ASSESSMENT OF HYPERPHAGIC BEHAVIOR IN PRADER-WILLI SYNDROME

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CHAPTER 1

INTRODUCTION

Prader-Willi syndrome (PWS) is the leading known genetic cause of obesity and is marked by a distinctive behavioral phenotype, including hyperphagia. Hyperphagia in Prader-Willi syndrome stems from an aberrant satiety response in affected individuals, especially a delay in satiety (Holland et al., 1995; Holland et al., 2003; Lindgren et al., 2000). Caused by a paternal deletion or maternal uniparental disomy of chromosome 15q11-q13, Prader-Willi syndrome affects about 1 in 15,000 births and results in developmental disabilities as well as significant maladaptive and compulsive behaviors such as tantrums, skin-picking, hoarding, and concerns with exactness and sameness (Dykens, Hodapp, & Finucane, 2000). Although persons with Prader-Willi syndrome have several cognitive and personality strengths (Dykens, 2002), their food-seeking behaviors and hyperphagia remain a life-long source of stress and challenge for them, as well as for their families and care-providers (Hodapp, Dykens, & Masino, 1997).

When hyperphagic behaviors are not carefully monitored or controlled, individuals are at heightened risk for serious medical problems. Indeed, complications of obesity remain the leading cause of death in this syndrome. Deaths in children with Prader-Willi syndrome often stem from illnesses associated with high fevers and respiratory infections, while deaths in adults are typically related to complications of obesity that involve the cardiovascular and

respiratory systems (Schrander-Stumpel et al., 2004; Vogels et al., 2004; Nagai et al., 2005). Compared to younger individuals, mortality rates are higher for adults with Prader-Willi syndrome aged 30 years and older (7% versus 3%; Whittington et al., 2001), with complications of obesity implicated in this higher rate among adults. Hyperphagic behaviors can also be dangerous in persons who are relatively slim, with increased risks of death due to choking while sneaking food, and gastric perforations after consuming more food than usual (PWSA, USA).

Although hyperphagia is a highly stressful, life-threatening feature of Prader-Willi syndrome, accurately measuring this complex behavior has long been a research challenge. Reliable measures are thus sorely needed, and in the last several years, researchers have tried three different approaches to measuring hyperphagia in Prader-Willi syndrome. First, in direct observational approaches, individuals with Prader-Willi syndrome are placed in an eating situation with ample food, with the outcome being the amount of food consumed. In innovative studies in the U.K., for example, Holland, Treasure, Coskeran, and Dallow (1995) provided persons with Prader-Willi syndrome unlimited access to food in a laboratory setting, with the primary outcome simply being the number of sandwich quarters consumed. Tan et al. (2004) also used sandwich consumption to measure response to a new agent hypothesized to reduce appetite in adults with Prader-Willi syndrome. Providing persons unlimited access to food, however, has proved challenging to implement in ongoing research programs in the U.S. due to university restrictions by institutional research boards.

To work around these restrictions, some researchers have observed how

persons with Prader-Willi syndrome behave in settings with limited access to food. Zarcone et al. (2004) individually placed 9 persons with Prader-Willi syndrome in a room that was baited with limited quantities of foods; these foods varied in their levels of acceptability, concealment, and contamination (Dykens, 2000). Only 3 individuals engaged in food-seeking behaviors or consumption; of note is that these 3 had lower BMI's than their counterparts. Similarly, we previously used a "snack task" in which persons with the syndrome were left in a room with the remainder of a low-calorie but desired snack food, and consuming the snack and/or covert food seeking was virtually nonexistent in our sample of 23 persons. These simulated settings do not seem to capture the covert food-seeking that parents and staff reported in these same participants at home, perhaps due to social desirability effects or to being in contrived laboratory as opposed to at-home settings.

In light of these difficulties, Dykens (2000) used a second approach, a visual-analogue interview, to measure hyperphagia in people with Prader-Willi syndrome. Dykens used individual interviews and visual analogues to identify willingness to eat contaminated foods, and appropriate and inappropriate food combinations, in adults with Prader-Willi syndrome and IQ-matched peers and controls. Despite their well-developed ideas about the purpose and fate of food, individuals with Prader-Willi syndrome were much more likely than controls to endorse eating contaminated foods as well as odd food combinations (Dykens, 2000). These findings suggest novel interventions, such as teaching persons with Prader-Willi syndrome about germs or the emotion of disgust. Yet the

hypothetical nature of these analogue tasks makes them less useful as outcome measures in clinical trials or other interventions.

A third approach to measuring hyperphagia in Prader-Willi syndrome relies on informant questionnaires. Using parents or caregivers as informants, these measures assess eating behavior in typically-developing children or children and youth with eating disorders. Such parent-informant measures include the Children's Eating Behavior Inventory (Archer, Rosenbaum, & Streiner, 1991) that assesses eating problems such as finickiness in typically developing children, and the Eating Disorders Inventory (Garner & Olmstead, 1983), designed for adolescents and young adults with anorexia or bulimia. While these measures have occasionally been used to describe eating problems in children with Prader-Willi syndrome (e.g., Sarimski, 1996), they do not capture the range and complexities of unusual food-seeking behaviors encountered in Prader-Willi syndrome. These unusual features include: food sneaking and theft, foraging through the trash for food, getting up at night to food seek, and eating unpalatable items.

Recently, however, Russell and Oliver (2003) introduced a questionnaire that specifically targets hyperphagic symptoms of Prader-Willi syndrome. The Food-Related Problems Questionnaire (FRQP) is a sixteen-item questionnaire that assesses persons with Prader-Will syndrome in three areas: preoccupation with food, impairment of satiety, and related negative behaviors. Items for FRPQ were derived from interviews and focus groups with 12 parents and care-providers of individuals with Prader-Willi syndrome; problems identified in the

interviews were clustered into themes, and 16 questions were developed that reflected these themes. The measure was subsequently given to 80 persons with Prader-Willi syndrome and their primary caregivers, showing robust psychometric properties.

While the FRPQ is a groundbreaking first step, it has three limitations. First, in order to be applicable, six of its sixteen items require a verbal response by an individual with Prader-Willi syndrome. Relying on a combination of self-report and caregiver report is challenging in persons with intellectual disabilities, who often have difficulty identifying, labeling and expressing feelings or behavior (Finlay & Williams, 2001). In this vein, we find that persons with Prader-Willi syndrome vary in their ability or willingness to talk openly about food—they know it is a highly charged subject. Some persons need considerable reassurance before talking openly about food (e.g., "Will you tell my mother?" "Will I lose my snack?"), and even then we find that persons may admit to a food misbehavior with one person but then later deny it to others. Further, in our ongoing work, we find a strong social desirability effect—persons may deny liking any highly-caloric or desirable foods, or despite evidence to the contrary, they may deny that they ever snitch or hide food. In this vein, the FRPQ could be a very helpful clinical tool in assisting persons with the syndrome and their caregivers to engage in a more open dialogue about an extraordinarily difficult topic. The FRPQ may be less useful, however, in situations that require a reliable measure of outcome over time.

Second, the FRBQ circumvents problems with self-report by providing the

respondent the option of "does not apply." Russell and Oliver (2003) excluded individuals for which "does not apply" was indicated twice or more out of a concern that limited verbal capacity would result in low scores on the measure. While only three individuals with Prader-Willi syndrome were excluded for this reason, of concern is that wider use of the scale would lead to the exclusion of larger numbers of persons who are not able to provide answers.

Third, while a strength of the FRBQ is that the three domains were derived from focus groups, data were not subject to analyses that confirmed these classifications, nor did the items assess symptom severity. While increased frequency of a specific hyperphagic symptom may imply increased severity, alternative and well-established ways of determining symptom severity are derived from psychiatric nosology, specifically the extent to which symptoms are time-consuming, distressing, and cause adaptive impairment.

The measure introduced in this study, the Hyperphagia Questionnaire, builds on the work of Russell and Oliver (2003). Specifically, we included separate assessments of symptom severity, and conducted factor analyses of items that were derived from parents and offspring reports in both clinic and research settings. Further, as the primary goal of any measure is to find relationships between constructs (Crocker & Algina, 1986), the study relates our measure of hyperphagia to non-food maladaptive and compulsive behavior in Prader-Willi syndrome. Relationships were also assessed between the Hyperphagia Questionnaire and such variables as age, gender, IQ, genetic subtype of Prader-Willi syndrome, and degree of obesity (Body Mass Index; BMI). Taken together,

the factor and correlational analyses in this study provide a critical next step toward the systematic measurement of hyperphagic behaviors in Prader-Willi syndrome.

CHAPTER II

METHOD

Participants

The parents or primary guardians of 153 persons (54.6% male, 45.4% female) with Prader-Willi syndrome ages 3 to 51 years (M = 20.2 years, standard deviation [SD] = 11.3) were administered the Hyperphagia Questionnaire (HQ).

Participants were recruited from a variety of sources including: the Lili Claire-UCLA Behavior Genetics Clinic, the Vanderbilt Kennedy Center for Research on Human Development, and annual conferences of the National Prader-Willi Syndrome Association. To rule out an ascertainment bias, we compared hyperphagic, maladaptive and compulsive behaviors across these recruitment sources. None of these ANOVAs were significant; therefore, participants were combined across the three recruitment sources.

Data pertaining to diagnoses of Prader-Willi syndrome were derived from parents or caregivers. Of these care providers, 62.9% reported that their offspring had paternal deletions at 15q11–13; 28% reported maternal uniparental disomy; 2.3% had other chromosome 15 anomalies (e.g., translocations) that resulted in a clinical diagnosis of Prader-Willi syndrome; 2,3% with imprinting errors; 2.3% with microdeletions; and the remaining 2.3% with either clinical diagnoses or positive methylation tests.

As measured by the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990), the average IQ of the sample was 66.08, SD = 14.67. IQ's were

in the range considered typical of those with Prader-Willi syndrome, and did not significantly differ by age or gender.

Degree of obesity was determined by the Body Mass Index—BMI (weight in kilos/[height in meters]^2). Body Mass Indexes were not significantly related to gender or IQ, though BMI did show an expected correlation with age, r =.404, p<001. . Obesity for adults is defined as a BMI equal to or greater than 30 (Centers for Disease Control, 2000). In this sample, participants had a mean BMI of 30.5 (SD=9.5), with 60% of adult participants reaching or exceeding the clinical definition of obesity, and morbid obesity (BMI 40+) indicated for 21% of adult participants.

Procedure

Participants were individually administered the Kaufman Brief Intelligence Test by trained research assistants, who also obtained each participant's height and weight. Caregivers reported on basic information about their child (e.g., age, gender, IQ, diagnostic history, and living status) and completed the instruments listed below.

Measures

Hyperphagia Questionnaire (HQ) is a 13-item instrument that specifically targets food issues in Prader-Willi syndrome. Items were gleaned from parent and offspring reports of hyperphagic symptoms in both research and clinic settings, and from informal discussions with families and colleagues at Prader-Willi Syndrome clinics and conferences. The HQ assesses specific food-related

behaviors, preoccupations and thoughts about food, as well as the severity of hyperphagic symptoms. Items on the Hyperphagia Questionnaire are listed in Table 1 and are rated on a 5 point scale (from 0=not a problem to 4=severe and/or frequent problem). Additionally, the HQ assesses overall severity of food behaviors as defined by symptom-related impairment in the *DSM-IV-TR (* APA, 2000). Caregivers used a 5-point scale (1=none to 5=extreme) that assessed: the amount of time spent talking about food or engaged in food behaviors; the degree of distress associated with food or when others try to stop the individual from talking about or engaging in food behaviors; and the degree to which food-related thoughts and behaviors interfere with adaptive functioning and daily routines. In our analyses, we summed the three severity items in order to calculate an overall HQ Severity score.

Kaufman Brief Intelligence Test. The K-BIT is designed to assess intellectual functioning in individuals from age 4 through adulthood and provides a composite IQ, along with standard scores for Vocabulary and Matrices. The K-BIT is a widely accepted instrument that has been successfully used in previous research of individuals with intellectual disabilities (Dykens, 2002).

Yale–Brown Obsessive Compulsive Scale. Caregivers completed an informant version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989). The informant version of the Y-BOC consists of 30 symptoms that are rated as occurring ever or in the last week. Additionally, informants rate the degree of distress and adaptive impairment caused by symptoms (0=none to

5=extreme). The Y-BOCS has good reliability and validity (Taylor, 1995) and has been used successfully in previous studies of children and adults with intellectual disabilities (e.g., Dykens, 2004). The Y-BOCS was used in this study in order to identify obsessive-compulsive symptoms rather than to establish diagnoses of obsessive-compulsive disorder. Symptoms were summed across obsessions and compulsions for a total score, but skin-picking was left out. Skin-picking was examined as a separate item because factor analytic work (Feurer et al., 1998) has shown that skin-picking has substantial unique variance that seems to distinguish it from all other compulsive behaviors in Prader-Willi syndrome.

Child Behavior Checklist (CBCL; Achenbach, 1991). This checklist requires caregivers to rate 112 problem behaviors on a 3 point scale (0=not true, 1=somewhat true, 2=very true). The CBCL provides an Internalizing factor (comprised of anxious/depressed, somatic complaints, and withdrawn clinical scales), and Externalizing factor (comprised of noncompliant and aggressive behavior clinical scales), as well as a Total score, which reflects the overall level of problem behaviors. In this study, raw scores for Internalizing, Externalizing, and Total score were used in analyses.

CHAPTER III

RESULTS

Hyperphagia Questionnaire.

All items except three severity items, which were separately summed to form the HQ Severity score, were included in a factor analysis with principal component extraction and varimax rotation. We used the Kaiser criterion (1960), retaining only factors with eigenvalues greater than one. Two items did not load onto these factors. These two items tapped the age of onset of hyperphagic behavior and the overall variability in preoccupation with food, respectively.

Two factors emerged for the HQ, accounting for 53.7% of the variance. These two factors reflected the split between food-related behaviors versus food ideation. The first factor, labeled Hyperphagic Behaviors, accounted for 38.2% of the variance and had a Cronbach's alpha of .83. The second factor, labeled Hyperphagic Ideation, accounted for 14.4% the variance and had a Cronbach's alpha of .80. Table 1 presents the factor loadings and specific items loading onto these two factors.

Table 1

Factor Analysis of the Hyperphagia Questionnaire (eigenvalues in parentheses)

Item	Hyperphagic Behaviors (3.83)	Hyperphagic Ideation (1.44)
Attempts to steal food	.80	
Forages through the trash for food	.77	
General level of cleverness exhibited in obtaining food	.76	
Gets up at night to food seek	.75	
Bargains or manipulates to get more food at meals	.75	
Ease in redirecting individual away from food		.90
How upset individual becomes when denied food		.86
Persistence in asking or looking for food even after being denied		.84

Principal component factor analysis with varimax rotation

Age

Age was not significantly associated with Hyperphagic Behaviors, or Severity, but was negatively associated with Hyperphagic Ideation, r (140) = -.20, p=.02. In order to further explore this correlation, we divided our sample into 4 age groups: 4 to 10 (N=29); 11 to 19 (N=50); 20 to 29 (N=43); and 30 and up (N=29). Our age groups divided our sample along developmental lines and allow us to examine and compare: children, adolescents, young adults, and older adults; we used a starting point of 4 years because hyperphagia sometimes does not emerge until after toddlerhood. Table 2 presents the means and SD's for Hyperphagic Behaviors, Hyperphagic Ideation, and Hyperphagic Severity across the 4 age groups, along with F and p values. As the correlation with age and ideation suggests, r (140) = -.20, p = .02, these scores decrease gradually across the age groups. More specifically, post hoc tests reveal that older individuals have significantly lower ideation scores than the 4 to 10 year olds. Similarly, the overall F for Hyperphagic Severity does not reach the level of significance, but in looking at the individual means in each age group, older people aged 30 and up have significantly lower severity scores than do young adults in their 20's. Thus, hyperphagic severity scores peak in the young adult years and decline significantly in older adults, reflecting a similar age-related trend earlier found with compulsivity and maladaptive behavior (Dykens, 2004),

Table 2.

Mean HQ Scores by Age Group with F tests

	Group 1		Group 2		Group 3		Group 4		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F
Hyperphagic Behaviors	9.80	3.81	10.48	5.68	11.49	5.24	10.74	5.03	1.44
Hyperphagic Ideation	9.88	2.52	8.02	3.84	8.00	3.01	7.56	3.01	3.00*
Hyperphagic Severity	3.87	2.43	4.23	2.29	4.33	2.03	3.33	1.99	0.59

Note. Group 1, 4 to 10 years; Group 2, 11 to 19 years; Group 3, 20-29 years; Group 4, 30 years and up.
**p<.05*

BMI

Although the correlation of BMI and hyperphagic behavior was modest when examining participants of all ages, $r(144) = .18$, $p=.05$, much stronger correlations between the two were seen during the adult years. Specifically, for people in their 20s, the correlation between BMI and Hyperphagic Behaviors equaled .51, $p < .001$, whereas adults aged 30+ years showed a significant correlation between BMI and Hyperphagic Severity, $r(29) = .45$, $p < .05$. No other correlations were found between BMI and either Hyperphagic Behaviors or Severity at other ages, nor did the BMI significantly correlate with Hyperphagic Ideation at any age.

IQ, Gender, and Genetic Status:

Correlations with gender and IQ were not significant for any of the three hyperphagic domains. Nor did genetic status (deletion, uniparental disomy, imprinting error, microdeletion, or translocation) reveal any significant relationships with Hyperphagic Behaviors, Ideation, or Severity.

Compulsive and Maladaptive Behavior

Compulsive and maladaptive behaviors were associated most consistently with Hyperphagic Ideation and Severity. Increased scores on Hyperphagic Ideation were associated with increased total and externalizing maladaptive behavior scores on the CBCL, $r(93) = .27$ and $r(121)=.30$, respectively, p's $< .01$, as well as increased aggressive behaviors on the CBCL, $r(129) =.33$, $p<.001$, and overall severity of compulsive symptoms, $r(131)=.27$, $p<.01$.

Higher HQ Severity scores were correlated with increased severity of compulsive symptoms on the Y-BOCS, $r(133) = .33$, $p< .001$, as well as with greater CBCL total, internalizing and externalizing scores, r's (94-126) = .53, .33, and .47, respectively, p's <.001. Additionally, HQ Severity was related to several specific clusters of maladaptive behavior on the CBCL, including attention and thought, delinquent and aggressive, withdrawn and social problems r's (125-138) =.41, .36, .36, .47, .37, .49, respectively, p's<.001. Hyperphagic Behaviors were related to CBCL Externalizing, $r(116) =.26$, $p<.01$ and delinquent behaviors, $r(124) =.35$, $p<.001$.

Age of Onset and Variability

Exploratory analyses were conducted with the 2 items that did not load onto factors, as they are of interest in terms of how people think about hyperphagia in Prader-Willi syndrome. Mean age of onset of hyperphagia was 3.5 years, with a standard deviation of 1.6. In order to investigate potential implications of early versus late onset of hyperphagia, we ran an ANOVA for age of onset (four age groups based on two year increments) and our three hyperphagic domains. Individuals who had experienced younger ages of onset of hyperphagia did not have significantly greater levels of Hyperphagic Severity, Hyperphagic Ideation, or Hyperphagic Behaviors. However, persons who experienced early onset of hyperphagia did tend to experience slightly greater difficulty with anxiety, attention, and internalizing on the CBCL, F's(3, 128)=2.43, 2.42, 2.16, respectively, p's<.05. We also wanted to explore potential implications of overall variability in preoccupation with food. We compared individuals with the least and most reported hyperphagic preoccupation (top and bottom 20%) and found no differences in the means of Hyperphagic Behaviors, Ideation, and Severity.

CHAPTER IV

DISCUSSION

This study introduces a new measure of food-related behaviors in Prader-Willi syndrome. Factor analyses produced robust factors that hang together conceptually and reflect Hyperphagic Ideation and Hyperphagic Behaviors. By highlighting hyperphagic ideation, behaviors, and severity, the HQ factors and Severity score capture the range of possible food-related problems in Prader-Willi syndrome as well as the functional impairment of these problems. The Hyperphagia Questionnaire is a promising tool for clinical trials aimed at monitoring and reducing problematic food behaviors.

Our hyperphagic domains, behaviors, ideation, and severity closely reflect the clinical picture of what families convey about hyperphagia. Additionally, by gauging hyperphagic severity, the HQ goes beyond depicting the presence or absence of specific symptoms to also capture a more holistic picture of the impact of these symptoms on individuals and their families. Having a tool that measures the degree to which hyperphagic symptoms are time-consuming, distressing, and cause adaptive impairment will be particularly useful for measuring meaningful changes in symptoms in intervention and longitudinal research. Our hyperphagic domains hold together statistically as well as conceptually. The Cronbach's alphas calculated for our factors were suggestive of excellent internal consistency, and based on our initial findings, the HQ holds much promise for future or

additional psychometric work (e.g., on test-retest reliability).

The HQ, along with the FRBQ, has immediate relevance for at least 3 lines of ongoing and future research. First, these questionnaires offer, for the first time, informant-based tools that can measure both blatant and subtler shifts in hyperphagic symptoms in novel clinical trials. Such trials are likely to increase, as they are tied to advances in the neurobiology of appetite regulation. Various neuropeptides, for example, are implicated in aberrant satiety in Prader-Willi syndrome, including reduced levels of oxytocin secreting neurons in the paraventricular nuclei of the hypothalamus (Swaab, 1997). Further, compared to controls, persons with Prader-Willi syndrome also have markedly elevated levels of ghrelin (Cummings et al., 2002; Delparigi et al., 2002). Ghrelin, a hormone predominantly produced in the stomach, acts on the hypothalamus to stimulate appetite and food consumption. Notably, the elevated levels of ghrelin in individuals with Prader-Willi syndrome are similar to those found in states of starvation, such as anorexia (Delparigi et al., 2002), supporting the idea that Prader-Willi syndrome is a genetic model of starvation (Holland et al., 2003). Clinical trials aimed at reducing ghrelin levels have been tried, and while somatostatins have been shown to lower plasma levels of ghrelin **(**Haqq et al., 2003; Tan et al., 2004**)**, such changes have not been shown to lead to reduced appetite in individuals with Prader-Willi syndrome, at least as measured by sandwich consumption in the laboratory setting (Tan et al., 2004) With these and other future trials, the FRBQ and HQ provide more nuanced, multi-faceted depictions of hyperphagia that extend beyond the laboratory, to the real-life

settings where persons with Prader-Willi syndrome live, work, and learn.

Second, the HQ extends previous work on behavioral differences across genetic subtypes of Prader-Willi syndrome. Relative to those with maternal uniparental disomy, those with paternal deletions have increased skin-picking and other maladaptive behaviors, as well as stronger visual-spatial functioning on standardized tasks and jigsaw puzzles (Butler et al., 2004; Dykens, 2004; Dykens, Cassidy, & King, 1999; Symons et al., 1999), Further, those with maternal UPD have relatively strong verbal and expressive language skills (Roof et al., 2002), but increased vulnerabilities to severe psychiatric illness in young adulthood, including psychosis and affective illness (Dykens, 2004; Beadsmore, Dorman, Cooper, & Webb, 1998; Vogels, Legius, Devriendt, & Fryns, 2003). In all this work, however, possible differences across genetic subtypes in the hallmark of the syndrome—hyperphagia--have yet to be rigorously studied, in part due to lack of adequate measures of this complicated symptom of Prader-Willi syndrome.

Third, with the HQ and FRPQ questionnaires at their fingertips, researchers can now ask how these relationships change over the course of development. Older adults with Prader-Willi syndrome aged 40 years or older show a robust mellowing in the number and severity of compulsive behaviors, skin-picking, and maladaptive behaviors such as tantrums (Dykens, 2004). It is less clear, however, if hyperphagic symptoms also abate in these older adults. While older adults may indeed mellow in hyperphagic behaviors, it may also be the case that those adults who are less obese, and presumably have less severe hyperphagia, are healthier and live longer than their more obese counterparts. It

is also unclear to what extent hyperphagic symptoms in adulthood vary as a function of residential placement, with less food seeking and ideation observed in settings where food is more restricted and less available. For the first time ever, the HQ and FRPQ allow these unresolved questions to be addressed in a systematic way. Future research is needed in order to identify the best fit and optimal sensitivity of these questionnaires across different studies, including treatment outcome studies, longitudinal, and comparative research.

In this study, we used the HQ to help characterize a broad view of how hyperphagic symptoms change over the course of development and into adulthood. Findings indicate that Hyperphagic Ideation decreases gradually with age, particularly after the age of 10. Hyperphagic Severity showed a trend to decrease with age, and when we split our sample into age groups, individuals ages 30 and up showed a significant decline from the young adults in their 20s. These age-related decreases in hyperphagic ideation and severity are consistent with previous findings of levels of maladaptive and compulsive behaviors in older versus younger persons (Dykens, 2004), which suggested elevated problems in the 20s with significant decreases in later years. In terms of BMI and hyperphagic scores, age was an important consideration. We found no correlation for BMI and any of our hyperphagic domains in children and adolescents. However, for individuals in their 20s, BMI was highly related to Hyperphagic Behaviors; in the thirties, the BMI was associated with Hyperphagic Severity. Thus, although BMI and hyperphagic scores are unrelated in children and adolescents, they appear to be related in various ways in adulthood. Several

potential explanations for this age-based association exist, including the fact that as individuals move into adulthood, they may be out in the community more, have greater access to food, higher risks for eating, and be less carefully supervised than in school settings.

In this study, we also used the HQ to investigate whether hyperphagia differs across genetic subtypes. Approximately 70% of individuals with Prader-Willi syndrome have a paternally derived interstitial deletion of 15q11-q13, whereas around 25% have maternal disomy 15 (UPD) (Butler et al., 2004). Individuals with paternal deletions have been found to have more maladaptive behaviors and skin-picking than individuals with maternal uniparental disomy, but hyperphagic symptoms had not been specifically examined across these genetic subtypes.

In line with previous work (Butler et al., 2004), we found that persons with parental deletions had significantly greater amounts of skin-picking than those with maternal uniparental disomy, but we found no differences across these subtypes in any of our hyperphagic indicators, including: Hyperphagic Ideation, Hyperphagic Behaviors, Hyperphagic Severity, age of onset of hyperphagia, and variability of hyperphagia. This lack of difference could indicate that hyperphagia is such a universal aspect of Prader-Willi syndrome that it does not vary by subtype, or it is possible that we might have found differences in hyperphagic symptoms if we had used more fine-tuned genetic subtyping, such as breaking the category of deletions into Type I and Type II deletions. Both Type I and Type II deletions are paternally derived, but Type I is a bigger deletion, and

in comparison to persons with Type II, those with Type I may have lower IQ and more behavioral problems (Butler et al., 2004). Thus far, no work has investigated hyperphagic symptoms in Type I and Type II deletions, but if we were to do so, we might expect that the drive for food on the HQ would be higher with Type I deletions, particularly since the drive for food and other maladaptive behaviors are correlated.

This study also investigated the relationship of food-related issues to other maladaptive behaviors. Although a Prader-Willi syndrome behavioral phenotype has been established (Dykens et al., 2000), very little work has identified how food and other features relate to one another. Despite the previous emphasis, if not sensationalism, of such unusual behaviors as eating odd or contaminated food combinations, or stealing food from trash, our findings suggest that maladaptive internalizing and externalizing behaviors are more closely aligned with overall food-related severity (time, distress, impairment) than with specific hyperphagic behaviors. . In fact, both HQ Severity and Hyperphagic Ideation were more predictive of non-food maladaptive behaviors than was Hyperphagic Behaviors.

Our results suggest that if an individual experiences a high level of hyperphagic impairment and distress, they are likely to also exhibit issues of compulsivity and ideation in other domains (as measured by Y-BOCS and CBCL Internalizing) and to have other problems as well (exhibited by CBCL Externalizing and Total score). Thus, HQ Severity scores were related to nearly each aspect of maladaptive behavior we included, from internalizing, to externalizing, to overall problem level, to the severity of compulsions.

Hyperphagic Ideation was related to overall problem levels, externalizing behaviors, as well as the severity of compulsive symptoms. In contrast, the "food behaviors" themselves were only predictive of externalizing behaviors. Thus, problems in food-related behaviors are fairly specific to food, whereas hyperphagic impairment and problems in food-related thinking are more general, predicting other, similar types of obsessions, internalizing, and even externalizing problems.

We examined hyperphagic age of onset and variability separately as possible predictors for food. Although neither of these HQ items loaded onto our factor structure, they are of interest in terms of how hyperphagia is described clinically. The onset of hyperphagia in young preschool children with Prader-Willi syndrome appears to coincide with the beginnings of such problems as temper tantrums and skin-picking in these children (Dimitropolous et al., 2001). Our study investigated the relationship between the age of onset of hyperphagia and current Hyperphagic Behaviors, Hyperphagic Ideation, and Hyperphagic Severity. Our results indicate that, while the emergence of hyperphagia may coincide with the emergence of other maladaptive problems, the age of onset is not a significant indicator of the future severity of hyperphagic symptoms. Thus, the age at which hyperphagic symptoms begin seems not to have implications for the severity of such symptoms.

This study has several strengths and weaknesses. Important strengths include the large number of participants, as well as the use of standardized measures of both compulsivity and maladaptive behaviors. Further,

questionnaires were subjected to factor analyses, and subsequent domains were analyzed with respect to salient participant variables (e.g., age, IQ, maladaptive behavior). Despite these strengths, however, the study has several shortcomings. In almost half of the sample, we relied upon parental reports of genetic subtyping, and in many cases, parents were unsure of this information. Thus, data were not analyzed by all possible genetic subtypes, which may have revealed important differences for further studies in genotype-phenotype correlations, or for intervention planning purposes. Also, we did not have reliable data on living situations for all participants. Many of the adults may live outside of the home either independently or in group facilities, and these factors could have some impact on hyperphagic behaviors. It may be, for instance, that individuals in group homes with predictable food routines, rules, and staff may fare better at managing hyperphagic symptoms than people in less structured or supervised settings. Finally, future research needs to examine the data derived from the HQ, FRPQ, and other in-vivo approaches in order to determine which measure is most appropriate for various types of studies.

Even so, this study introduces a measure that provides a fuller picture of hyperphagic behavior in Prader-Willi syndrome. Although parents and professionals have known for years that the drive for food varies from individual to individual with Prader-Willi syndrome, until recently it has been difficult to quantify these individual differences and track them over time. With the introduction of the HQ, we now have two measures in the field that can investigate possible sources of individual variation in hyperphagia, including such

mechanisms as genetic subtypes of Prader-Willi syndrome, neurobiological factors, development and aging, and residential status. These measures also provide, for the first time, quantifiable outcomes for novel clinical trials that aim to curb the life-threatening hyperphagic symptoms of Prader-Willi syndrome.

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