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Examining Weight Suppression as a Transdiagnostic Factor Influencing Illness Trajectory in Bulimic Eating Disorders

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Abstract

Recent research indicates that weight suppression (WS: defined as the difference between highest lifetime and current weight) prospectively predicts illness trajectory across eating disorders characterized by binge eating, including AN binge-purge subtype (ANbp), bulimia nervosa (BN), and binge eating disorder (BED), collectively referred to as bulimic eating disorders. Through a series of studies, we have developed a model to explain the link between WS and illness trajectory in bulimic eating disorders. Our model posits that WS contributes to reduced circulating leptin, which leads to reduced postprandial glucagon-like peptide 1 (GLP-1) response. Diminished leptin and GLP-1 function contribute to alterations in two reward-related constructs in the Research Domain Criteria (RDoC): reward value/effort and reward satiation. Respectively, these changes increase drive/motivation to consume food and decrease ability for food consumption to lead to a state of satiation/satisfaction. Combined, these alterations increase risk for experiencing large, out-of-control binge-eating episodes. The following review presents evidence that contributed to the development of this model as well as preliminary findings from an on-going project funded to test this model.

Weight suppression (WS) represents the difference between highest lifetime weight and current weight[1]. Recent research indicates that WS has relevance for understanding illness trajectory across bulimic eating disorders, including AN binge-purge subtype (ANbp), BN, and BED[2]. Through a series of studies and literature review, we have developed a model to explain the link between WS and illness trajectory in bulimic eating disorders. Our model (see Figure 1) posits that WS contributes to reduced circulating leptin, which leads to reduced postprandial glucagon-like peptide 1 (GLP-1) response. Diminished leptin and

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GLP-1 function contribute to alterations in two reward-related constructs in the Research Domain Criteria (RDoC): reward valuation/effort and reward satiation[3]. Respectively, these changes increase drive/motivation to consume food (valuation/effort) and decrease ability for food consumption to lead to a state of satiation/satisfaction. Combined, these alterations increase risk for experiencing large, out-of-control binge-eating episodes, explaining the link between WS and illness maintenance over time across bulimic eating disorders.

Both AN and BN are characterized by weight and shape concerns and extreme efforts to achieve weight loss but differ in the extent to which these efforts result in objectively low weight. This difference is codified in the DSM-5 which defines AN by "significantly low body weight," which is further defined as "a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected" (p. 338)[4]. Because there is considerable symptom overlap between ANbp and BN, the DSM-5 goes on to require that BN cannot occur "exclusively during episodes of anorexia nervosa" (p. 345). Thus, a diagnosis of ANbp trumps a diagnosis of BN in the DSM-5 – which largely ensures that patients with BN are not underweight. In contrast, BED is not defined by body image disturbance in the DSM-5. Further, the DSM-5 precludes use of inappropriate compensatory behaviors, such as purging, fasting, or excessive exercise. Potentially reflecting these definitional differences, patients' BMI range from normal weight to overweight or obese. However, when patients with BED are compared to BMI-matched non-eating disorder controls, they endorse greater body image concerns and greater efforts to lose weight[4].

Eating disorder diagnosis predicts outcome, with ANbp demonstrating greater treatment utilization, lower treatment response, greater chronicity and mortality compared to BN, and BN demonstrating worse outcomes in these domains compared to BED[5]. While predictive validity contributed to the identification of these as three diagnostic categories in the DSM-5[4], we posit that the underlying dimension of WS contributes to these patterns, with ANbp demonstrating the greatest WS and worst outcomes, BN demonstrating intermediate and variable WS and intermediate and variable outcomes, and BED demonstrating the lowest WS and more favorable outcomes. Further, we posit that WS contributes to diagnostic migration commonly observed in large clinical samples of AN from the restricting subtype to the binge-purge subtype and weight gain that leads to migration to a diagnosis of BN[6] or to remission in community-based samples[7,8].

Conceptualizing diagnostic categories as residing along underlying biobehavioral dimensions is consistent with the NIMH's Research Domain Criteria (RDoC) initiative. This approach seeks to identify core constructs that can be measured across multiple units of analysis (e.g., physiology, self-report, and behavior) that contribute to the emergence of mental illness. Mental illness is viewed on a continuum with normal behavior, such that the same processes that give rise to adaptive weight control and ingestive behavior contribute to maladaptive weight control and ingestive behavior. The RDoC matrix is divided into separate domains[3]. Among them, the Positive Valence Domain identifies core constructs thought to explain excessive or deficient engagement in rewarding behaviors that may contribute to patterns of comorbidity often seen in mental disorders. As such, the RDoC framework seeks to identify transdiagnostic biobehavioral mechanisms that account for psychopathology. Our model posits that WS contributes to alterations in two RDoC core

constructs, reward valuation/effort and reward satiation, to explain the link between WS and eating disorder trajectory. In our model, trajectory refers to illness course, which can range from changes in symptom severity that result in worsening, maintenance, or remission, as well as migration from one symptom presentation to another. Although weight changes are only relevant to defining remission for ANbp, weight gain (or lack thereof) may impact illness trajectory for bulimic eating disorders more broadly.

Weight Suppression and Eating Disorder Trajectory

In addition to differing in BMI, eating disorders differ in WS, with greater mean WS in ANbp (>14 kg)[9,10] than BN (> 7 kg)[11–19], in BN than BED (>6 kg)[20,21], and in all eating disorders than controls (<3 kg)[22]. In AN, WS is associated with illness severity and predicts bulimic symptom severity[9]. Although women with BN often have normal weight (e.g., 21 kg/m^2); mean WS is 7.8 kg across studies[11–19], indicating substantial weight loss is the norm. Three longitudinal studies, each in independent samples, support prospective associations between greater WS and BN maintenance, including BN patients from a randomized controlled trial[11], naturalistic follow-up of a treatment-seeking BN sample[13], and naturalistic follow-up of bulimic eating disorder cases identified in the community[14]. In addition to supporting that greater WS is a prospective risk factor for illness maintenance, multivariable models found significant effects for WS, controlling for age, BMI, body image disturbance, and dietary restraint[14,19], suggesting that the effects of WS are not better accounted for by these other variables. Moreover, WS demonstrates very weak correlations with BMI in BN, with mean r=.01[12,14,18,19,23], suggesting that it is weight relative to a prior maximum, rather than current weight, that matters. Other studies[15–17,24] have not found an association between WS and eating disorder maintenance, potentially due to smaller samples[15,16,24], restricted range of WS[15–17], exclusion of participants who did not complete treatment [15,16,24], or inclusion of obese participants[16,17]. Individuals who are significantly overweight or obese are known to have other metabolic disturbances which may alter the association between WS and illness trajectory[25,26]. Our model may not extend across the BMI range.

Across studies examining the association between WS and illness maintenance, the mean weighted effect size is quite small (β=.07)[11,13–17,24], suggesting the importance of larger samples to detect reliable associations. This small effect size may reflect limitations in how WS has been measured because the highest weight for height may have occurred before an individual reached their current height. Calculating WS as the difference between highest and current BMI percentile for age and sex permits evaluation of WS across development. This more developmentally appropriate measure of WS has demonstrated stronger associations with current eating disorder severity than the traditional approach to calculating WS[27]. In addition, even a very small effect (e.g., r=.05) for predicting a single event can have meaningful consequences over time[28].

Finally, there is robust evidence that greater WS is a significant predictor of greater weight gain over follow-up[9,10,12,15,23,24,29]. For patients with AN, this means that WS may actually facilitate recovery. Weight gain reduces both WS and could reverse alterations in underlying mechanisms contributing to disorder maintenance, further accounting for null findings in

some studies[10,24,30]. Moreover, the relative rarity of cross-over from AN to BN in community-based samples may reflect the high remission rate in these samples as recovery would signify both weight gain and reduction of WS[7,8]. Alternatively, recent data from a large longitudinal epidemiological study suggest that AN cases identified in the community have lower premorbid BMI percentile compared to those who do not develop eating disorders, and those who go on to develop BN or BED have higher premorbid BMI percentiles[31]. Thus, AN cases from community samples may not possess the same degree of WS observed in patients with AN drawn from clinical samples. Further, clinical samples of AN may represent cases in whom low weight and WS persist, increasing their likelihood of both seeking treatment[32] and developing binge eating over time[6] compared to community samples of AN[7,8].

Given that WS reflects a history of greater weight relative to current weight *and* increases risk for weight gain, WS may heighten underlying cognitions that drive weight loss behaviors, and this could explain the link between WS and illness trajectory across eating disorders. Indeed, in a 20-year follow-up study, we found that greater WS prospectively predicted increases in drive for thinness, which prospectively predicted increased bulimic symptoms and that drive for thinness mediated the association between WS and bulimic symptom maintenance over 20-year follow-up[33]. However, the presence of a psychological explanation for the link between WS and illness trajectory does not rule out the presence of a biological explanation. Weight loss has biological consequences that promote weight gain, including defensive increases in metabolic efficiency as well as alterations in ingestive behaviors[34]. These same behaviors would also influence risk for binge-eating episodes.

Weight Loss and WS Reduce Leptin and GLP-1 Release

Leptin is produced by the *ob* (Lep) gene of white adipose tissue, such that higher fat mass results in higher circulating leptin levels (r-values>.90 in humans)[35]. Importantly, weight loss and WS impact leptin independently of BMI[35]. In non-eating disordered women, a 5–10% weight loss caused significant (40–60%) declines in leptin[35,36] (r=.61, reflecting a large effect size for change in weight and leptin)[36]. Thus, individual differences in WS should predict differences in leptin levels among individuals of apparently similar weight. Supporting our model, we recently published on the significant association between greater WS and lower leptin, controlling for BMI and percentage of body fat[22]. Specifically, compared to controls, women with BN demonstrated no significant differences in current BMI. However, they had significantly greater WS, and greater WS was associated significantly with lower leptin concentrations. In a separate sample, we demonstrated that WS predicted leptin while controlling for BMI and that leptin statistically mediated the association between WS and reported duration of illness in bulimic disorders[37].

Importantly, although acute changes in leptin are observed with fasting[34,38], neither WS nor leptin change dramatically throughout the day. So, changes in leptin do not directly influence initiation or cessation of food intake in a given meal or binge episode. To understand dynamic influences on food consumption during binge episodes, it is important to consider the role of meal-related signals, such as GLP-1. GLP-1 is released in response to food intake by L cells in the intestine and acts as a peripheral signal of acute changes in

nutritional status. Postprandial increase in GLP-1 is a satiation signal that contributes the end of a meal in normal feeding. Peripheral GLP-1 release is potently stimulated by leptin via leptin receptors on L cells of the intestine[39,40]. Thus, individuals with higher leptin levels also demonstrate more robust GLP-1 responses to food intake[41]. These associations appear to reflect the influence of leptin on GLP-1 levels rather than the reverse as neither meal-induced increases in GLP-1 nor exogenous GLP-1 administration influence leptin levels in healthy volunteers[42,43]. Alterations in GLP-1 release observed peripherally may reflect central processes because leptin crosses the blood-brain barrier where it could impact central GLP-1 function.

Given that ANbp is defined by maintenance of low weight, one would expect hypoleptinemia in ANbp and reduced postprandial GLP-1 response. Given that mean WS in BN is 7.8 kg and ranges from 2.3 kg[17] to 12.0 kg[12] across studies, one would expect both reduced and variable leptin levels in BN with concomitant alterations in GLP-1 function. Given that BED is associated with obesity, one would expect hyperleptinemia, though, depending on level of WS, leptin may still be depressed relative to leptin receptor sensitivity [44] which may still result in blunted GLP-1 responses in BED. Literature reviewed below supports these expectations.

Leptin Varies Across Eating Disorders and GLP-1 Response is Reduced

Low leptin levels have been found consistently in AN[45–49], with lower leptin in the binge-purge compared to the restricting subtype and a significant association between lower leptin and higher binge frequency[50]. According to our model, WS and resulting hypoleptinemia may explain diagnostic migration from restricting AN to bulimic eating disorders observed in a majority of AN patients[6,51]. Of note, in community-based samples, diagnostic cross-over is less likely; however, this may reflect the much higher likelihood of weight gain and remission in community-based samples of AN[7,8]. A small minority of AN patients maintain WS and low leptin levels and never binge, suggesting the presence of other key processes in the maintenance of restricting AN, including the possibility that reduced leptin levels may influence reinforcing value of excessive exercise. Moreover, we do not propose that a single set of mechanisms can explain all eating disorders, and this model clearly does not explain chronic presentations of AN restricting subtype.

Given that mean WS in BN is 7.8 kg and ranges from 2.3 kg[17] to 12.0 kg[12] across studies, one would expect both reduced leptin levels and considerable variability in levels in BN. Supporting this expectation, several investigators have reported significantly reduced leptin levels in BN compared to control participants despite no differences in BMI[38,44,45,52,53]. In addition, Monteleone[44] noted large leptin variability among BN patients in their[38,45] and others' studies[52] and found significant inverse associations between leptin levels in BN and both current symptom severity and reported illness duration. Women recovered from BN demonstrated similar leptin levels to controls but had higher percent expected body weight[54].

Although obese women with BED have higher leptin than healthy-weight controls[45,55], comparisons to obese controls have revealed lower leptin[56], higher leptin[57], and no

significant differences[58]. All studies involved small samples, and none examined WS or associations between leptin and illness duration within BED. Collectively, studies provide compelling support for associations between leptin and maintenance of BN but limited data for a full BMI range of bulimic eating disorders. Moreover, studies did not assess WS and examined associations cross-sectionally, making it impossible to evaluate whether WS contributes to observed alterations in leptin or whether reduced leptin levels predict illness maintenance. Indeed, an alternative interpretation of cross-sectional associations is that longer illness duration leads to lower leptin levels. Recently, we examined this possibility in statistical mediation models. Analyses supported a model in which leptin mediated associations between WS and illness duration but did not support an alternative model in which illness duration mediated associations between WS and leptin[37]. While these findings provide preliminary support for our model, longitudinal data are needed to establish prospective associations between WS, reduced leptin, and illness maintenance over time.

Consistent with lower leptin observed in ANbp and BN and the influence of leptin on GLP-1 release, studies found significantly lower pre- and post-prandial GLP-1 levels in AN[59] and BN[60,61] compared to controls. Peak GLP-1 was lower in obese BED (10 pM/ml) compared to obese controls (15 pM/ml)[62], but this did not reach statistical significance due to very small samples (n=10 BED; n=9 controls). Transdiagnostically, leptin may explain shorter illness duration in BED compared to BN and in BN compared to AN[4] with differences in leptin function secondary to differences in BMI and WS across diagnostic groups. Further, alterations in GLP-1 response emerging from hypoleptinemia or leptin resistance[44] may account for differences between those with eating disorders and controls.

Our transdiagnostic model is informed by extensive animal-based research regarding the biological and behavioral consequences of altered leptin and GLP-1 function. Findings from basic research informed both our hypotheses and methods for testing these hypotheses. Following the RDoC's focus on translating findings from basic science to examinations of clinical populations, we review the relevant animal literature below.

Peripheral Leptin and GLP-1 Impact Reward Value/Effort and Satiation through Distinct Neural Circuits

Circulating leptin crosses the blood-brain barrier and binds to leptin receptors throughout several brain regions, including the ventral tegmental area (VTA)[63] and the hypothalamus (discussed below)[64]. Dopamine (DA) projections from the VTA to the nucleus accumbens (NAc) are directly implicated in many aspects of reward value[65,66], and contribute to greater effort in a progressive ratio (PR) task for reinforcers (e.g., food, sex, intracranial self-stimulation [ICSS])[67–70]. At the cellular level, peripheral leptin administration *inhibits* firing of DA neurons in the VTA[63]. To dissociate leptin's effects in the VTA from its effects in the hypothalamus, neuroscientists have used site-specific alterations in leptin function. Leptin infusions in the VTA, but not in the arcuate nucleus of the hypothalamus (Arc), reduced the amount of work rats were willing to do for a given threshold of ICSS[71]. Further, using microinjections of a viral vector to knock down leptin receptors in the midbrain (where the VTA is located), but not the lateral hypothalamus, increased break point (BP) on a PR task

for food; disabling leptin function in the midbrain increased reward value for food assessed through rats' effort to obtain food[72].

Leptin also binds to receptors throughout the hypothalamus, including the Arc, paraventricular nucleus (PVN), and ventromedial and lateral hypothalamus (VMH and LH), where it modulates neural responses to gut-derived satiation signals. In the Arc, leptin inhibits neurons containing neuropeptide Y and agouti-related protein (NPY/AgRP) and activates neurons containing pro-opiomelanocortin and cocaine and amphetamine-related transcript (POMC/CART)[64]. POMC/CART activation decreases food intake in animals and humans[73]. In contrast, NPY and AgRP stimulate increased food intake[64]. Thus, when an organism loses adipose tissue (a state ensured by WS), leptin levels decrease, activation of POMC/CART containing neurons decreases, and NPY/AgRP neurons remain active and drive a defensive increase in *ad lib* feeding to return the organism to a state of energy balance[64]. These effects have been replicated in numerous rodent experiments applying food restriction to various degrees and for periods ranging from acute (24–72 hours) to chronic (≥4 weeks)[64,74–76]. Leptin infusions in the Arc[71] decrease food intake in rats, and selective deletion of leptin receptors in POMC and AgRP neurons increased meal size in mice[77]. Thus, lower leptin levels contribute to diminished responsiveness to satiating signals during food intake.

Peripheral GLP-1 binds to GLP-1 receptors on the vagus nerve causing stimulation of vagal afferents, which activate several neurons projecting from the nucleus solitary tract (NTS), including preproglucagon cells that release GLP-1 centrally[78]. Similar to the effect of leptin on GLP-1 release in the periphery, central leptin administration enhances GLP-1 release from preproglucagon neurons of the NTS [79,80]. GLP-1 neurons of the NTS project to multiple brain regions, including the VTA and NAc where GLP-1 influences reward value/effort[39,80–83]. In the VTA, 50% of DA neurons express GLP-1 receptors[81] and 30% of GLP-1 neurons in the NTS project to the VTA[84] and 40% project to the NAc[82,84], making GLP-1 a prime candidate for examining how *acute* changes in food intake influence reward pathways in the brain. Infusion of GLP-1 to the NAc core reduced food intake, while its receptor antagonist increased food intake[82]. Injection of a potent GLP-1 agonist, Exendin 4, in the VTA or NAc decreased palatable food intake, and a GLP-1 receptor antagonist decreased intake[84]. Infusion of Exendin 4 in the VTA and NAc reduced the BP on a PR task for food[85], and Exendin 4 diminished conditioned place preference for cocaine[86], a function which implicates GLP-1 signaling in reducing activation of the mesolimbic DA pathway for a non-food, non-caloric reinforcer. In healthy volunteers, a meal pattern that increased GLP-1 levels reduced willingness to work for food rewards, with a very large effect size (d=2.29)[87]. Thus, similar to leptin, GLP-1 appears to reduce reward value.

GLP-1 projections from the NTS to the Arc and PVN contribute to satiation[39,83]. ICV administration of Exendin 4 increased activation of POMC/NPY neurons in the Arc, similar to leptin's effects[88], and central GLP-1 administration reduces food intake in rats[89,90]. In humans, peripheral GLP-1 infusion increased satiation and decreased food intake[91], and a meal pattern that increased GLP-1 response was associated with a 10% reduction in food intake during a subsequent *ad lib* test meal, reflecting a large effect size (d=.80)[87].

In summary, leptin and GLP-1 reduce reward value through inhibitory effects in the mesolimbic DA pathway and increase satiation through a combination of inhibitory and excitatory actions in the hypothalamus. Thus, lower leptin and GLP-1 response observed in eating disorders should contribute to both increased reward value/effort and decreased satiation. These behavioral consequences translate into increased risk for weight gain and increased risk for experiencing large, out-of-control binge-eating episodes. Research supports that disorders characterized by binge-eating episodes are characterized by increased reward value/effort and decreased satiation.

Increased Reward Value/Effort and Decreased Satiation in Eating Disorders

By definition, individuals with AN binge-eating/purging type, BN, or BED experience a loss of control over eating and consume an excessive amount of food when they binge. Because food is a primary reinforcer, investigators have posited that this reflects increased food reward value[92,93]. As a measure of reward value/effort, the PR task has many advantages, including high test-retest reliability, associations between BP on a PR task and food consumption in an *ad lib* test meal, and ability to use PR tasks with minimal modification in animals and humans, such that careful experimental manipulations of physiological factors in animal models may be translated into clinical phenomena observed in humans[94]. Despite these advantages, surprisingly few studies have employed PR tasks to measure reward value in eating disorders. These studies support increased reward value for food[22,95–98] and cigarettes[95] in BN compared to controls, specifically in a fed vs. fasted condition[95,96]. In a fed state, effect sizes have ranged from moderate (d=.50)[95] to large (d=1.52)[96] for responses elicited in a PR task for food *relative* to a non-food reinforcer. Notably, most studies[95–97] have employed an adapted PR task to measure *relative* reinforcing food value by presenting participants with a choice between working for two rewards simultaneously (e.g., food vs. money[95]), which is not sensitive to how individual differences in central leptin or GLP-1 function might alter reward value across both food *and* non-food rewards. In eating disorders, as in most mental disorders, comorbidity is the rule rather than the exception [99], and our model would predict that alterations in reward value and satiation may explain why women with eating disorders are at increased risk for substance use disorders.

Schebendach and colleagues[98] compared women with BN (n=10) to healthy control participants (n=10) using a PR task to evaluate absolute reinforcing value of food, which is most relevant to our model. Indeed, we adapted their PR task for our current research and review their methods here to provide the context for our approach. Participants in their study began a computerized PR task at 2 pm in which they pressed a computer key to earn strawberry yogurt shake portions. Across 12 trials, the amount of work required to receive a 175 ml portion increased in increments of 200 (trial 1=50, trial 2=250, … trial 12=2250 presses). As participants completed trials, the computer screen displayed an image of a pitcher filling up with shake, and an actual pitcher filled with yogurt shake next to the computer. Participants could earn up to 2.1 liters of shake and were free to discontinue as soon as they had earned as much shake as they felt they could consume per instructions. After completing the PR task, participants waited until 3 pm, at which time they were given 30 min to consume the amount of shake they had earned. Under instructions to work for the amount “you can binge on”/”you can overeat,” women with BN had a significantly higher

BP than controls with a large effect size (d=1.24). Importantly, controls did not actually consume the total amount of shake earned under, resulting in a weak association between BP and shake consumption in controls (r=0.05). This suggests that controls' motivation for shake may have declined more precipitously while consuming the shake than was reflected in their BP. In contrast, BN participants consumed almost all shake earned (r=0.98 for the association between what was earned and what was consumed). Given that binge instructions would map on to processes in which patients feel a loss of control over their eating, the BP difference between controls and BN participants likely reflects greater reward value for food in BN. However, results do not capture how reward value dynamically changes during food consumption because no food was consumed *during* the PR task. According to our model, controls consumed less of the shake than they earned because their intact GLP-1 response to food both reduced reward value and increased satiation during food consumption compared to BN participants.

Although animal-based studies of reward value/effort permit animals to consume rewards earned during the PR task, no prior study using PR tasks in BN [95–98] permitted participants to consume rewards earned during the PR task. Although this approach prevents the potential satiating effects of food from compromising assessment of approach motivation, it precludes evaluation of how individual differences in post-prandial GLP-1 response may alter reinforcing value of food *during* consumption. To measure willingness to work for food *during* food consumption, we adapted the approach used by Schebendach et al. Our machine shop created an M&M's® dispenser, connected to a computer on which participants complete the PR task schedule used by Schebendach et al.[98]. Participants were told they could earn M&M's® by pressing a computer key, that the task consisted of 10 trials, and that at the end of each trial they would receive and consume 10 M&M's®. Participants were instructed to work for the amount they wanted, that they could press the key as little or as much as they chose, could stop at anytime, and there were no right or wrong answers. Participants were then left alone and asked to notify the experimenter when they completed all 10 trials or decided to stop. Each time the participant reached the criterion for a trial, the dispenser distributed 10 M&M's® for consumption. Unlike Schebendach et al.[98], we did not instruct participants to work for the amount of food they "can binge on" and did not provide enough food to replicate a binge. This ensured that the total amount of food that could be earned (100 M&M's®; 426 kcal in 3 oz.) was consumable by all participants. Thus, differences in response primarily reflect differences in reward value for M&M's®. According to our model, individual differences in leptin concentration should contribute to differences in BP for M&M's®. Individual differences in GLP-1 response during consumption of the M&M's® should further enhance differences in reward value, such that the rate at which M&M's® become less rewarding (and willingness to work declines) should be less robust in those with lower GLP-1 responses. Individual differences in leptin and GLP-1 response also may contribute to individual differences in the extent to which participants begin to feel satiated. However, we wanted our PR task for food to most closely reflect processes that drive food intake *during* a binge, which include sufficient quantities of food to elicit individual differences in GLP-1 response[61]. BP, keyboard presses, key strokes/sec by trial, and M&M's® consumed were recorded. We used real-time digital video monitoring to ensure that participants followed instructions. We examined test-retest

reliability by having participants complete the task twice under the same conditions over a one-week interval to ensure that we captured stable individual differences in reward valuation/effort. Test-retest reliability (r=.95) and the correlation between BP and M&M's® consumed (r=.99) were high, suggesting reliable and valid indicators of individual differences in approach motivation for food that translate into actual food consumption.

On the PR task, BN participants (n=30) had a significantly higher BP (754±430) than controls (n=30) (498±380) (t(56)=2.39, p=.02; d=.63)[22]. Examining dimensional associations, we observed significant associations between greater WS and higher BP (r=.35, p<.01 in the full sample/r=.37 in BN), and, in BN, greater binge size (r=.47, p<.01), severity (r=.36, p=.02), and duration of illness (r=.44, p=.04). Consistent with a model in which hedonic and homeostatic regulation of food intake are integrated, we found a significant association between higher BP and lower self-reported satiation (r=−.31, p=.05/r=−.27), more severe loss of control over eating (r=.36, p=.04/r=.20), and, in BN, longer duration of illness (r=.34, p=.05). Although lower leptin was linked to higher BP, controlling for BMI and %body fat (β=−.13/β=−.11)[22], the modest sample size constrained power to find a significant association for this small effect size, and we did not assess postprandial GLP-1 response in this study.

To further address influences of GLP-1 on approach motivation independently of its influences on satiation, we developed a novel PR task for a non-food reinforcer. Our biomedical engineers programmed a PR task that required participants to press a key on a keyboard to gain access to playing 1 min of Angry Birds per trial completed, using the same instructions, number of trials, and PR schedule used in our M&M's® PR task. We developed this task because we wanted a non-food reinforcer that participants would find rewarding (popularity of Angry Birds supported this) and could consume during the PR task so that both the food and non-food tasks measure approach motivation for primary reinforcers, which most closely models animal-based research, and factors that could explain loss of control over a range of positively reinforced behaviors. We interpret play as a primary reinforcer because it produces pleasure and because the access to game play was not exchanged for any other reinforcer[100]. This task eliminates the influence of individual differences in GLP-1 on satiation as consumption of game play does not affect nutritional state. To infer whether GLP-1 response might influence approach motivation independently of its influence on satiation, we compared responses for the non-food reinforcer in the fed vs. fasted state. Thus, we are using a fixed meal to experimentally manipulate GLP-1 levels to examine the impact of physiological changes on approach motivation. If peripheral changes in GLP-1 reflect central changes in GLP-1 that reduce DA activation in the mesolimbic reward pathway, then we should observe lower BP for the non-food reinforcer in the fed vs. fasted state even though game play itself does not contribute to satiation.

Preliminary findings support these hypotheses. As part of an ongoing study, we have behavioral data on 108 women with bulimic disorders and 26 controls on reward value of a non-food reinforcer in the fed vs. fasted state. BP for Angry Birds was significantly higher in the fasted (824.63±456.48) compared to the fed (587.31±386.55) state (t(133)=7.17, p<.001). BP in the fasted condition was significantly correlated with BP in the fed condition (r(134)=.60, p<.001), supporting stability in individual differences in reward value for the

non-food reinforcer. We found higher BP for the non-food reinforcer in our bulimic eating disorder participants compared to our control participants (t(133)=2.33, p=.02). In participants who have completed PR tasks for M&Ms and Angry Birds in the fasted and fed condition, we have found significant correlations between BP for M&Ms and Angry Birds in the fasted (r(133)=.44, p<.001) and fed conditions (r(132)=.42, p<.001), supporting our hypotheses that behavioral responses for food and non-food reinforcers reflect shared underlying processes. Importantly, we are currently completing assays of GLP-1 response to the fixed test meal used in the fed condition of the Angry Birds PR task, and analyses of associations GLP-1 response and changes in Angry Birds BP between the fasted and fed condition are planned to test this part of our model.

In contrast to the limited use of PR tasks to measure approach motivation in eating disorders, several studies have used *ad lib* test meal to measure satiation[101]. Across studies, women with bulimic disorders consumed significantly more food during *ad lib* test meals[102–108] with moderate (d=.45)[107] to very large (d=2.5)[109] effect sizes, but reported either similar[102,104,106] or lower[103,110] levels of fullness following food intake compared to controls. In our lab, participants completed a single-item *ad lib* meal in the afternoon after consuming a standardized breakfast in the morning. Immediately before and after the *ad lib* meal, participants completed VAS items to assess subjective satiation. A one-quart (946 ml) serving of vanilla frozen yogurt (1.5 kcal/g) was served at an individual place setting. Participants were presented with the meal and instructions in print and on tape recorder to eat until they felt satiated, similar to prior studies[104,111,112]. Yogurt was weighed before and after the meal using a top-loading, self-calibrated electronic balance, and total intake was calculated in grams and kcal. BN and control participants did not differ in meal duration or subjective ratings of satiation after the *ad lib* meal (mean VAS rating=77 out of 100). However, to achieve the same level of satiation, mean intake was significantly greater in BN vs. controls (t(86)=3.36, p=.001; d=.70) [113]. Thus, individuals with BN demonstrate decreased satiation in a behavioral *ad lib* test meal.

Within our ongoing study, we are using an *ad lib* test meal to measure reward satiation and its associations with WS and reward value/effort. Because behavioral tasks are completed over a series of visits to avoid fatigue, we are able to measure WS and changes in weight and their associations with study variables. First, those with greater WS at their first study visit report greater food intake in interviews of binge-eating (r(103)=.35, p<.001), consume larger amounts in the *ad lib* test meal to achieve satiation (r(132)=.24, p=.006), and demonstrate the greatest increase in body weight by their fourth study visit (r(134)=.28, p=.001). Additionally, consumption during the *ad lib* test meal is significantly associated with BP for the food reinforcer (r(130)=.53, p<.001) and the non-food reinforcer (r(132)=.25, p=.004). Importantly, these findings are preliminary as we have only collected data from less than half of our total target sample at baseline and have insufficient longitudinal data to examine differences in illness trajectory and insufficient biological data to test hypotheses related to leptin and GLP-1.

Complementary Future Directions for Alternative Methods and an Expanded Model

Our model examines peripheral release of leptin and GLP-1, but does not directly assess central processes. Other studies have used functional magnetic resonance imaging (fMRI) tasks to evaluate differences in brain activity that may explain binge eating. However, no neuroimaging studies have examined reward effort directly in individuals with bulimic eating disorders. One study[114] examined a related construct, expected value (EV) which is related to the RDoC subconstruct of Probabilistic and Reinforcement Learning, in participants with restricting AN (n=28), participants recovered from AN (n=20), participants with BN (n=20) and healthy controls (n=43). EV was derived from a Pavlovian learning paradigm in which fractile images were paired probabilistically with receipt of a sweet solution, a neutral-tasting solution or nothing and then neural responses to these conditions and violation of expected reward receipt were measured. This approach is distinct from effort exerted to consume food or non-food rewards that we measure in our operant PR task. Across groups, BMI was negatively correlated with EV in the right anterior cingulate cortex (ACC), and this association extended to the analyses of a subgroup with normal to high normal weight, for whom EV in the left ACC was greatest in those with the lowest BMI. In addition, AN-ill had greater EV than all other groups, who did not differ from each other significantly. These results support an association between increased EV and reduced weight but do not speak to WS *per se* and do not support altered EV in BN. Moreover, these findings add to the work supporting increased prediction error as an index of increased Reward Learning and predictor of treatment outcome in AN (for review see, [115]). In addition to this study, several studies have used neural responses to images or Pavlovian learning paradigms to infer elevated reward valuation of food using fMRI tasks with food-related stimuli. The majority of these studies have examined differences between individuals with and without eating disorders in neural response to food versus non-food (neutral) images [116,117] or high versus low calorie food images [118]. Compared to controls, individuals with binge eating have demonstrated greater neural response to palatable food stimuli in the ventromedial prefrontal cortex [116], medial orbitofrontal cortex [117], insula [117,119], and (ACC) [117,118]. However, one study noted decreased activation in the ACC in individuals with BN compared to healthy controls [120], and others have failed to demonstrate significant differences between those with and without bulimic eating disorders in reward region response to food images [121] or to anticipatory food cues [122]. Thus, independent fMRI studies have supported that individuals with binge eating have elevated reward region responsiveness. However, neural correlates of approach motivation (reward effort) have yet to be examined. Moreover, to our knowledge, none of the above-mentioned studies compared responses during fasted and fed states that may better capture the construct of reward satiation. Thus, a complementary direction for our model would involve use of fMRI to examine neural activity in reward regions during PR tasks for food and non-food rewards in fed and fasted states in controls and individuals with bulimic eating disorders.

Eating behavior is determined by a complex interaction among various peptides[123], including, but not limited to, leptin and GLP-1. Our current model focuses on two peptides implicated in both the homeostatic and hedonic regulation of eating that are dysregulated in

the bulimic eating disorders. Future research of this model could examine peptides that are 1) altered in response to weight loss, 2) dysregulated across bulimic eating disorders, and 3) implicated in both homeostatic and hedonic regulation of eating. The strongest candidate may be ghrelin, an orexogenic peptide. Ghrelin increases in response to weight loss [124] and decreases in response to weight gain [125]. Ghrelin levels are positively associated with binge-purge behavior in AN-bp and BN-p [126]. Additionally, ghrelin levels tend to be elevated in both AN and BN relative to healthy controls; however, ghrelin levels tends to be lower in BED relative to controls [127]. Although this maps onto findings for leptin, prior evidence that leptin is lower in obese BED compared to obese controls provides more support for leptin in our model. Finally, like leptin, ghrelin crosses the blood-brain barrier and is implicated in both the homeostatic and hedonic control of food intake [128,129]. Thus, ghrelin may play an important role in mediating the link between WS and binge eating.

Other candidates for future work include insulin and brain-derived neurotrophic factor (BDNF). Insulin levels are correlated with body fat mass and implicated in reward function [130]. The available data suggest that insulin levels and insulin response are lower in AN than healthy controls [126,131,132], whereas insulin levels and insulin response tends to be higher in BED compared to healthy controls [133]. There is limited evidence for dysregulated insulin response in BN[134,135]; thus, the overall pattern of insulin dysregulation in bulimic eating disorders presents a less clear connection to the presence of binge eating transdiagnostically. Insulin's role in homeostatic regulation of weight control and food intake is well characterized[136]. Additionally, animal data implicate insulin in the enhancement of dopaminergic signaling in the NAcc[137] and indicate insulin administration in the VTA reduces the consumption of palatable food in a sated state[138]. However, intranasal insulin manipulations failed to support a link to hedonic eating in women[139].

Turning to BDNF, serum levels are positively correlated with BMI, and studies of anorexia nervosa suggest that BDNF is reduced through weight loss[55,140]. Additionally, BDNF is reduced in BN relative to healthy controls, but does not appear to be dysregulated in BED[55], creating some challenges for understanding its role transdiagnostically. Finally, BDNF has been implicated in both the homeostatic and hedonic regulation of food intake[141]. Taken together, investigating ghrelin, insulin, and BDNF in future work may further elucidate how WS contributes to binge eating in eating disorders. Further, the literature has and will continue to grow as we continue the current five-year study. It is inevitable that new findings will emerge that were not available at the time we developed our model, and these new findings will likely suggest both future and alternative directions.

One alternative direction may involve examining the interplay between premorbid weight and risk for bulimic eating disorders[31]. Our model posits that WS directly impacts reward valuation and satiation, but research related to weight gain and obesity suggests that overeating also may contribute to reward region responsiveness to palatable food cues (i.e., reward valuation)[142]. Thus, recent work supports dynamic relationships among weight, WS, reward valuation/effort, satiation, and binge eating that may contribute to illness maintenance.

Conclusion

WS in bulimic eating disorders prospectively predicts illness trajectory. WS is likely to contribute to decreased leptin levels due to loss of adipose tissue. Decreased leptin diminishes GLP-1 response to food intake, and reduced leptin and GLP-1 response contribute to greater reward value and decreased satiation. In particular, a less robust GLP-1 response during food intake would maintain greater drive to eat despite changes in nutritional status that should normally diminish this drive, and this combined with decreased ability to achieve satiation would contribute to both a sense of loss of control over eating and consumption of excessive amounts of food during – the defining features of binge episodes in eating disorders. Importantly, factors that influence illness maintenance may or may not be relevant to illness onset. Although Ancel Keys' landmark study[143] established that significant weight loss produced the onset of binge eating, this was observed in 30% of participants. This suggests that several other factors, including genetic risk, are important to understanding how WS may impact risk for binge eating. Moreover, the effect size for the association between WS and illness maintenance across studies is small, suggesting that it is one among many factors worthy of investigation.

We are currently in the third year of a five-year, NIMH-funded study to test our model in a longitudinal design of 320 participants. Our goal is to retain 260 participants through 6- and 12-month follow-up assessments to obtain reliable estimates of associations. If our model is supported, this work can significantly impact both conceptualization and clinical practice for eating disorders. Data regarding the predictive validity and clinical utility of distinguishing among three DSM-5 eating disorders may be reconceptualized as reflecting a single underlying dimension, such that three DSM-5 bulimic eating disorder categories are reframed as one bulimic eating disorder. Alternatively, findings may reveal new thresholds for distinguishing among these disorders. For example, if our model does not extend to the upper BMI range of bulimic eating disorders, differences between BN and BED may shift from emphasizing presence versus absence of compensatory behaviors to emphasizing BMI regardless of compensatory behaviors. In addition, results can impact assessment. Established assessments probe weight only for diagnosis of AN, ignoring weight for BN and BED, and none evaluates history of highest weight. Thus, there is no current standard for evaluating WS in eating disorders. If findings demonstrate that WS predicts illness maintenance transdiagnostically, then future assessments will incorporate simple, yet key questions for WS. Finally, data demonstrating that biological processes longitudinally mediate the association between WS and illness course will promote innovative treatment development for eating disorders characterized by binge eating, such as exploring the efficacy of GLP-1 agonists currently FDA-approved for Type 2 diabetes as a new intervention for eating disorders.

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Highlights

- Weight suppression (WS) reflects the difference between lifetime highest adult weight and current weight.
- WS predicts illness trajectory in bulimic eating disorders.
- We review the literature and present new findings supporting that biological consequences of WS may alter responses to food to increase binge eating.

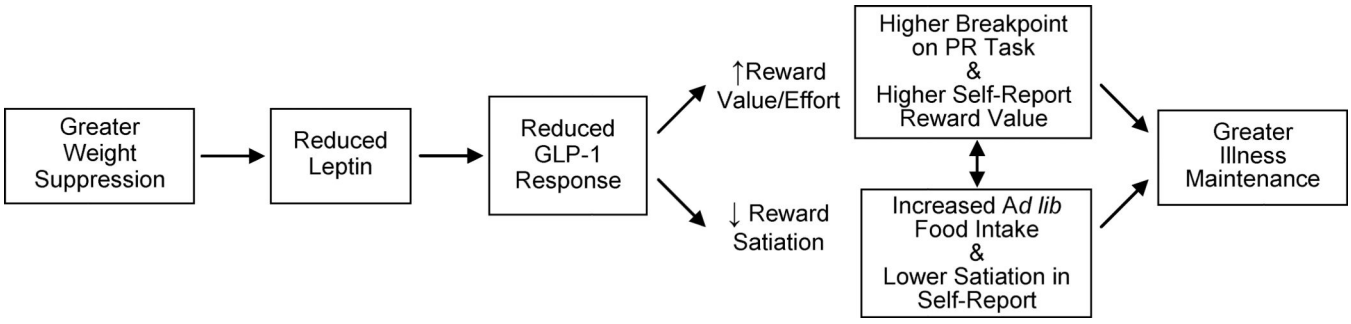

Figure 1.
Explanatory Model for Association between WS and Bulimic Eating Disorder Maintenance