermann et al. 2012). Similarly, carriers of at least one C allele of the Bc*l*I GR polymorphism with exposure to child maltreatment are at greatest risk for BN (Steiger et al. 2011). Consistent with a diathesis-stress model, acute threat exposure may promote the expression of latent genetic risk-factors for LOC-eating via expressed NVS dysfunction in serotonergic and glucorticoid signaling (Trace et al. 2013). There is increasing recognition, however, that genetic and environmental factors perpetually impact each other to modulate risk for LOC-eating (Campbell et al. 2011, Strober et al. 2014). Epigenetic responses to sustained childhood threats are likely mechanisms for the development of binge-type EDs. Indeed, preliminary data implicate altered DNA methylation in specific GR and BDNF promoter regions in BN (Steiger et al. 2013, Thaler et al. 2014), which may program early vulnerability to stressors that manifest as persistent anxiety, depression, and LOC-eating later in development.

Neural Circuits

LOC-eating and binge-type EDs may reflect structure and functioning in circuits encompassing the amygdala, insula, and prefrontal cortex (PFC), that mediate NVS responses (Phillips et al. 2008, Dillon et al. 2014). Aberrant circuitry responses upon exposure to NVS stressors may override homeostatic feeding circuitry and result in non-homeostatic LOC-eating behaviors generating increased motivation to eat and/or degraded executive functioning (Dallman 2010). While structural MRI studies are useful (see Supplementary Table 2), the current review emphasizes neural circuit functioning tied to specific NVS constructs. Since diverse methodologies make directly comparing findings across studies challenging, findings are hypothesis-generating.

Acute- and Potential-Threat Paradigms

Corticolimbic hyperactivation during acutely threatening social evaluations of one's body may contribute to binge-type EDs. When comparing their own body with other women's thin bodies, women with BN have greater response in the insula and cerebellum than healthy controls (Van den Eynde et al. 2013). Enhanced responsivity could indicate greater NVS engagement during social-evaluative processing, suggesting distorted emotional experiences of acute threat may promote LOC-eating. No group differences in corticolimbic activation emerge when women with and without BN evaluate their own bodies relative to line drawings of other women, perhaps because drawings (vs. images) are less threatening (Uher et al. 2005). Yet, in women with BN only, greater amygdala and medial PFC response is associated with higher fear and disgust ratings of women's bodies (Uher et al. 2005), supporting a role of these structures in aversive body-related emotions that may trigger LOC-eating.

Neural mechanisms underlying the known association between social-appearance anxiety, a potential NVS construct, and BN symptoms (Koskina et al. 2011, Levinson et al. 2013) are

examined when women imagine that someone is comparing their own bodies to other women's (Spangler and Allen 2012). Women with BN demonstrate greater activity in the rostral-ventral anterior cingulate cortex than healthy controls upon exposure to obese (vs. thin) bodies (Spangler and Allen 2012). Women with BN also have greater ventromedial PFC response than controls when selecting between potentially ego-threatening (vs. neutral) body image words (Miyake et al. 2010). Findings suggest that binge-type EDs may be linked to dysregulated NVS engagement during potentially threatening social evaluations of "fatness" and/or disturbed emotion processing with regard to cognitive aspects such as emotion identification, appraisal, and recall (Phillips et al. 2008, Dillon et al. 2014).

Importantly, negative self-evaluations in various contexts are tied to perturbed engagement in the amygdala, medial PFC, and dorsolateral PFC among women with BN (Miyake et al. 2010, Pringle et al. 2011). Comparable perturbations occur in other clinical scenarios relevant to the NVS domain (Rottenberg et al. 2005, Schlund et al. 2013, Dillon et al. 2014). LOC-eating, therefore, may occur as a dysfunctional means to avoid negative emotions or compensate for emotion blunting. In contrast to patients, increased response in these corticolimbic structures is observed among healthy controls (Miyake et al. 2010, Pringle et al. 2011), potentially indicating that normative anxiety levels are not well-tolerated and adaptive regulatory mechanisms are deficient in those with binge-type EDs. It is possible that such poor regulatory capacity upon exposure to threats may contribute to impulsive-decision making or a reduced ability to control the type or quantity of food consumed by individuals with LOC-eating.

Loss Paradigms

Aberrant NVS responses to social defeat are linked to pediatric LOC-eating (Jarcho et al. 2015). In overweight girls with LOC-eating, reduced engagement is observed in the ventromedial and dorsolateral PFC in response to peer rejection. By contrast, girls without LOC-eating increase engagement in the ventromedial PFC, while their dorsolateral PFC response does not differ between rejection and acceptance feedback. In addition, greater activity in the fusiform face area in response to rejecting feedback from desirable peers is associated with more subsequent energy intake at a test meal among girls with LOC-eating only. These data suggest that NVS-mediated alterations in perceptual processing, potentially in combination with reduced corticolimbic engagement of regulatory mechanisms, during social-evaluative losses may promote LOC-eating patterns.

NVS hypoactivation during the anticipation, but not receipt, of non-social losses may contribute to LOC-eating (Balodis et al. 2013). When anticipating monetary loss (vs. no outcome), BED is associated with reduced engagement of numerous corticolimbic structures. Failure of individuals with BED to engage corticolimbic circuitry sufficiently in response to potential threat suggests a lack of adaptive anticipatory anxiety (Nitschke et al. 2006), which could motivate impulsive, emotion-driven behaviors (Knutson and Greer 2008), such as LOC-eating. Striatal hypoactivation during the anticipatory phase may also reflect inefficient learning from loss outcomes, placing individuals with BED at higher risk of continuing to enter defeating situations.

Negative self-referential processing is considered a loss construct because it involves a loss-of-control over limiting reflections on negative personal thoughts and emotions (i.e., rumination). When self-evaluating their body shape, women with BN have decreased neural responses in the default mode network structures, whereas healthy controls exhibit increased responses (Uher et al. 2005, Miyake et al. 2010, Vocks et al. 2010, Van den Eynde et al. 2013). This could reflect aberrant attention shifts (Whitfield-Gabrieli and Ford 2012). LOC-eating may, therefore, be precipitated as an attempt to reestablish an emotional and neurophysiological balance. Findings may also reflect negative ruminative and self-evaluative tendencies (Whitfield-Gabrieli and Ford 2012) that could lead to LOC-eating as a means to escape self-awareness.

Physiology

NVS neuroendocrine systems include the sympathetic-adrenomedullary (SAM)-axis and hypothalamic-pituitary-adrenal (HPA)-axis. Both the SAM- and HPA-axes are crucial to the regulation of NVS stressor responses and energy intake. As such, NVS physiological dysfunction may at least partly underlie the known relationship among stress, negative affect, and LOC-eating patterns. Again, there is a paucity of pediatric data and so developmental implications are extremely tentative.

SAM-Axis

The SAM-axis is activated, triggering the release of epinephrine and some norepinephrine from the adrenal medulla, when stressors are perceived as imminently threatening or demanding, yet controllable, in nonclinical samples (Adam and Epel 2007). Most adult studies of binge-type EDs demonstrate blunted SAM-axis activity at rest (Pirke et al. 1992, Koo-Loeb et al. 2000) and during acute psychosocial stress (Pirke et al. 1992, Koo-Loeb et al. 1998, Messerli-Bürgy et al. 2010, Monteleone et al. 2011, Het et al. 2014). SAM-axis hypoactivity reflects a reduced physiological capacity to respond adaptively to acute threats and predictable NVS stressors, as well as a biased perception that seemingly innocuous stressors are uncontrollable (Charmandari et al. 2005). Exaggerated/maladaptive emotional responses to such stressors may drive individuals toward LOC-eating as an alternative means of coping. Yet, relationships between SAM-axis hypoactivity and LOC-eating persist when adjusting for mood variables (Pirke 1996, Koo-Loeb et al. 1998), suggesting an independent role in binge-type EDs.

In healthy populations, threat-induced SAM-axis activation is accompanied by simultaneous reductions in parasympathetic tone (Charmandari et al. 2005). Following stressor cessation, shifts back toward parasympathetic control are important for adaptive recovery (Charmandari et al. 2005). BN is distinguished from BED and controls by parasympathetic dominance at rest and during acute stressors (Messerli-Bürgy et al. 2010, Hilbert et al. 2011, Het et al. 2014). The more persistent, severe dietary restriction reported by individuals with BN may partly account for this difference, as chronic deprivation contributes to vagal insensitivity (Vögele et al. 2009). Following psychosocial stressors, individuals with binge-type EDs exhibit persistent sympathetic activation coupled with little-to-no parasympathetic increase compared with controls (Messerli-Bürgy et al. 2010, Hilbert et al. 2011). This poor physiological NVS capacity to recover from psychosocial stressors may lead individuals

toward LOC-eating to regulate prolonged negative affective states and physiological disruption.

HPA-Axis

The HPA-axis is preferentially activated in response to stressors perceived as uncontrollable, potentially threatening, defeating, or difficult to manage (Adam and Epel 2007). In nonclinical samples, exposure to such stressors stimulates glucocorticoid release, primarily cortisol, from the adrenal cortex that triggers metabolic effects to support adaptive responses and provides negative feedback signals to terminate HPA-axis activity (Charmandari et al. 2005). Sustained elevated cortisol, particularly in palatable food environments, promotes non-homeostatic consumption, thereby linking the NVS to LOC-eating (Adam and Epel 2007).

Individuals with BN exhibit HPA-axis hyper-reactivity and inhibitory feedback insensitivity (Copeland et al. 1988, Kaye et al. 1989, Neudeck et al. 2001, Bruce et al. 2012). An extreme weight loss history amplifies this dysregulation, which may in turn exacerbate LOC-eating (Lo Sauro et al. 2008). By contrast, obese adults with BED generally display normal HPA-axis function at rest, though several studies suggest hyper- or hypo-reactivity (Yanovski et al. 1993, Monteleone et al. 2003, Gluck et al. 2004, Rosenberg et al. 2013). Equivocal findings may stem from comorbid obesity, which itself is linked to HPA axis dysregulation (Nieuwenhuizen and Rutters 2008) and altered cortisol metabolism (Morton and Seckl 2008).

During stressors, individuals with binge-type EDs may exhibit steeper cortisol increases than controls, which has been associated with increased desire to binge (Koo-Loeb et al. 1998, Koo-Loeb et al. 2000, Gluck et al. 2004, Gluck et al. 2004). Yet, other studies find blunted cortisol response (Pirke et al. 1992, Ginty et al. 2012, Rosenberg et al. 2013) or no group differences (Tuschen-Caffier and Vogele 1999, Monteleone et al. 2011, Schulz et al. 2011, Gluck et al. 2014). Blunted cortisol response likely reflects a compensatory downregulation of the HPA-axis due to repeated activation from sustained stressors, persistent depression, and/or LOC-eating (Rosenberg et al. 2013). Such downregulation results in prolonged HPA-axis responses and impaired recovery from stressors, conferring higher sensitivity to stressors that may lead to exacerbated LOC-eating (Rosenberg et al. 2013).

In light of heterogeneous findings, the nature of HPA-axis dysfunction may reflect multicausality, as binge-type EDs may arise from impaired functioning in disparate NVS constructs. Greater HPA-axis dysfunction, regardless of the nature or cause, is associated with greater binge-eating severity, anxiety, depression, and rumination among individuals with binge-type EDs (Díaz-Marsá et al. 2008, Lo Sauro et al. 2008, Bruce et al. 2012, Rosenberg et al. 2013, Monteleone et al. 2014). Thus, aberrant HPA-axis responses to potential harm and losses may be linked to exacerbated negative affective states that trigger recurrent LOC-eating.

Behavioral Paradigms

Performance in behavioral paradigms capturing NVS constructs suggests that LOC-eating patterns are linked to cognitive disturbances in response to threats and social losses. Adolescents with LOC-eating have greater inhibitory control degradations during peer exclusion than youth with ADHD and healthy controls (Hartmann et al. 2013), indicating that youth with LOC-eating experience greater cognitive control difficulties in response to social losses. Adolescents and adults with binge-eating or BN exhibit strong interference effects on Emotional Stroop paradigms utilizing stimuli indicating threats to one's weight/shape, social status, self-worth, or autonomy (McManus et al. 1996, Waller et al. 1996, Kuhnpast et al. 2012, Aspen et al. 2013, Cardi et al. 2013, Kanakam et al. 2013). Interference effects may indicate heightened attention orienting toward salient cues, reflecting hypervigilance and anxiety, or poorer cognitive control upon threat exposure, manifesting as intensified negative affect, impulsivity, or rumination. Greater interference effects are further associated with more severe LOC-eating (McManus et al. 1996, Lokken et al. 2006), suggesting that greater executive dysfunction upon exposure to potentially threatening cues may contribute to recurrent LOC-eating patterns. Women with LOC-eating also exhibit greater cognitive avoidance of ego-threatening stimuli than controls (Meyer et al. 2005, Blechert et al. 2009, Blechert et al. 2010). Overall, these stressor-induced cognitive dysfunctions indicate that LOC-eating may represent a maladaptive coping strategy for exacerbated negative affect and negative self-referential processing, and/or an impulsive behavioral response occurring when cognitive resources are degraded.

Emerging data suggest that threat and loss exposure enhances the salience of palatable foods (Adam and Epel 2007, Dallman 2010), which may partly explain why individuals with LOC-eating turn towards food to cope with NVS stressors. Among adults with LOC-eating, those with high social-threat sensitivity are more willing to work to obtain palatable foods (vs. non-food alternatives) than adults with low social-threat sensitivity or those without LOC-eating (Goldfield et al. 2008). Among women with BN, higher anxiety, dietary restraint, and weight/shape-related ruminations are associated with greater attention orienting biases toward food stimuli (Brooks et al. 2011). These data suggest that NVS perturbations contribute to a pathological motivation to eat among individuals with LOC-eating. Women with BN and high negative affect demonstrate greater interference effects for palatable food cues (Rofey et al. 2004), indicating that NVS disturbances may impair cognitive control over palatable foods in those prone to LOC-eating.

Laboratory Test-Meals

Laboratory test-meal studies directly link psychological indicators of NVS construct dysfunction to LOC-eating behaviors, thereby precisely mapping the ways in which the RDoC NVS construct links to a particular behavior relevant to BE-type eating disorders. Although exposure to sad (vs. neutral) mood inductions do not differentially impact overall intake in children with LOC-eating relative to those without LOC-eating (Hilbert et al. 2010, Goldschmidt et al. 2011), overweight girls with LOC-eating consume more energy from fat following a sad film (Goldschmidt et al. 2011). Additionally, greater pre-meal negative affect predicts more energy consumed from snack-type foods (Ranzenhofer et al. 2013) and

an increased likelihood of experiencing LOC during a meal (Goldschmidt et al. 2011). These pediatric findings are consistent with adult studies that also link negative affect to palatable food consumption and the experience of LOC (Telch and Agras 1996, Levine and Marcus 1997, Agras and Telch 1998, Chua et al. 2004). Youth with LOC-eating report greater increases in anxiety, confusion, and fatigue, but similar anger, depression, and tension changes, compared to controls (Tanofsky-Kraff et al. 2009). Since confusion and fatigue may align with "numbing" experiences reported by youth during LOC-episodes (Tanofsky-Kraff et al. 2007), it is possible that youth with LOC-eating could dissociate while eating to avoid simultaneous anxiety increases. Other laboratory studies find that youth with LOC-eating and adults with binge-type EDs report negative affect reductions after eating (Munsch et al. 2008, Hartmann et al. 2012, Vannucci et al. 2012, Ranzenhofer et al. 2013). Overall, laboratory findings suggest a regulatory role of LOC-eating in alleviating negative affect.

Dietary restraint appears to have little impact on laboratory LOC-eating in human beings. Neither acute energy deprivation in adults with binge-type EDs (Telch and Agras 1996, Agras and Telch 1998, Hetherington et al. 2000, Moreno Domínguez et al. 2012) nor chronic dietary restraint in adults with binge-eating (Chua et al. 2004) differentially impact energy intake or the occurrence of self-defined binges compared with controls. Dietary restriction also does not interact with negative mood inductions to influence energy intake (Agras and Telch 1998, Chua et al. 2004). These data contrast with findings in animal models (Hagan et al. 2002, Boggiano and Chandler 2006), potentially resulting from greater experimental control that ensures sufficiently prolonged, severe, and stressful energy deprivation. However, it is also likely that LOC-eating in humans emerges from numerous factors not present in rodents.

Although there is no prospective laboratory study in humans, animal models indicate that sustained early social-threats and losses lead to the development of LOC-eating. Prolonged maternal separation and low maternal care during the neonatal period leads to increased palatable food intake during the pre-adult period when mice are exposed to novel acute stressors, such as social isolation from peers and fasting-refeeding cycles (Jahng 2011, Maniam and Morris 2012). Chronic subordination and social defeat also induce LOC-like-eating (Sanghez et al. 2013, Razzoli et al. 2015). Increases in anxiety- and depressive-like behaviors tend to accompany LOC-like-eating (Jahng 2011). Behavioral effects of neonatal stressors were not observed during other developmental periods (Maniam and Morris 2012), implicating the pre-adult period as a sensitive time for activating social stressor-induced LOC-eating. Based on these preliminary data, it is conceivable that chronic childhood social stressors precipitate NVS dysfunction and manifests as LOC-eating in response to novel NVS stressors much later in development.

Psychological Self-Reports

Ecological momentary assessment (EMA) involves real-time assessment in the natural environment of an individual's emotional state and associated behaviors. Such studies generally indicate that NVS disturbances proximally promote LOC-eating. Adult EMA studies consistently find links among negative affect, stress, and binge-eating (Haedt-Matt and Keel 2011, Goldschmidt et al. 2012, Berg et al. 2014, Goldschmidt et al. 2014). Greater

daily variability in negative affect, a proxy of stressor sensitivity, also predicts higher binge-eating frequency in adults (Engel et al. 2007, Zander and Young 2014). However, pediatric EMA studies do not find such associations (Hilbert et al. 2009, Ranzenhofer et al. 2014), possibly due to methodological or developmental differences. Independent of negative affect, increases in dissociative/numbing experiences are found prior to binge-episodes (Engelberg et al. 2007, McShane and Zirkel 2008).

Specific NVS constructs are salient LOC-eating triggers. Greater body-related cognitions precede LOC-episodes in children (Hilbert et al. 2009), but do not predict binge-episodes in adults with binge-type EDs (Hilbert and Tuschen Caffier 2007). This developmental difference highlights the potential importance of weight/shape-related ruminations in contributing to pediatric LOC-eating, perhaps prior to self-reported negative affect predominating as an LOC-eating trigger in adulthood or full-syndrome binge-type EDs. Interpersonal stressors, primarily involving conflicts or defeat, predict the onset of LOC-episodes in adolescents (Ranzenhofer et al. 2014) and adults (Steiger et al. 1999, Freeman and Gil 2004, Goldschmidt et al. 2014). Moreover, increases in negative affect and self-referential criticisms mediate this relationship in adults (Steiger et al. 1999, Goldschmidt et al. 2014), indicating that aberrant responses to NVS social-threats and losses contribute to LOC-eating. NVS dysfunction in acute threat, frustrative non-reward, and loss constructs are linked to LOC-eating, as state ratings of fear, anger/hostility, sadness, and guilt increase prior to, and decrease following, LOC-episodes in women with BN (Smyth et al. 2007, Berg et al. 2013). Guilt remains a robust predictor of LOC-eating even after adjusting for other facets of negative affect (Berg et al. 2013), implicating an important role for loss response disturbances. The role of dietary restraint in predicting binge-eating is unclear due to mixed findings, likely resulting from divergent assessment methods and complex interactions with restraint chronicity, stress, and coping strategies (Engelberg et al. 2005, Zunker et al. 2011, Holmes et al. 2014). Together, these findings suggest that aberrant NVS responses to social-threats and loss, with potentially the exception of dietary restraint, may be particularly salient to momentary causes of LOC-eating.

Importance of Development

The role of NVS in LOC-eating risk may developmentally vary. Childhood anxiety disorders, especially social anxiety disorder, may predict later-life binge-type EDs (Bulik et al. 2001, Kaye et al. 2004), but findings from prospective data are inconsistent (Tanofsky-Kraff et al. 2011, Hilbert et al. 2013, Hilbert and Brauhardt 2014). Body dissatisfaction, elevated depressive symptoms, low self-esteem, and ruminative tendencies during early adolescence more consistently predict the onset and persistence of LOC-eating in late adolescence and young adulthood (Stice et al. 2002, Nolen-Hoeksema et al. 2007, Goldschmidt et al. 2014). While adolescent dieting and extreme weight control behaviors also predict LOC-eating patterns (Haines and Neumark-Sztainer 2006, Keel and Forney 2013), negative affect may be more salient when both constructs are considered together (Goldschmidt et al. 2012). Overall, these data (see Supplementary Table 3) suggest that the NVS alone is insufficient to characterize LOC-eating, and identify adolescence as a potential sensitive period for the increasing influence of NVS disturbances on LOC-eating.

Severe and chronic stressors may disrupt typical developmental processes, causing increased risk for the early onset of LOC-eating and emergence of binge-type EDs in adolescence and young adulthood. Reports of childhood abuse and other traumatic experiences predict risk for binge-type EDs in adulthood (Striegel-Moore et al. 2005, Degortes et al. 2014, Hilbert et al. 2014). Parental over-focus on eating, weight, and shape, and weight-related teasing by family members and peers represent specific risk-factors for LOC-eating in childhood and binge-type EDs in adolescence and young adulthood (Haines and Neumark-Sztainer 2006, Keel and Forney 2013). Furthermore, perceived social pressures to be thin or lose weight and internalization of the sociocultural "thin ideal" body size, which likely lead to ego-threatening social comparisons with others' bodies, predict the emergence of LOC-eating and binge-type EDs in adolescents (Stice et al. 2002, Field et al. 2012, Sonneville et al. 2012). Childhood exposure to sociocultural stressors, especially those involving acute threat and body-related social-evaluative threats, may give rise to altered gene expression and NVS neurophysiological disturbances that contribute to LOC-eating in vulnerable individuals.

The age of LOC-eating onset influences development. Individuals reporting LOC-eating onset during childhood, relative to adulthood, are more likely to endorse severe binge-eating, use of multiple purging behaviors, and a BN diagnosis (Brewerton et al. 2014). Similarly, early relative to later-onset binge-type EDs manifest greater binge-eating and purging frequencies, weight/shape concerns, and mood disturbances (Marcus et al. 1995, Sullivan et al. 1996). Taken together, this suggests that early onset increases risk for more severe and persistent pathology. Other data link childhood onset of LOC-eating to familial emotional problems and trauma (Brewerton et al. 2014) (Marcus et al. 1995, Brewerton et al. 2014), further demonstrating the ways in which NVS construct disturbances relate to binge-type EDs.

Towards a Negative Valence Systems Model of Binge-type Eating Disorders

NVS disturbances appear to increase risk for LOC-eating and the development of binge-type EDs; Figure 1 illustrates a framework considered preliminary due to the early stage of developmental research in this area.

Genetic factors are hypothesized to influence expression of negative emotionality traits and emotional-eating tendencies that emerge early in life, are stable throughout development, and predispose youth to LOC-eating. Indeed, genetic effects account for approximately 38–77% of the associations between LOC-eating and temperaments characterized by persistent negative mood and negative urgency, which refers the tendency to act impulsively in response to negative affective states (Racine et al. 2013, Koren et al. 2014). Additionally, emotional-eating is considered as a heritable appetitive trait (Carnell et al. 2013) that contributes to LOC-eating onset in children (Allen et al. 2008) and adolescents (Stice et al. 2002). Evidence suggests that genetic predispositions toward altered signaling of serotonin, catecholamines, glucocorticoids, and/or BDNF, which impact corticolimbic circuitry and neuroendocrine systems mediating NVS responses, may play an important role in the causal relationship between NVS trait disturbances and the early development of LOC-eating. These genetic vulnerabilities may also predispose youth to experience stressors linked to LOC-eating more frequently, either through selecting environments or eliciting reactions

from others that are consistent with NVS traits (Trace et al. 2013). Since not all children with LOC-eating develop binge-type EDs (Tanofsky-Kraff et al. 2011, Hilbert et al. 2013), youth with genetic vulnerability to aberrant NVS responses and environmental stressors present early in development are likely at highest risk for the emergence of such EDs.

Childhood stress may shape development of corticolimbic circuitry and neuroendocrine stress response systems that influence LOC-eating behaviors. Findings from animal and human studies reveal that sexual and physical abuse, maternal separation, and social isolation from peers predict significant structural and functional remodeling of corticolimbic neurons (Lupien et al. 2009, Eiland and Romeo 2013), altered functional connectivity between corticolimbic regions (Burghy et al. 2012), SAM- and HPA-axis hyperreactivity to stressors, and diminished inhibitory effects of cortisol on the HPA-axis (Sinha and Jastreboff 2013, Sominsky and Spencer 2014). These disturbances are linked to abnormal NVS responses often observed among individuals with binge-type EDs and psychological risk-factors for LOC-eating. Such stressor-induced biological alterations may serve as mechanisms through which sustained childhood stressors increase risk for binge-type EDs (Steiger et al. 2001, Díaz-Marsá et al. 2007). Childhood appears to represent a sensitive period for the impact of chronic stressors, as more persistent and atypical neurodevelopmental alterations in corticolimbic circuitry emerge when sustained threats and losses occur at an earlier age and for a longer duration (Lupien et al. 2009).

The effects of early sustained threats and losses on corticolimbic and neuroendocrine dysregulation often are not apparent until adolescence and are more robust in females (Shin and Liberzon 2010, Burghy et al. 2012), which may partly account for the increased risk for binge-type EDs in adolescent females. Puberty may be a necessary driving force for these relationships. Indeed, genetic effects on disordered eating symptoms, including LOC-eating, do not emerge until post-puberty in females (Klump et al. 2012) and with higher levels of estradiol (Klump et al. 2010). Estradiol is proposed to mediate the relationship between genetic risk and binge-type EDs since it is involved in gene expression and provides signals for the profound neural development and reorganization that occurs during adolescence (Klump 2013). Estradiol promotes the expression of genes linked to NVS functioning (Klump 2013). Therefore, it is possible that epigenetic effects stemming from childhood stressors do not influence NVS perturbations linked to LOC-eating until adolescence, particularly in girls. Similar to children at high risk for anxiety and depression (Casey et al. 2008), children with LOC-eating may have a pre-existing imbalance between subcortical limbic and prefrontal cortical structures or dysfunctional neuroendocrine stress systems that is amplified during adolescence. Vulnerable youth, such as those entering puberty with LOC-eating, a history of sustained childhood stressors, and/or NVS gene variants, may be at particularly high risk for disproportionate increases in negative mood intensity, affect lability, emotion dysregulation, exacerbated LOC-eating patterns, and the early emergence and maintenance of binge-type EDs.

Future Directions

Numerous areas of exploration are needed to further elucidate our proposed developmental NVS model of binge-type EDs. The field would benefit from an increased focus on

individual differences and traits that are known to promote risk for binge-type EDs. Since LOC-eating appears to be an early behavioral marker of worsening eating disturbance, NVS construct dysfunctions that predict LOC-eating also require examination. Longitudinal studies of brain development and interactions with genetic, physiological, and behavioral levels of analysis will be crucial to distinguish cause from consequence. Since not all youth with LOC-eating develop binge-type EDs, prospective studies will also identify trajectories associated with LOC-eating cessation and may inform novel prevention targets. Additionally, developmental trajectories that differentiate individuals who develop BN versus BED would also be beneficial for improved outcome prediction. RDoC may provide an exciting opportunity to conduct such systematic studies by examining constructs within the NVS-domain.

Consistent with the RDoC approach, we believe that binge-type EDs represent a behavioral outcome of NVS dysfunction as well as disturbed functioning in other RDoC domains. RDoC stresses the importance of heterogeneous contributions to similar phenotypes. Binge-type EDs, which are diagnoses derived from symptom-based categories, are likely comprised of individuals with diverse neurophysiological dysfunction. However, dysregulation in the NVS-domain clearly plays an important role in many binge-type ED vulnerabilities and should be a focus of future work. Incorporating interactions with other RDoC domains into developmental NVS models for binge-type EDs will also be important. RDoC's ambitious approach provides a framework that may prove crucial for identifying, and ultimately intervening with, those at greatest risk for developing binge-type EDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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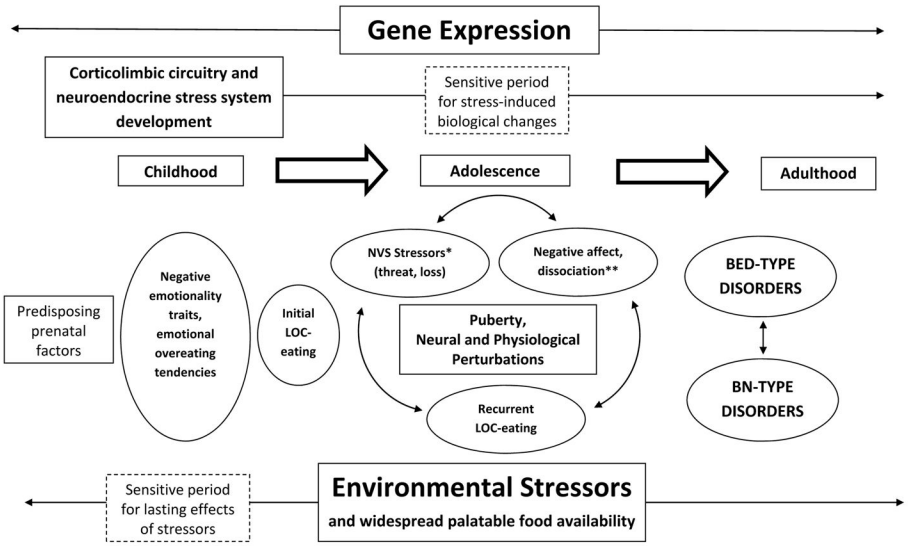

Figure 1.

Working Developmental Negative Valence Systems (NVS) Model of Binge-type Eating Disorders.

Note: NVS = negative valence systems; LOC = loss of control; BED = binge eating disorder; BN = bulimia nervosa

*NVS stressors encompass all Research Domain Criteria NVS constructs, including situations involving acute threat, potential harm, frustrative nonreward, and loss. See Table 1 for description and examples of these stressors.

**Negative affect and dissociation represent two of the most common pathological responses to NVS stressors linked to LOC-eating. See Table 1 for additional examples of clinical manifestations of NVS responses.

Table 1

RDoC Negative Valence Systems Constructs.

Construct	Definition	Clinical Manifestations	Paradigms
Responses to acute threat	Situations in which the threat of harm is immediate and highly probable; stimuli may be conditioned and unconditioned; unfold over a short time course (minutes to hours)	• Fear • Panic • Defensive aggression (behaviors directed at ending the threat) • Freezing	• Fear-potentiated startle • Fear conditioning • Cold pressor stress test • Negative social evaluations of self in relation to others • Exposure to threatening words, pictures, or films • Open field activity
Responses to potential harm	Situations in which harm may occur but there is low or uncertain immediacy and probability; unfold over a short time course (minutes to hours)	• Anxiety • Worries or concerns • Vigilance • Avoidance • Emotional detachment • Numbing	• Trier social stress test • Attention bias paradigms (dot-probe, spatial cueing, eye-tracking) • Exposure to potentially threatening sensory stimuli • Anticipation of social evaluation (chatroom)
Responses to sustained threat	Long-term exposure to situations or stimuli that pose an actual or potential possibility of harm; unfolds over a long time span (weeks to months or years)	• Chronic distress and aversive emotional states	
Frustrative nonreward	Situations that block the attainment of rewards or avoidance of aversive stimuli; inability to obtain desired goal despite repeated efforts	• Anger • Frustration • Irritability • Physical and relational aggression	• Dictator game • Ultimatum game • Resident/human intruder test • Point subtraction aggression paradigm • Social dominance test • Chronic subordination
Responses to loss	Perceived or actual loss or deprivation of relationships, social status, loved ones, behavioral control, housing, food, etc.; May be social or nonsocial; could be episodic or sustained	• Sadness, grief (episodic) • Depression (prolonged) • Guilt • Shame • Rumination • Negative self-referential thinking, low self-esteem • Dietary restraint, fasting	• Social rejection (chatroom) • Social exclusion (cyberball) • Maternal separation • Ultimatum game (loss context) • Self- and social-identity tasks • Monetary incentive delay task • Energy deprivation • Restriction-refeeding cycles