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Individuals with Smith-Magenis syndrome display profound neurodevelopmental behavioral deficiencies and exhibit food-related behaviors equivalent to Prader-Willi syndrome

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ABSTRACT

Smith-Magenis syndrome (SMS) is a neurodevelopmental disorder associated with intellectual disability, sleep disturbances, early onset obesity and vast behavioral deficits. We used the Behavior Problems Inventory-01 to categorize the frequency and severity of behavioral abnormalities in a SMS cohort relative to individuals with intellectual disability of heterogeneous etiology. Self-injurious, stereotyped, and aggressive/destructive behavioral scores indicated that both frequency and severity were significantly higher among individuals with SMS relative to those with intellectual disability. Next, we categorized food behaviors in our SMS cohort across age using the Food Related Problems Questionnaire (FRPQ) and found that problems began to occur in SMS children as early as 5–11 years old, but children 12–18 years old and adults manifested the most severe problems. Furthermore, we evaluated the similarities of SMS adult food-related behaviors to those with intellectual disability and found that SMS adults had more severe behavioral problems. Many neurodevelopmental disorders exhibit syndromic obesity including SMS. Prader-Willi syndrome (PWS) is the most frequent neurodevelopmental disorder with syndromic obesity and has a well-established management and treatment plan. Using the FRPQ we found that SMS adults had similar scores relative to PWS adults. Both syndromes manifest weight gain early in development, and the FRPQ scores highlight specific areas in which behavioral similarities exist, including preoccupation with food, impaired satiety, and negative behavioral responses. SMS food-related behavior treatment paradigms are not as refined as PWS, suggesting that current PWS treatments for prevention of obesity may be beneficial for individuals with SMS.

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1. Introduction

Smith-Magenis syndrome (SMS) is a complex neurodevelopmental disorder caused by haploinsufficiency of *RAI1* due to either a deleterious point mutation or an interstitial deletion of chromosome band 17p11.2. SMS is routinely characterized by variable intellectual disability, sleep disturbances, craniofacial and skeletal changes, early onset obesity and a number of distinctive behavioral abnormalities including self-injury, aggression, and stereotypies (Elsea & Girirajan, 2008). Maladaptive behaviors are common among individuals with intellectual disability, but some neurodevelopmental disorders have a more severe manifestation than others. Maladaptive behaviors in SMS vary with age but are a key component for identifying the disorder; however, it is unclear how frequent and severe SMS behavioral problems are relative to disorders with intellectual disability (Edelman et al., 2007; Gropman, Elsea, Duncan, & Smith, 2007; Smith, Dykens, & Greenberg, 1998; Wolters et al., 2009).

In addition to specific behavioral hallmarks, hypotonia and feeding difficulties during infancy are very common among individuals with SMS (Gropman, Duncan, & Smith, 2006). Interestingly, 90% of individuals with SMS are at or above the 90th percentile for weight by age 14 (Burns et al., 2010). The transition in food-related behavioral patterns during infancy to the onset of obesity in early adolescence is not well understood. SMS mouse model work has demonstrated a similar feeding behavioral pattern where *Rai1* haploinsufficient ($Rai1^{+/-}$) mice throughout early development are similar in weight relative to wild-type littermates but transition to an obese phenotype in early adulthood (Burns et al., 2010). However, a recent study has shown that the growth rate and weight gain during early developmental stages significantly increased when $Rai1^{+/-}$ mice are fed either a high carbohydrate or a high fat diet, suggesting that dietary content early in development is important in obesity outcomes in SMS (Alaimo, Hahn, Mullegama, & Elsea, 2014). In addition, $Rai1^{+/-}$ mice also consume more food and have reduced satiation compared to wild type mice implicating a dysregulation of signaling systems underlying eating behavior (Burns et al., 2010).

Phenotypic food-related behaviors are found across a variety of neurodevelopmental disorders and cohorts of subjects with intellectual disability. One such neurodevelopmental disorder with phenotypic food-related behaviors is Prader-Willi syndrome (PWS). PWS is the leading known genetic cause of obesity and has a very similar phenotype to SMS including intellectual disability, comparable behavioral problems, early onset of obesity and hyperphagia. In early infancy, individuals with PWS have severe hypotonia and feeding difficulties, but by 6–10 years of age individuals are typically obese (Wollmann, Schultz, Grauer, & Ranke, 1998). Targeted interventions that consist of a strict diet of reduced fat, modified carbohydrates and limited access to food are extremely effective in limiting weight gain in these individuals, despite the juncture of time when the interventions are introduced (Bonfig, Dokoupil, & Schmidt, 2009; Schmidt, Pozza, Bonfig, Schwarz, & Dokoupil, 2008). Therefore, PWS weight management treatments provide a model for intervention, which may also discriminate, to SMS individuals; however, the degree of similarity between the food-related behavioral patterns observed in each disorder remains unclear.

Comparing phenotypically similar but genetically different neurodevelopmental syndromes may reveal a comprehensive understanding of the genetic basis of behavioral problems. Therefore, the aim of the present study was two-fold. The first aim was to discern the nature and extent of neurobehavioral deficits in SMS and to compare these deficits to a sample with intellectual disability using the Behavior Problems Inventory-01. The second aim was to compare food-related behavioral phenotypes using the Food Related Problems Questionnaire in adults with SMS relative to an adult sample with intellectual disability and to PWS to determine behavioral similarities between each disorder.

2. Materials and methods

2.1. Participants

Of the 100 respondents of the surveys 85% were female and either the biological or the adoptive parent (95%) of the SMS individual. All SMS individuals had a confirmed diagnosis of SMS and a chromosomal deletion (90%) was predominantly reported as the molecular finding. Additionally, 91% resided at home while 9% resided in a residential facility. Seventy-seven percent of the responders identified that their child has or had received special education services or remedial education. All 100 respondents completed the Food Related Problems Questionnaire (FRPQ) and 99 respondents completed The Behavioral Problems Inventory (BPI)-01. One respondent did not complete both surveys. On the BPI-01, participants with SMS, as described by their parent/caregiver, had a mean age of 13.5 years ($SD = 9.8$) ranging from 1.5 to 51 years, were 57% female, and 79% white of a non-Latino background. Individuals with SMS described on the FRQP were categorized by school age: 15 preschool age with a mean age of 3.2 years ($SD = 1.0$) ranging from 1.5 to 4 years; 36 primary school age with a mean age of 8.0 years ($SD = 1.9$) ranging from 5 to 11 years; 27 secondary school age with a mean age of 14.7 years ($SD = 1.8$) ranging from 11.8 to 18 years; and 22 adults with a mean age of 28.4 years ($SD = 9.3$) ranging from 20 to 51 years. Characteristics of participants are shown in Table 1 (Rojahn, Matson, Lott, Esbensen, & Smalls, 2001).

2.2. Procedure

All participants were recruited through the SMS outreach group Parents and Researchers Interested in SMS (PRISMS) via the organizations website, electronic mailing list, and Facebook group. The surveys were administered online via

Table 1
Participant characteristics.

Parameter	BPI-01	FRQP			
	SMS	Preschool	Primary	Secondary	Adults
n	99	15	36	27	22
Mean age (years. months)	13.5	3.2	8.0	14.7	28.4
SD	9.8	1.0	1.9	1.8	9.3
Range	1.5–51	1.5–4	4–11	11.83–18	20–51
Gender (%)					
Male	41	47	50	37	23
Female	57	53	50	59	77
Ethnicity (%)					
White	79	60	75	85	91
Other	20	40	25	15	5
Weight classification (%)					
Underweight	15	20	19	11	9
Average	44	67	50	33	32
Overweight	24	7	22	37	23
Obese	12	0	3	15	37

www.surveymonkey.com at the same time and available for 5 months. Informed consent was obtained from parents or legal guardians of all participants. All aspect of the study were approved by the Virginia Commonwealth University Institutional Review Board.

2.3. Measures

Questionnaires administered included a demographic questionnaire, the Behavior Problems Inventory (BPI)-01 (Rojahn et al., 2001, 2012), and the Food Related Problems Questionnaire (FRPQ) (Russell & Oliver, 2003).

2.3.1. Demographic questionnaire

The demographic questionnaire assessed age, gender, ethnicity, diagnostic status, residence, weight classification, past or present history of special or remedial education, responders gender, and responders relationship to the individual.

2.3.2. Behavior Problems Inventory-01

The Behavior Problems Inventory (BPI)-01 is designed to assess behavior in individuals with developmental disabilities (Rojahn et al., 2001). Briefly, the BPI-01 is a 49-item measure containing three subscales that include 14 self-injurious behavior items, 24 stereotyped behavior items, and 11 aggressive/destructive behavior items. Each item is rated on a five-point Likert scale (never = 0, monthly = 1, weekly = 2, daily = 3, hourly = 4) and a four-point severity scale (no problem = 0, a slight problem = 1, a moderate problem = 2, a severe problem = 3) over the past 2 months (Rojahn et al., 2001). Scores for the self-injurious subscale can range from 0 to 56 for frequency and 0 to 42 for severity. Scores for the stereotyped subscale can range from 0 to 96 for frequency and 0 to 72 for severity. Scores for the aggressive/destructive behavior subscale can range from 0 to 44 for frequency and 0 to 33 for severity. Frequency and severity scores are highly correlated for each subscale ranging from $r = .91$ to $r = .93$. Cronbach's alpha values have indicated an acceptable internal consistency for each subscale with alpha values ranging from .74 to .92. An aggregated group of individuals with intellectual disability of heterogeneous etiology ranging from mild to profound from a total nine different international sites in the US (three sites in Virginia, one site in Minnesota, one site in Louisiana), United Kingdom (one site in England, one site in Wales), Netherlands, and Romania served as a reference sample (Rojahn et al., 2001, 2012). The overall dataset consisted of a total 1335 cases. There were 213 cases with BPI-01 scores of 0 that were not utilized, leaving the number of 1122 cases remaining in the dataset. The overall sample was 58% ($n = 768$) male and 42% ($n = 549$) female. The mean age was 34.47 years old ($SD = 20.24$) ranging from 2.1 years old to 93 years old. Of the total sample of 74% ($n = 986$) was derived from individuals residing in residential facilities while 26% ($n = 349$) were derived from schools or day facilities The sample reported 3.4% ($n = 45$) with mild intellectual disability, 8.8% ($n = 118$) with moderate intellectual disability, 26.6% ($n = 355$), 33.2% ($n = 443$) with profound intellectual disability, and information for intellectual disability was missing for 342 cases. A more detailed description can be found in Rojahn et al. (2012).

2.3.3. Food Related Problems Questionnaire

The Food Related Problems Questionnaire (FRPQ) is designed to assess food-related problems seen in individuals with PWS (Russell & Oliver, 2003). Briefly, the FRPQ is a 16-item measure that contains 3 subscales: (1) preoccupation with food, (2) impairment of satiety, and (3) composite negative behaviors. The composite negative behavior contains 3 categories: (1) takes and stores food, (2) eats inedibles, and (3) inappropriate response, which are rated on a seven-point frequency scale

(from never = 0 to always = 6). Total FRQP scores can range from 0 to 96. The maximum possible score for preoccupation subscale is 18, impairment of satiety is 30, and composite negative is 48, where takes and stores food has a maximum score of 18, eats inedible items has a max score of 12, and inappropriate response has a maximum score of 18. Cronbach's alpha coefficient has indicated an acceptable internal consistency for total score of the FRPQ of 87, suggesting good internal consistency. We utilized previously published FRPQ results from adults with PWS and adults with intellectual disability of heterogeneous etiology within the United Kingdom as comparison groups. The PWS group consisted of 23 individuals with a mean age of 27.7 years (SD = 6.5) ranging from 19 years old to 38.9 years old. Eight (34.8%) were female and 15 (65.2%) were male. All 23 were a part of a PWS specialist residential group home; ten (43.5%) attended college and seven (30.4%) adults attended onsite workrooms. The level of intellectual function was not available. The intellectual disability group consisted of 12 individuals with a mean age of 43.1 years (SD = 5.2) ranging from 33 years old to 51.9 years old. Five (41.7%) were female and seven (58.3%) were male while all 12 (100%) were living in the same residential setting within a group home. Four (33.3%) attended college and six (50%) attended onsite work rooms. A more detailed description can be found in Russell and Oliver (2003).

2.4. Data analysis

2.4.1. Missing values

BPI-01 missing survey values were treated as previously described (Rojahn et al., 2012). Briefly, items with a frequency score coded as zero, but a missing severity score were also coded as zero. Frequency scores that were greater than zero but had a missing severity score were imputed with the same score. A total of 3 severity scores were missing when a frequency score was present in the self-injurious subscale, 22 were missing in the stereotyped subscale and 8 were missing from aggressive/destructive behavior. Eighteen of 22 missing stereotyped values were from one respondent. Severity scores that were greater than zero but had a missing frequency score were imputed with the same score. A total of 1 frequency score was missing when a severity score was greater than zero in the self-injurious subscale, 8 were missing in the stereotyped subscale and 3 were missing in the aggressive/destructive subscale. FRPQ missing survey values were treated as described above. Only one respondent had missing values which totaled 8, and all of which were coded as zero.

2.4.2. Statistical analysis

BPI-01 subscale values were averaged and compared to the Rojahn et al. (2012) reference group subscale values by performing multiple one-sample t-tests for both frequency and severity. FRPQ subscale values were averaged and compared by one way analysis of variance (ANOVA) with Tukey's post hoc analysis across each SMS age group and for comparisons of adults with SMS to Russell and Oliver (2003) comparison samples. All statistical analyses were performed using Graphpad Software Prism 6.

3. Results

3.1. The Behavior Problems Inventory-01

3.1.1. SMS BPI-01 scores are significantly greater relative to individuals with intellectual disability of a heterogeneous etiology

We analyzed each subscale BPI-01 score from the SMS cohort relative to a reference sample of adults with intellectual disability of heterogeneous etiology. Our SMS cohort had a mean frequency score for self-injurious behaviors of 11.65 (SD = 6.09) ranging from 0 to 28 while the mean severity score was 9.296 (SD = 4.866) ranging from 1 to 24. A one-sample t-test found that both frequency and severity of self-injurious behaviors in the SMS sample were significantly greater than the intellectual disability reference sample (frequency; $t = 13.13$, df = 98, $P < 0.0001$; severity; $t = 13.83$, df = 97, $P < 0.0001$) (Fig. 1A and B). Stereotyped behaviors in the SMS sample had a mean frequency score 21.10 (SD = 15.58) with values ranging from 0 to 62 and a severity mean score of 9.26 (SD = 9.27) with values ranging from 1 to 41. Both the frequency and severity scores for stereotyped behavior was significantly greater within the SMS group than within the intellectual disability reference group (frequency; $t = 5.24$, df = 98, $P < 0.0001$; severity; $t = 7.93$, df = 97, $P < 0.0001$) (Fig. 1C and D). Finally, aggressive and destructive behaviors in the SMS sample had a mean frequency of 9.82 (SD = 8.43) ranging from 0 to 41 and a severity mean score of 9.075 (SD = 7.10) ranging from 1 to 32. Both the frequency and severity scores for aggressive and destructive behaviors was significantly greater among SMS than the intellectual disability reference group (frequency; $t = 5.83$, df = 98, $P < 0.0001$; severity; $t = 7.05$, df = 92, $P < 0.0001$) (Fig. 1E and F). Taken together, these results suggest that individuals with SMS have more frequent and severe behavioral problems than what is typically observed in individuals with intellectual disability.

3.1.2. Self-injurious, stereotyped, aggressive and self-destructive behaviors are prevalent in SMS sample

We sought to classify which behaviors of the BPI-01 were prevalent in the SMS sample (Table 2). In our cohort, self-injurious behaviors affecting greater than 50% of individuals were hitting head (self or with objects) (89%), teeth grinding (62%), hitting (self or with objects) (68%), self-biting (57%), and onychotillomania (57%), with 99% of participants demonstrating some type of self-injury during the two-month period. The average frequency for the self-injurious behaviors was weekly. Many stereotyped behaviors were also present including yelling and/or screaming (86%), clapping hands (70%),

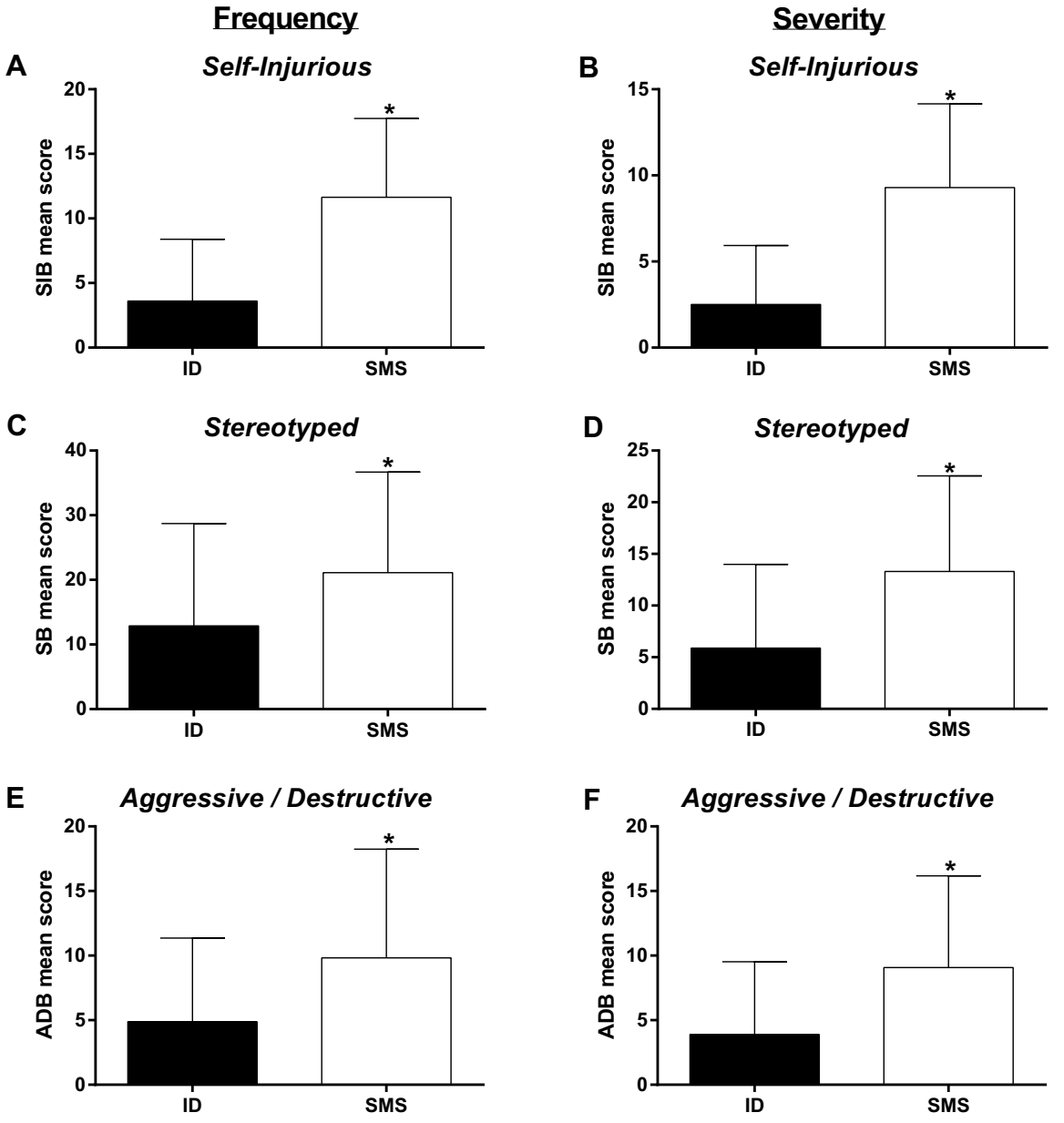

Fig. 1. SMS individuals have higher BPI-01 scores relative to ID of heterogeneous etiology. SMS individuals scored significantly higher in self-injurious behaviors frequency (A) and severity (B) relative to ID. Similar results were observed for stereotyped behaviors (C and D) and aggressive/destructive behaviors (E and F). $^{*}P < 0.0001$. Error bars indicate standard deviation. ID = intellectual disability; SIB = self-injurious behaviors; SB = stereotyped behaviors; ADB = aggressive destructive behaviors.

manipulating objects (55%), and repetitive hand movements (53%), with 99% demonstrating some type of stereotypies on a weekly basis during the two-month period. Aggressive or destructive behaviors included hitting of others (73%), destruction of items (59%), pushing of others (56%), and grabbing or pulling of others (57%), with 94% reporting some type of aggressive or destructive behavior with an average frequency of weekly during the two-month period. These findings are consistent with other reports in the literature related to stereotyped and self-injurious behaviors (Elsea & Girirajan, 2008), but this is the first detailed report of the type of aggressive behaviors targeted toward others observed in SMS. In addition, our BPI results describe the frequency and severity of these individual behaviors for the first time among individuals with SMS.

3.2. Food Related Problems Questionnaire

Lack of satiety, food-seeking, and obesity have previously been reported concerns for some individuals with SMS (Elsea & Girirajan, 2008). Therefore, utilizing the FRPQ, we asked if food-related problems in SMS increase during specific

Table 2
BPI-01 results in SMS.

Behavior Problems Inventory-01	
Self-injurious behavior	Percent of sample (*n*)
Self-biting	**58.6% (58)**
Hitting head (self and/or with objects)	**79.8% (79)**
Hitting body (self and/or with objects)	**66.7% (66)**
Self-scratching	46.5% (46)
Vomiting (self-induced)	10.1% (10)
Self-pinching	29.3% (29)
Pica	37.4% (37)
Polyembolokoilamania	32.3% (32)
Onychotillomania	**53.5% (53)**
Inserting fingers into body openings	28.3% (28)
Air swallowing	8.1% (8)
Hair pulling	20.2% (20)
Extreme drinking	22.2% (22)
Teeth grinding	**59.6% (59)**
Stereotyped behavior	
Rocking back and forth	37.4% (37)
Sniffing objects	24.2% (24)
Spinning own body	31.3% (31)
Waving or shaking arms	40.4% (40)
Rolling head	17.2% (17)
Whirling, turning around on spot	31.3% (31)
Engaging in repetitive body movements	47.5% (47)
Pacing	15.2% (15)
Twirling things	44.4% (44)
Repetitive hand movements	**52.5% (52)**
Yelling and/or screaming	**80.8% (80)**
Sniffing own body	14.1% (14)
Bouncing around	45.5% (45)
Spinning objects	32.3% (32)
Bursts of running around	37.4% (37)
Complex hand and finger movements	27.3% (27)
Manipulating objects	**55.6% (55)**
Sustained finger movements	21.2% (21)
Self-rubbing	33.3% (33)
Gazing at hands or objects	27.3% (27)
Bizarre body postures	16.2% (16)
Clapping hands	**66.7% (66)**
Grimacing	30.3% (30)
Waving	37.4% (37)
Aggressive/destructive behavior	
Hitting	**76.8% (76)**
Kicking	44.4% (44)
Pushing	**57.6% (57)**
Biting	27.3% (27)
Grabbing and pulling	**57.6% (57)**
Scratching	29.3% (29)
Pinching	29.3% (29)
Spitting	28.3% (28)
Verbal abuse	40.4% (40)
Destroys things	**66.7% (66)**
Mean or cruel	41.4% (41)

developmental stages. In addition, we analyzed FRPQ scores of SMS adults relative to two other reference samples: an adult cohort with intellectual disability and an adult cohort of individuals with PWS.

3.2.1. FRPQ scores increase significantly with age in the SMS individual

Due to the nature of previously reported food behaviors within SMS (Burns et al., 2010; Elsea & Girirajan, 2008; Elsea & Williams, 2011), we sought to categorize a specific age range to refine the timing of the manifestation of the behaviors. We chose to categorize the developmental stages according to school age (preschool, primary, secondary, and adults). Therefore, prior to FRPQ score statistical analysis, we performed a one-way ANOVA ($F_{5,129} = 151.1$, $P < 0.0001$) across the SMS sample and found that each developmental stage mean age was significantly different from one another (Table 1) rendering the categorization scheme effective. We found that preschool total scores had a mean score of 30.8 ($SD = 14.49$) ranging from 10 to 62. Primary school age scores had a mean score of 34.44 ($SD = 13.63$) ranging from 0 to 77. Secondary school age scores

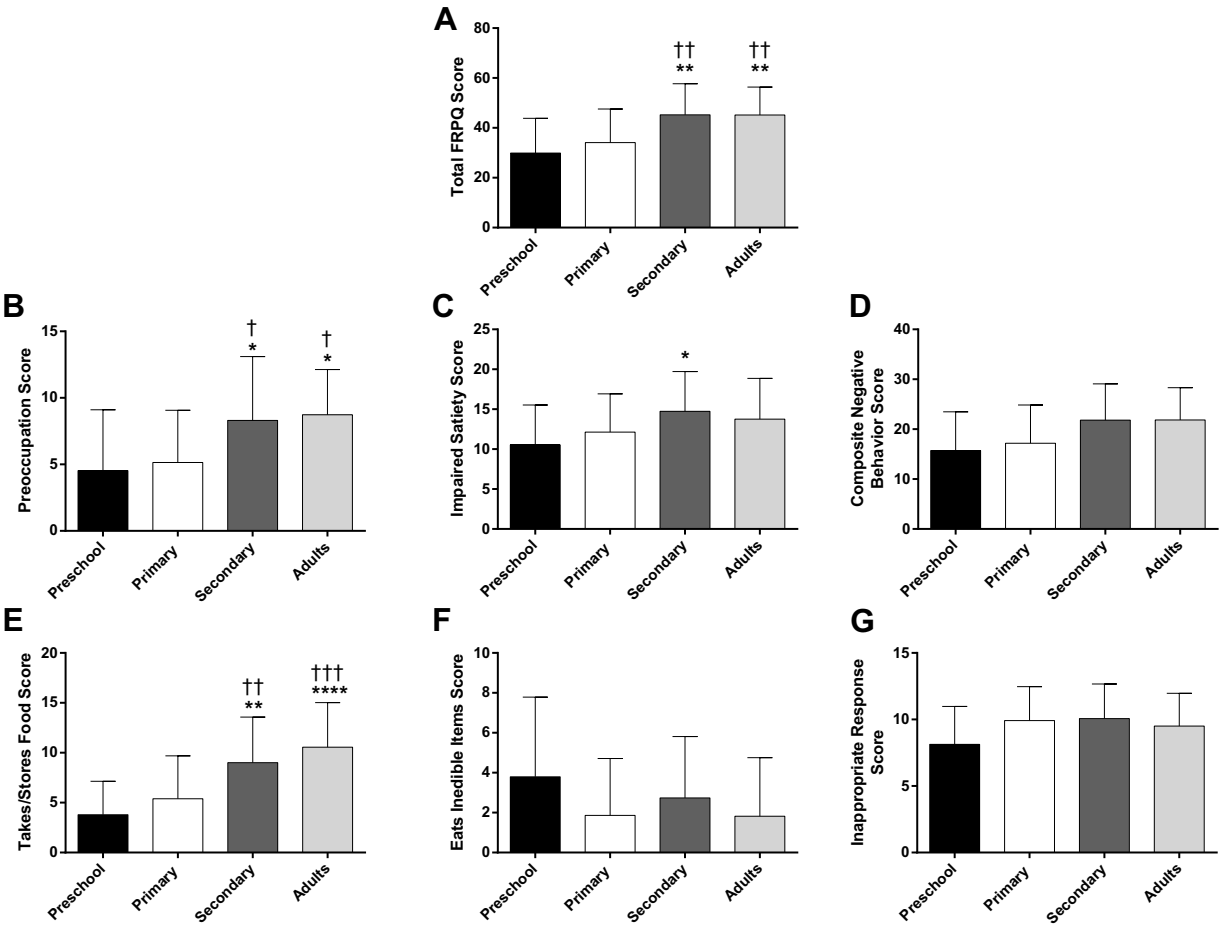

Fig. 2. SMS food-related problems increase during specific developmental periods. (A) Secondary (11.8–18 years) and adult (>18) age individuals with SMS scored higher in the overall FRPQ relative to younger age SMS individuals. (B) Preoccupation scores were significantly higher in adults relative to all age groups, while secondary age SMS individuals also had significantly higher scores than younger aged SMS individuals. (C) Impaired satiety scores were significantly higher in secondary school relative to preschool (1.5–4 years) SMS individuals. (D) No significance was observed across each age group in scores for composite negative behavior. (E) Both adults and secondary age SMS individual had higher scores for takes and stores food relative to preschool and primary age groups. (F) Eats inedible items and (G) inappropriate response scores were not significantly different across each age group. Significance relative to preschool: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$. Significance relative to Primary: $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, $^{\dagger\dagger\dagger}P < 0.001$. Error bars indicate standard deviation.

had a mean score of 44.85 ($SD = 12.65$) ranging from 21 to 69. Lastly, adults had a mean score of 44.36 ($SD = 11.42$) ranging from 21 to 59. Next, we asked if each FRPQ total score increased across each developmental stage by one-way ANOVA ($F_{3,96} = 8.087$, $P < 0.0001$) with Tukey's post hoc testing and found that preschool and primary school aged children had similar total scores (Fig. 2A). However, secondary school aged children and adults had significantly increased total FRPQ scores relative to preschool (secondary $P = 0.0019$; adults $P = 0.0032$) and primary school (secondary $P = 0.0053$; adults $P = 0.01$) age children, but scores for the secondary school group and adults were not different from each other (Fig. 2A).

Next we sought to determine if any specific food-related behaviors were lost or gained in each age group by examining each FRPQ subscale. Interestingly, one-way ANOVA ($F_{3,96} = 6.072$, $P = 0.0008$) with Tukey's post hoc testing found preoccupation with food scores were significantly increased in adults relative to preschool ($P = 0.0177$) and primary ($P = 0.0107$) (Fig. 2B). The secondary school age children also had significantly higher preoccupation with food scores relative to both preschool ($P = 0.0308$) and primary ($P = 0.0193$) age groups (Fig. 2B). The secondary age sample had a significantly higher impaired satiety score relative to preschool age children ($P = 0.0457$), while no other significant differences were observed across other group comparisons (Fig. 2C). Finally, we observed no significant differences in food-related negative behavior scores ($F_{3,96} = 4.149$, $P = 0.0082$; Fig. 2D). There were some comparisons that trended toward significance, such as preschool scores relative to secondary and adult scores ($P = 0.055$ and $P = 0.0665$ respectively) and primary scores relative to secondary scores ($P = 0.0683$). However, we did observe differences in the takes or stores food subscale of the negative behavior category ($F_{3,95} = 11.11$, $P < 0.0001$) in secondary aged children and adults relative to preschool (secondary $P = 0.0016$; adults $P < 0.0001$) and primary (secondary $P = 0.0073$; adults $P = 0.0002$) age groups (Fig. 2E). The two remaining

Table 3
FRPQ results in Smith-Magenis syndrome.

Food-Related Problems Questionnaire	Percent of sample (%)	Average Likert scale response (1–6)
Preoccupation		
Compares size of meal content with others	22%	3.3
Talks about food	87%	3.5
Associated people, places and/or occasion with specific food	73%	3.9
Impairment of satiety		
Still hungry after normal size meal	70%	3.3
Goes without food when tired, ill or upset	73%	3.0
Shares food with others	89%	3.8
Describes feeling full	69%	3.4
Eats more than a standard sized meal	71%	3.8
Composite negative behavior		
Takes/stores food		
Helps themselves to food they should not have	87%	4.3
Hides or hoards food	30%	4.0
Parent and/or caregiver has to lock away food	57%	4.1
Eats inedible items		
Eats non-edible items	32%	2.9
Eats food not suitable for consumption	47%	3.1
Inappropriate response		
Accepts explanation if meal is delayed	83%	3.7
Negative response when denied food	92%	4.3
Behavioral difficulties when food item is not expected or wanted	82%	3.1

subscales, eats inedible food items ($F_{3,95} = 1.715$, $P < 0.1692$) and inappropriate responses ($F_{3,95} = 2.097$, $P < 0.1058$) to food scores, were not different across each age group (Fig. 2F and G).

3.2.2. High prevalence of food-related problems in SMS

Using the entire SMS sample, we addressed the response rate for each question in the FRPQ for individuals manifesting some degree of frequency of the behavior as reported in the survey by a Likert score ≥ 1. We found that "talks about food" and "associations to specific foods" within the preoccupation subcategory of our cohort had high response rates of 87% and 73% respectively (Table 3).

All questions within the impairment of satiety subscale affected $\geq$69% of the entire sample, with Likert scale responses averaging from 3.0 to 3.8 (Table 3). Interestingly, 70% of the cohort reported an incident of "hunger after a meal;" however, 69% "described feeling full", even though 71% "ate more than a standard size meal." In addition, 89% of the sample "shares food with others" which is likely attributed to the social personality of SMS individuals.

The takes and stores food subscale of the composite negative behavior category revealed that 87% "helped themselves to food they should not have, 30% "hid or hoarded food", and 57% of "parents and/or caregivers locked away food". Likert scores within the takes and stores food subscale averaged $\geq$4.0. The eats inedible items subcategory of the composite negative behavior category did not affect the overall cohort at >50%, but "eats food not suitable for consumption" affected 47% of the sample. Finally, the inappropriate response to food subcategory of composite negative behavior showed very high response rates for "accepts explanation if meal is delayed" (83%), "negative response when denied food" (92%), and "behavioral difficulties when food item is not expected or wanted" (82%) (Table 3).

3.2.3. SMS FRPQ scores are similar to PWS but significantly higher than general intellectual disability

To determine where SMS food problems fall relative to other genomic disorders associated with syndromic obesity and impaired satiety, we compared SMS total FRPQ and each subscale to PWS, as well as a sample of adults with intellectual disability of an idiopathic etiology. Prior to FRPQ score statistical analysis, we performed a one-way ANOVA across the SMS sample and each reference group to determine if age differences were present ($F_{5,129} = 151.1$, $P < 0.0001$). The SMS adult mean age was significantly lower relative to the intellectual disability sample ($P < 0.0001$), but similar to the PWS mean age (Table 1). Despite the SMS secondary age group having a similar total FRPQ score to SMS adults (Fig. 2A), the mean age was significantly lower ($P < 0.0001$) but more importantly, significantly lower than the PWS sample ($P < 0.0001$) (Table 1); therefore, the SMS adult group was used in comparisons to each of the reference samples. Through a one-way ANOVA ($F_{2,148} = 20.55$, $P < 0.0001$), we found that total FRPQ scores were significantly elevated in PWS and SMS relative to intellectual disability (PWS and SMS $P < 0.0001$); however, there were no significant differences between PWS and SMS ($P = 0.6387$) (Fig. 3A). To further dissect the food-related behaviors between each disorder, we analyzed the FRPQ subscales for each sample. One-way ANOVA ($F_{2,48} = 11.07$, $P < 0.0001$) found both PWS and SMS had significantly increased preoccupation with food scores relative to intellectual disability (PWS $P = 0.0013$; SMS $P = 0.0001$) (Fig. 3B). Interestingly, SMS adults and PWS adults had similar scores for preoccupation with food ($P = 0.7938$) (Fig. 3B). Impaired satiety was

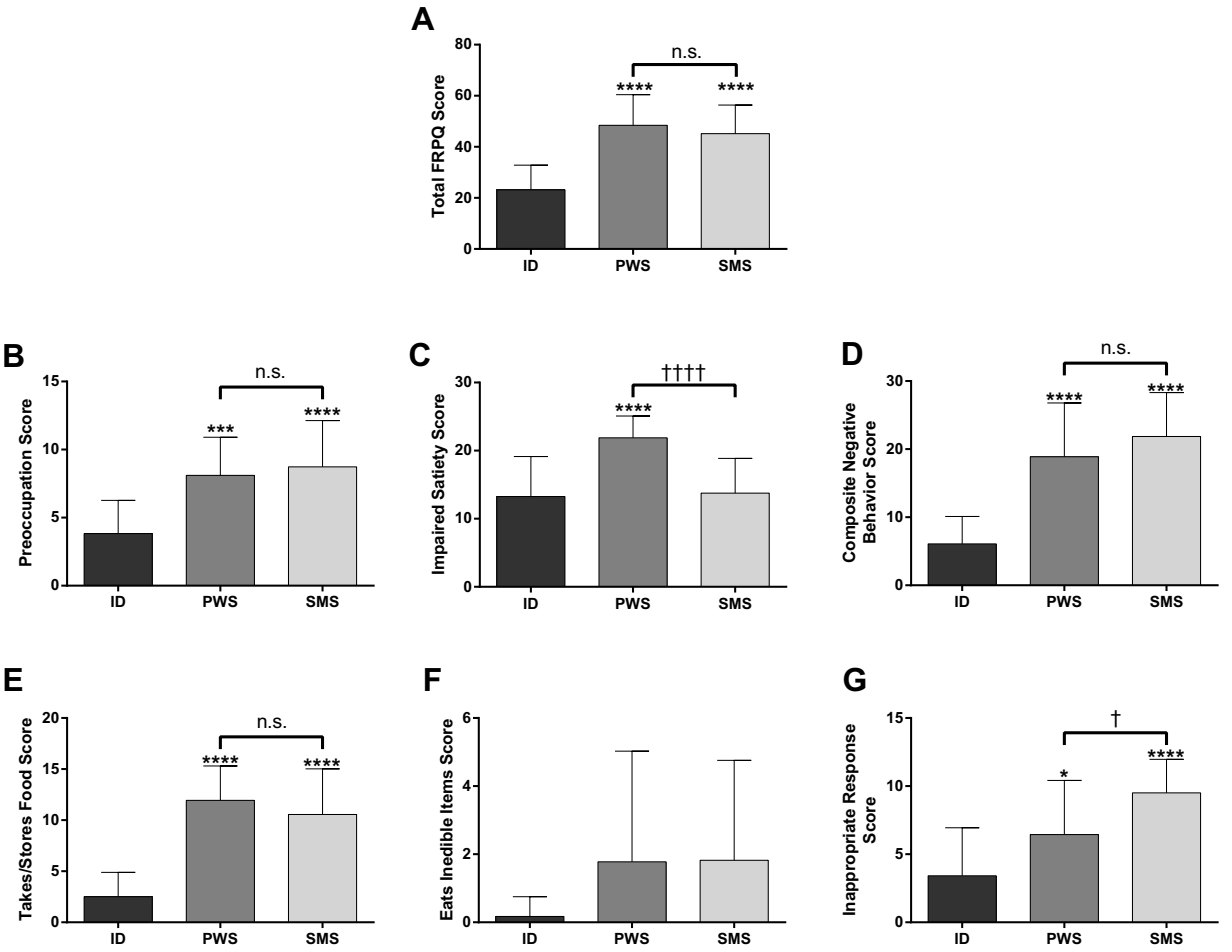

Fig. 3. Adult SMS food-related behaviors are more frequent than ID but similar to PWS. (A) SMS and PWS total FRPQ scores for adults are significantly higher relative to ID but are not different from each other. (B) Preoccupation scores were significantly higher in SMS relative to both ID and PWS while PWS was significantly higher than ID. (C) Impaired satiety scores were significantly higher in PWS relative to both SMS and ID, while SMS and ID were not different. (D) Composite negative behavior scores were significantly higher in PWS and SMS relative to ID but were not different from each other. (E) Both PWS and SMS groups had higher scores for takes and stores food relative to ID, but scores were similar among each other. (F) Eats inedible items was not different across each group. (G) Both PWS and SMS had significantly higher inappropriate response scores relative to ID while SMS scores were also higher than PWS. Significance relative to ID: $^{*}P < 0.05$, $^{***}P < 0.001$, $^{****}P < 0.0001$. Significance relative to PWS: $^{\dagger}P < 0.05$, $^{\dagger\dagger\dagger\dagger}P < 0.0001$. Error bars indicate standard deviation.

significantly elevated in the PWS sample relative to both intellectual disability ($P < 0.0001$) and SMS ($P < 0.0001$); however, SMS and intellectual disability scores were similar ($P = 0.9502$) ($F_{2,48} = 17.35$, $P < 0.0001$) (Fig. 3C). The food-related negative behaviors were significantly higher in both PWS and SMS groups relative to intellectual disability (PWS and SMS $P < 0.0001$) but not different from each other ($P = 0.3438$) ($F_{2,48} = 23.46$, $P < 0.0001$) (Fig. 3D). Interestingly, PWS and SMS have similar behavioral scores for taking and storing food, both of which are significantly higher than intellectual disability (PWS and SMS $P < 0.0001$) ($F_{2,52} = 27.51$, $P < 0.0001$) (Fig. 3E). No differences were observed between any groups for eats inedible items subscale, likely attributed to the large standard deviation (Fig. 3F) ($F_{2,48} = 1.648$, $P < 0.2031$). Finally, inappropriate responses to food subscale scores were significantly elevated in PWS and SMS relative to intellectual disability (PWS $P = 0.04$; SMS $P < 0.0001$), but SMS scores were significantly higher than PWS ($P = 0.0123$ ($F_{2,52} = 12.86$, $P < 0.0001$) (Fig. 3G).

4. Discussion

4.1. SMS behavioral problems

Individuals with SMS have a wide range of behavioral problems that are often variable across age and the most difficult to manage (Elsea & Girirajan, 2008; Elsea & Williams, 2011; Smith et al., 1998). Using the BPI, we found that our SMS cohort displayed a significantly increased frequency and severity of self-injurious, stereotyped, and aggressive/destructive behaviors relative to individuals with intellectual disability (Fig. 1A–G).

Our cohort displayed similar percentages of self-injurious behaviors as previously reported, such as self-hitting and polyembolokoilamania, but onychotillomania was higher than the previously reported at 53.5% (prior report = 25–30%) (Table 2) (Elsea & Girirajan, 2008; Elsea & Williams, 2011; Greenberg et al., 1991). However, a recent study has documented onychotillomania at a similar percentage of 57.9% but within a much smaller cohort of 19 SMS individuals (Osorio, Villaverde, & Sampaio, 2013). Stereotyped behaviors in our cohort were also similar to previously reported studies, including rocking back and forth (Dykens & Smith, 1998; Smith et al., 1998). Interestingly, aggressive episodes seem to be a definitive characteristic of SMS; however, not much is known about what specific phenotypes are present. The BPI data showed that some aggressive or destructive behaviors are not self-inflicted but rather directed toward others and include verbal abuse, meanness, and acts of cruelty (Table 2). One confounding variable is the role of environment in the manifestation of each behavior. Recent studies have shown that SMS aggression is more frequently associated with environmental contingencies suggesting that particular scenarios can either exacerbate or decrease aggressive behavioral responses (Finucane, Dirrigl, & Simon, 2001). Other studies have suggested that an established daily routine helps mitigate the aggressive or destructive behaviors; however, it is unclear how many participants in this study were on such daily routines (Elsea & Girirajan, 2008). There are some limitations to consider in the interpretation of the data presented here. The findings of this study are subject to a potential parent reporting bias since parents answered behavior surveys instead of trained observers or clinicians. The race, gender and age of the SMS cohort were different from the reference population, which limited the generalizability of our findings. Another limitation is the sample size of the SMS cohort compared to the BPI reference population which may limit our analysis and interpretation. Finally, medications utilized by the SMS cohort could confound the responses of the survey. In the future, a longitudinal study that collects behavior data at different ages could shed light on if there are changes with behavior due to age. Overall the BPI-01 has revealed the striking neurobehavioral deficiencies in the SMS sample and the degree of such deficiencies.

4.2. Age specific food-related problems in SMS

SMS adolescents and adults tend to have a shift in their weight as they age (Table 1), and studies have shown that greater than 90% are at or above the 90th percentile for weight by age 14 (Burns et al., 2010). Using the FRPQ, we found that secondary school age (11.8–18) and adults had significantly higher FRPQ scores (Fig. 2A), while 52% of the secondary school age and 60% of adults were considered overweight or obese by parent or caregiver report, further implicating this age range in the onset of weight gain and obesity. In addition, it appears that both secondary school age and adults have specific deficits in food-related behaviors, as observed in the preoccupation and takes/stores food subscales of the FRQP (Fig. 2A–G). We acknowledge that there are some limitations with using the FRPQ. The FRPQ was created to capture the problematic food-related behaviors prevalent in PWS, thus there may be more subtle, unexplored features of eating behaviors in the SMS cohort. In the future, adding the Hyperphagia Questionnaire (Dykens, Maxwell, Patino, Kossler, & Roof, 2007) that addresses the limitations of the FRPQ could strengthen this study. Due to the nature of SMS food-related behaviors, it is not surprising to see children older than 12 years manifest such behaviors, especially since most are likely more capable physically and cognitively. While many children with SMS are obese, a small subset of children ($\sim$10%) is not affected by excessive weight gain (Burns et al., 2010). Therefore, dissecting the specific eating behaviors and food-related concerns of individuals with SMS that lead to obesity is important for the development of practice guidelines and specific preventive interventions. Our data suggest that at around age 12, these behaviors may become problematic (Fig. 2A–G). Interestingly, our overall sample had a high incident of "hunger after a meal" despite "eating more than the standard sized meal," thus confirming previous SMS mouse studies showing impaired satiety signaling (Burns et al., 2010) (Table 3). However, a high incidence of "feeling full after consumption of a meal" was reported which suggests that SMS individuals may be able to recognize some degree of satiety cues emanating from the gut or other tissues, but deficiencies may lie within the pathways that recognize and/or transmit such signals beyond the peripheral tissues.

4.3. SMS food-related problems have similarities to PWS

PWS is considered the leading genetic cause of syndromic obesity. We used the FRPQ survey to compare and contrast the food behavioral problems between SMS and PWS. The overall FRPQ scores were similar (Fig. 3A), but the subscale for inappropriate responses of the total composite negative behavior in SMS were higher (Fig. 3G), while the subscale for impaired satiety were lower relative to PWS (Fig. 3C). The major limitation in this comparison between SMS and PWS was the sample size, and most importantly the FRPQ is designed for a PWS cohort. Additionally, there were differences in the gender distribution between the SMS and PWS groups, and the PWS sample was also in a residential group while the SMS cohort primarily resided at home. PWS is well-known for severe hyperphagia (Lindgren et al., 2000); however, our SMS cohort did not display similar frequency scores on the FRPQ for impaired satiety despite SMS mouse model work implicating such impairments (Burns et al., 2010) and 70% of the group experiencing hunger after a meal. SMS mouse studies and our survey data suggest that individuals with SMS have some form of satiety impairment. Although not as severe as individuals with PWS, this is still problematic. Additionally, inappropriate responses to food frequency scores were significantly higher in SMS relative to PWS, but both groups had higher frequency scores relative to individuals with intellectual disability suggesting that overall both disorders display problematic behaviors.

Extensive studies detailing the mechanistic regulation of food intake though the brain-gut axis of the hypothalamus in PWS have uncovered that POMC containing neurons in the arcate nucleus fail to depolarize due to the loss of function of MAGEL2 (Mercer et al., 2013). Therefore, a lack of POMC excitation fails to promote satiety despite the presence of leptin (Mercer et al., 2013). SMS mouse model work has suggested that key genes within the brain–gut axis of the hypothalamus are significantly dysregulated. POMC and BDNF expression are significantly reduced, while MC4R gene expression is significantly elevated (Burns et al., 2010). However, the direct effects of the dysregulation of these genes in POMC and AGPR neuronal activity and signaling to the paraventricular nucleus are unclear. A further understanding of the similar hypothalamic dysfunctions and neural mechanisms underlying hyperphagia in both SMS and PWS could lead to an improved understanding of homeostatic pathways involved in obesity.

Effective treatments in the form of environmental controls with the early institution of a low-calorie, well-balance diet, regular exercise, rigorous supervision, and restrictive access to food are extremely effective in obesity management within PWS patients (Bonfig et al., 2009; Schmidt et al., 2008). Other studies have shown a combination of approaches can still be effective despite the juncture of time the treatment is rendered (Bonfig et al., 2009; Schmidt et al., 2008). However, food and weight interventions in SMS are exceedingly less sophisticated, but recent work in SMS mouse models has shown that high-carbohydrate and high-fat diets exacerbate obesity outcomes in adolescent and early adult mice suggesting that a specific diet must be followed in order to maintain a normal weight range by adolescents (Alaimo et al., 2014). A recent clinical study in PWS patients has identified a specific macronutrient diet consisting of 30% fat, 45% carbohydrates, 25% protein, 20 grams of fiber, and 60–80% reduction of energy intake per day in children aged 2–10 years old as an effective method for improving body composition and weight (Miller, Lynn, Shuster, & Driscoll, 2013). Children under the diet had a reduced body fat percentage of about 25% and maintained BMI scores. In addition, just reduced energy intake alone is not effective in reducing the proportion of adipose tissue in PWS (Miller et al., 2013). Similar clinical studies within the SMS sample have not been implemented, and our survey data indicate that both SMS and PWS samples have overlapping food-related behavioral problems suggesting that similar interventions may be successful. The genetic etiology is quite different between both disorders; however, the phenotypic overlap is quite striking and likely explains why PWS is listed the differential diagnosis when patients are evaluated for SMS. Despite the differences in genetic etiology, each disorder may have the similar genetic pathways affected that lead to food-related phenotypic overlap. Overall, our survey data provide a basis for further investigations of PWS food interventions among individuals with SMS.

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