Published in final edited form as:

Int J Eat Disord. 2013 July ; 46(5): . doi:10.1002/eat.22101.

Pediatric Disinhibited Eating: Towards a Research Domain Criteria Framework

Marian Tanofsky-Kraff^{1,2}, Scott Engel³, Jack A. Yanovski², Daniel S. Pine⁴, and Eric E. Nelson⁴

¹Department of Medical and Clinical Psychology, Uniformed Services University of the Health Sciences, Bethesda, MD

²Section on Growth and Obesity, Program in Developmental Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (NIH), DHHS, Bethesda, MD

³Neuropsychiatric Research Institute, Fargo, ND

⁴Section on Development and Affective Neuroscience of the National Institute of Mental Health, National Institutes of Health (NIH), DHHS, Bethesda, MD

Children with disinhibited eating behaviors rarely meet full criteria for *DSM*-defined eating disorders. Further, there is overwhelming agreement that the current system of psychiatric diagnosis does not adequately address the symptoms and problems with which patients of all ages present. With advances in neuroscience, questions have been raised regarding the degree to which measures of brain function can be used to address these problems in psychiatric nosology. The National Institute of Mental Health's Research Domain Criteria (RDoC) program provides a guide for attempts to incorporate such measures into psychiatric classification by encouraging research on dimensions of observable behavior and neurobiology.¹

In brief, RDoC is a framework that integrates advances in neuroscience and research in psychopathology. In order to facilitate basic and clinical research, fundamental components or "domains" were identified (See Table 1 for RDoC matrix). These domains isolated specific behaviors and their presumed underlying neural architecture, focusing on behaviors that manifest across multiple disorders currently classified as nosologically distinct. RDoC includes domains and associated brain systems tied to negative valence, positive valence, cognitive, social processes, and arousal/regulation that are broken down further into constructs.² Units of analysis integrate genetic, neurobiological, physiological, behavioral, environmental, and experiential assessments. In line with its dimensional approach, RDoC aims to determine the full range of variation, from normal to abnormal, within a population of individuals with similar psychological symptoms. Unlike current nosology that is organized around clinical presentations, RDoC domains are structured based on brain-behavior relationships. Thus, RDoC is atheoretical in terms of its connections with existing theories of psychiatric classification.

RDoC is an exciting proposal both because it acknowledges vexing problems in current psychiatric classification and because it prioritizes research in neuroscience as a solution.

Correspondence: Marian Tanofsky-Kraff, PhD, Associate Professor, Department of Medical and Clinical Psychology, USUHS, 4301 Jones Bridge Road, Bethesda, MD 20814; Phone: 301-295-1482; Fax: 301-295-3034; marian.tanofsky-kraff@usuhs.edu.

Disclaimer: The opinions and assertions expressed herein are those of the authors and are not to be construed as reflecting the views of USUHS, the U.S. Public Health Service, or the U.S. Department of Defense.

Yet, moving from the current broad RDoC framework to tangible research questions and associated designs involves developing an approach that is both feasible and specific. A particular set of clinically important behaviors must be selected that are also tractable from the perspective of neuroscience. The current “Idea Worth Researching” applies the RDoC approach to research on disinhibited eating behavior, viewed from a developmental perspective. We propose a design highly specific in nature by determining selected units of analysis that may be linked based upon prior literature. Although our proposed study focuses solely on one domain, we conclude by broadly discussing how the other domains might fit into a more exhaustive, future RDoC study of disinhibited eating. We readily acknowledge that there are numerous other neural, genetic, physiological, and behavioral constructs that are relevant to disinhibited eating and the development of adverse outcomes. We also fully recognize that the constructs that we suggest for study may be relevant to multiple domains.

Studying Pediatric Disinhibited Eating within an RDoC Framework

Since RDoC is a dimensional approach, research designs should involve samples individuals with symptoms that contribute to recognizable disorders. Disinhibited eating patterns involve a lack of healthy restraint over eating. Patterns can range in their expression, from relatively mild levels of eating in the absence of hunger in response to external or emotional cues to more overt, out-of-control eating episodes.³ Despite considerable overlap among these behaviors, most research has examined each individual eating pattern independently. Loss of control (LOC) eating is one of the most studied forms of disinhibited eating behavior in youth. By self-report and laboratory observation, LOC meals are comprised of high-carbohydrate, low-protein, energy-dense palatable foods. LOC is associated with symptoms of depression and anxiety, low self-esteem, and poor interpersonal functioning. Over time, youth with reported LOC experience worsening mood symptoms, excess weight gain, exacerbated metabolic functioning, and the development of binge eating disorder (BED).

The literature on LOC eating provides a potential starting point for selecting relevant constructs from the RDoC matrix to study. Much of the adult BED and binge eating literature has focused on underlying neural pathways linked to “positive valence” (e.g., dopaminergic reward). However, in retrospective interview reports and prospective ecological momentary assessment (EMA) of negative mood, children with LOC experience adverse affective states prior to and after eating. To potentially elucidate this affect-driven aspect of disinhibited eating, our “Idea Worth Researching” is an examination of the “negative valence” domain to understand neural substrates underlying the robust link between LOC and stressful negative affective states. Since RDoC initiates with the brain, we begin with neural circuitry and then outline possible units of analysis (moving from left to right across the RDoC matrix) within the negative valence domain. Then, we describe our “Idea Worth Researching” shortly thereafter.

Neural Circuitry

While several brain regions regulate feeding, involvement of the orbitofrontal cortex (OFC) and amygdala (AMY), key nodes in brain circuitry that support emotion regulation,⁴ might explain the strong connections among negative affective states and feeding. The OFC is crucial for feeding behavior modulation through its influence on food cue processing and representations that vary based upon satiety state, and direct behavior accordingly. The AMY interacts with the OFC to regulate feeding as part of a tightly-connected circuit. The AMY-OFC circuit is a hub of mood-related psychopathology, and shared involvement of this circuit in both regulation of feeding and aspects of mood may explain the strong connection between eating behavior and emotional states. Both areas are salient in modulating energy intake through their hypothalamic interconnections, thereby shaping

feeding behavior through interactions between the processing of sensory and satiety signals. The AMY-OFC responds to emotional stress, providing a conduit through which stress-induced changes in brain function may alter eating behavior that manifests as LOC. Thus, negative affect might interfere with food intake regulation by altering food reward signaling, biasing food choices towards those with high carbohydrate, energy-dense content (similar to LOC episodes). Preliminary evidence suggests that the “AMY-OFC circuit” may be particularly relevant for stress-related changes in eating behavior. Data in overweight adults link fMRI response in this circuit to the processing of food-related cues. Other data suggest changes in AMY-OFC circuitry due to stressful experiences may cause negative mood states to impact feeding. Over time, stress may shape AMY-OFC function through the reverberating influences of repeated episodes of carbohydrate craving on mood and subsequent stress, forming a cyclical pattern. Ultimately, it is hypothesized that this perpetuating cycle results in exacerbated disordered eating, psychopathology, and obesity and associated metabolic complications as have been reported in the pediatric LOC literature.

Genes

Ascending serotonin pathways have been shown to modulate the AMY-OFC circuit. Indeed, when serotonergic pathways are under-active, the AMY-OFC does not function as efficiently. Among the potential genes of interest, the serotonin transporter gene (*SLC6A4*) has a degenerate repeat locus, referred to as the serotonin-transporter-linked polymorphic region (5-HTTLPR),⁵ that is associated with reduced synaptic levels of serotonin, which leads to increased AMY activity in response to stress. Individuals with the short allele of the 5-HTTLPR polymorphism tend to consume meals that are high in carbohydrate and low in protein, similar to LOC eating episodes. Some data suggest that the short-allele variant may be more common in adults with BED, although a clearer relationship has been established with anorexia and bulimia nervosa. Interestingly, one study found adolescents reporting depressive symptoms exhibited greater increases in emotional eating over time if they had at least one short allele of the 5-HTTLPR polymorphism. The *FTO* rs9939609 risk allele may be indirectly linked to the AMY-OFC. *FTO* has consistently been associated with excess body weight in adults and children. Hypothalamic expression of *FTO* may be regulated by energy intake. Indeed, *FTO* is associated with impaired satiety responsiveness and associated eating behaviors prompted by cues other than hunger and fullness – for example, *negative affective states* – to determine intake. Notably, youth with at least one *FTO* rs9939609 risk allele have been shown to be more likely to report LOC, beyond the contribution of adiposity, than youth without risk alleles. The minor allele of the *FTO* SNP rs9939609 has also been linked to increased leptin (see “*Physiology*” section), a peripheral hormone believed to be relevant for meal initiation or termination, and possibly related to markers of stress. Both *SLC6A4* and *FTO* may be important genes to study.

Physiology

Emotional stress-related hormones are of particular interest to our proposal.⁶ Cortisol, a lipid soluble glucocorticoid hormone associated with stress responses, is linked to AMY functioning through the hypothalamic-pituitary-adrenal (HPA) axis. Adults with BED have higher basal cortisol levels compared to those without the disorder. The AMY has also been linked to heart rate variability in response to negative emotions. Notably, adults with BED experience increased heart rate and decreased heart rate variability following laboratory mood inductions. A developing body of research links heart rate variability and chronic sympathetic activation with the appetitive hormone leptin, especially among women. Leptin is an adipose tissue derived hormone that acts as a feedback signal to influence energy homeostasis, eating behaviors, and appetite regulation. Leptin regulates food intake by acting on receptors in the hypothalamus. Some, but not all, research indicates increased

serum leptin concentrations among adults with BED. Our preliminary data suggest that fasting leptin may be associated with pediatric LOC eating, beyond the contribution of adiposity.

Behavior/Paradigm

RDoC research studies should generally involve behavioral paradigms that map onto the other units of analysis (Table 1). The behavioral presentation of disinhibited eating can be successfully captured via a laboratory test meal immediately following a stress task aimed to induce a negative affective state. The Chatroom rejection task is a highly effective stress task that can be used to assess neural response to anticipated peer acceptance or rejection. The Chatroom rejection task has effectively induced brain changes in the AMY-OFC circuit in adolescents with anxiety disorders.⁷ It remains untested in samples of youth with disinhibited eating.

Self-report

In addition to questionnaires and interviews, ecological momentary assessment (EMA), a technique that relies on portable measurement strategies that can be applied in “real time” in the natural environment, is proposed to capture emotional states and symptoms as they occur in the natural environment. In adult BED, EMA shows a relationship between negative mood states and binge episodes. Our preliminary data suggest that adolescent girls with LOC eating experience social stress and negative affect leading up to LOC episodes.

An Idea Worth Researching

Based on our review of systems within the Negative Valence Domain, we propose studying overweight girls aged 8–14 years reporting disinhibited eating behaviors using multiple sophisticated and complimentary methods: genetic analysis, assessment of appetitive hormones, and fMRI that involves the Chatroom rejection task that is immediately followed by reports of state affect and a laboratory meal designed to capture a disinhibited eating episode. We have chosen the middle-childhood/early adolescent time period since disinhibited eating manifests during this time and it is also a time of rapid brain growth and marked social development – and a key developmental period for delineating pathophysiological processes that give rise to such episodes and exacerbated disordered eating. Notably, the limbic system is active during adolescence, but the frontal lobe is not yet fully developed. Thus, adolescents may have limited cognitive resources for dealing effectively with negative affect and thus might use food to cope with stressful emotions. Girls may be particularly vulnerable to this cycle as they are more sensitive to social stress than males.⁶ Overweight girls commonly report disinhibited eating and are at higher risk for eating disorders than males.² Repeated assessments into adulthood will provide an ideal design to identify those at greatest risk for BED and obesity, as well as comorbid psychiatric and adverse medical outcomes.

Broad Assessment across Other Domains—Conceivably, all RDoC domains might be represented in a group of individuals with disinhibited eating. As a forward-thinking exercise, we broadly propose additional neural circuits, genes, and hormones that we would examine within the four other RDoC domains (see Table 1 for the constructs of interest). Our proposal is not exhaustive but is guided by the pediatric LOC literature and adult BED studies.

Positive Valence

Disinhibited eating has been also theorized to serve as a momentary reward for susceptible individuals. Circuitry involving the striatum is of interest, as BED has been linked to

neurotransmitters involved in food reinforcement such as dopamine (e.g., TaqIA1+allele of the *DRD2* gene) and hedonics such as opioids (e.g., A118G polymorphism of the *OPRM1* gene). The TaqIA1 allele is associated with decreased dopamine D2 receptor density in the striatum and hypo-functioning of dopamine signaling. The A118G allele may increase activation of the mu-opioid receptors in the striatum, and AMY has been linked to increased experience of hedonic pleasure from palatable foods. Thus, BED (and possibly LOC) may be characterized by hyper-sensitivity to the reinforcing and hedonic properties of palatable food.

Cognitive Systems

The OFC is also involved in many disease states that include impaired inhibitory and cognitive control behaviors similar to LOC eating. Emerging data in adults with BED point to the possibility that youth with disinhibited eating may have an attention bias toward highly palatable food. Notably, the AMY and the ventral striatum (as well as visual orienting regions, e.g., the superior colliculus) may be involved in such attention biases.

Social Processes

The AMY-OFC circuit responds to social stress, particularly among girls, providing a pathway through which stress-induced changes in brain function may alter eating behavior that manifests as LOC. There are no clear data on genes that might be linked to LOC or BED in relation to social processes. Yet, there are data implicating genetic variation of the A118G polymorphism of the *OPRM1* gene to individual sensitivity to social rejection.

Arousal Regulatory Systems

Many neural circuits, including the AMY-OFC, are likely involved in regulatory systems through their links with the hypothalamus. Brain-derived neurotrophic factor (BDNF) regulates food intake, and hyperphagia is reported in those with haploinsufficiency for *BDNF*. The Met-allele of the *BDNF* Val66Met polymorphism has been linked to binge eating in adolescent girls with severe dietary restriction. Regarding physiology, ghrelin is an appetitive hormone that controls the synthesis and secretion of several neuropeptides in the hypothalamus that regulate feeding. Ghrelin serum concentrations have been shown to be lower prior to a meal and to decline more slowly after ingestion in adults with BED. Ghrelin has also been shown to increase after successful treatment of binge eating.

Conclusions

RDoC is an exciting opportunity to describe disordered eating and elucidate etiology and outcome in youth. Our “Idea Worth Researching” may generate formative knowledge that will provide early identification of those at greatest risk for psychiatric disturbance and adverse health outcomes upon which preventive interventions may be developed. Multi-modal approaches have not been used in the field of disordered eating, and rarely implemented in science at large. Therefore, examining early disinhibited eating and outcome making use of state-of-the-science methods within the laboratory and in the natural environment may push research to a new frontier. Although still in the nascent stages of development, such proposals may ultimately inform our understanding of the etiology and classification of clinically significant disordered eating.

Acknowledgments

We wish to thank Anna Vannucci, M.S. for her thoughtful review and insights.

References

1. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am J Psychiatry*. Jul; 2010 167(7):748–751. [PubMed: 20595427]
2. Sanislow CA, Pine DS, Quinn KJ, et al. Developing constructs for psychopathology research: research domain criteria. *J Abnorm Psychol*. Nov; 2010 119(4):631–639. [PubMed: 20939653]
3. Shomaker, LB.; Tanofsky-Kraff, M.; Yanovski, JA. Disinhibited eating and body weight in youth. In: Preedy, VR.; Watson, RR.; Watson, CR., editors. *Handbook of Behavior, Food and Nutrition*. Springer Publishers; 2011. p. 2183-2200.
4. Rolls, ET., editor. *The Brain and Emotion*. New York: Oxford Press; 1999.
5. Calati R, De Ronchi D, Bellini M, Serretti A. The 5-HTTLPR polymorphism and eating disorders: A meta-analysis. *Int J Eat Disord*. 2011 Apr; 44(3):191–9. [PubMed: 20209488]
6. Dallman MF. Stress-induced obesity and the emotional nervous system. *Trends Endocrinol Metab*. 2010; 21:159–165.
7. Guyer AE, Lau JY, McClure-Tone EB, et al. Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Arch Gen Psychiatry*. Nov; 2008 65(11):1303–1312. [PubMed: 18981342]

Table 1
Constructs to assess for a multi-modal study of early disinhibited eating and outcomes.

	Units of Analysis					
Domain/Construct	Genes	Circuits	Physiology	Behavior/Paradigm	Self-reports	
Negative valence	<i>SLC6A4, FTO</i>	AMY-OFC	Cortisol, Heart rate variability, Leptin	Social stress task followed by laboratory test meal modeled to capture disinhibited eating	EMA to test negative affect in relation to disinhibited eating in the natural environment	
Positive valence	<i>DRD2, OPRM1</i>	Dopaminergic Reward Pathway				
Cognitive		OFC				
Social processes	<i>OPRM1</i>	OFC-AMY	BDNF, Leptin, Ghrelin			
Arousal/regulatory	<i>BDNF FTO</i>	Hypothalamic				