Published in final edited form as:

Dev Neuropsychol. 2018 ; 43(2): 152–161. doi:10.1080/87565641.2017.1367395.

Eye tracking as a marker of hyperphagia in Prader-Willi syndrome.

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Abstract

This study examined the feasibility of eye tracking measures as markers of hyperphagia in 42 children and adults with Prader-Willi syndrome (PWS). Gaze data collected during free visual exploration of complex displays revealed that food images may not have an overall superior salience in PWS. However, increased attention to food in the context of other high-interest items was associated with higher scores on caregiver reports of hyperphagia. The study also provided preliminary evidence of test-retest reliability of eye tracking measures, suggesting that gaze characteristics may be a promising objective marker of food-related interests in PWS.

Keywords

hyperphagia; food; eye tracking; Prader-Willi syndrome; salience

Prader-Willi syndrome (PWS) is a genetic disorder associated primarily with a deletion on paternal chromosome 15q11–13 (70% of cases) or duplication of the maternal chromosome 15 (maternal uniparental disomy, mUPD, 25% of cases) (Butler, 1990; Nicholls et al., 1989). In addition to intellectual disabilities and compulsivity, the PWS phenotype includes hyperphagia, or intense hunger and overeating, and heightened risk of obesity (Dykens & Cassidy, 1999; Milner et al., 2005). Although the neurobiological mechanisms underlying hyperphagia in PWS remain unclear, it is associated an impaired satiety response (Heymsfield et al., 2014). Increased interest in food in persons with PWS typically emerges in early childhood between 3–6 years of age (Miller et al., 2011), followed by hyperphagic behavior. Without dietary interventions, food restrictions, and careful monitoring of food-seeking behaviors, individuals with PWS become morbidly obese and are at high risk for premature death related to complications of obesity (Einfeld et al., 2006). Hyperphagia is thus a life-long, life-threatening challenge for individuals with PWS and their families and caregivers (Hodapp et al., 1997).

Accurately measuring hyperphagia in PWS is critically important for monitoring the onset and course of this complex behavior over time, and for evaluating treatment effects. Yet, systematic investigation of hyperphagia in PWS has proven challenging. The body mass index (BMI) is not a valid indicator of hyperphagia in PWS. With effective dietary and environmental controls in place, many individuals with PWS remain hyperphagic but do not become obese. One previously used behavioral observation approach gave individuals with PWS open access to food and directly observed their actions and food consumption within a discrete time period (Holland et al., 1995; Tan et al., 2004). This approach, however, raises research safety and ethics concerns, and its reliability or feasibility in clinical trials has not been tested. Others have covertly observed adults with PWS left alone in a room baited with desired food, but given the contrived laboratory setting, participants did not generally engage in food seeking (Zarcone et al., 2004). A visual-analogue interview probing willingness to eat different combinations of food shed light on cognitive and emotional correlates of hyperphagia in PWS, but is too hypothetical and unwieldy for use in clinical trials (Dykens, 2000). Yet another approach have used questionnaires completed by individuals with PWS and their parents or caregivers (Russell & Oliver, 2003). However, obtaining reliable self-report is difficult in young children, and persons with PWS vary greatly in their ability or willingness to talk openly about food consumption. Thus, an informant-based measure was developed to evaluate hyperphagic behaviors, drive, and severity in people with PWS (Dykens et al., 2007). Although this questionnaire is psychometrically sound and has been responsive to treatment effects, it is nevertheless an indirect measure of food-related behaviors in PWS and subject to potential respondent bias.

This study takes advantage of recent advances in the development of noninvasive and low-cost measures of physiological processes, such as eye movements, as a potential means to directly evaluate food-related interests in persons with PWS. Eye movements are a natural human behavior that does not require extensive training and can be used throughout the lifespan. Indeed, with single stimuli, interpretable eye tracking data have been acquired in infants as young as 6–9 months of age (Merin et al., 2006; Key & Stone, 2012), and complex visual displays have been successfully used in studies of children starting at 2 years of age (Sasson et al., 2011). The low behavioral demands make eye tracking measures optimal for use across levels of intellectual or verbal ability while also circumventing any social desirability confounds. Eye tracking is thus an attractive means to investigate hyperphagia in PWS.

Previous studies have established that more salient stimuli attract an increased number and duration of eye fixations (Colombo et al., 1995; Sasson et al., 2007, 2008). Food-related eye tracking studies in the general population have used paired presentations of food and nonfood images (e.g., household or office objects) and found that gaze duration for food stimuli decreased between the states of hunger and satiety (Castellanos et al., 2009). In contrast, obese participants showed prolonged attention and faster orienting to food items regardless of changes in the physiological state (see also Hendrikse et al., 2015 for review).

Other studies, however, used similar procedures and observed no group differences between obese and normal weight individuals, or between the states of hunger and satiety (e.g., Nijs et al., 2010; Werthmann et al., 2015). This variability in outcomes had been attributed to

specific task instructions, timing of testing relative to food intake, and possible differences in gaze quantification methods. For example, Giel et al. (2011) studied the effects of food restriction on visual attention in persons with anorexia nervosa and typical controls. There were no group differences in the initial attention capture by the food stimuli, as reflected in a comparable number and duration of the first fixations following image onset. Instead, voluntary food avoidance in persons with anorexia was associated with reduced attentional engagement with food images, quantified as total gaze duration.

In this proof-of-concept study, we aimed to examine the feasibility of using eye tracking measures to identify novel objective markers of food interest and hyperphagia in persons with PWS. Given the variability in the results of the studies using paired stimulus presentation, we followed the data acquisition and analytic procedures of Sasson et al. (2008), who used eye tracking during a visual exploration task (VET) to examine the salience of social and nonsocial stimuli in children with autism spectrum disorders. The advantage of the VET design is its concurrent presentation of multiple exemplars from different perceptual categories (e.g., high- and low-salience items). Doing so allows documentation of not only interest in one type of stimulus over another, but also the extent of visual exploration (number of different items looked at) as a means to quantify the effect of specific interests on information processing.

Our study examined gaze patterns of persons with PWS while they viewed complex visual arrays of multiple images of food, household objects, and animals. The latter stimulus category was included as a high-interest non-food control condition due to its increased salience for individuals with PWS, who often exhibit strong nurturing behaviors and a desire to take care of animals or pets (Dykens, 2006). We hypothesized that given their increased subjective state of hunger, persons with PWS would evidence increased visual attention to food compared to nonfood images during spontaneous visual exploration. Further, we expected that greater attention to food stimuli would be associated with increased hyperphagia as reported by caregivers. For each of the three stimulus categories (food, objects, animals), visual attention was quantified as the number of images looked at, total duration of fixations, and the number of gaze returns to an image after looking away. Although we did not have a specific hypothesis regarding the effects of the genetic subtype, it was included as an exploratory factor based on prior evidence of phenotypic differences between individuals with the deletion vs. mUPD subtype of PWS (e.g., Butler et al., 2004; Dykens & Roof, 2008), including in food-related information processing (e.g., Holsen et al., 2008; Key & Dykens, 2008). Finally, we examined test-retest stability of these eye-tracking measures in a subset of participants who completed the experimental paradigm on two separate occasions.

Method

Participants

Forty-two persons with PWS aged 6 to 35 years ($M = 15.47$, $SD = 6.59$ years) participated in the study (see Table 1 for participant characteristics). Twenty-nine individuals (M age = 15.33, $SD = 6.22$; 12 female) had the deletion subtype of PWS, and 13 had the maternal UPD subtype (M age = 15.77, $SD = 7.61$; 10 female). Three additional participants (2

mUPD, 1 Deletion) were excluded due to insufficient amount of eye tracking data (gaze data not available for 50% or more of the stimulus arrays). All participants had normal or corrected-to-normal vision. The mean total IQ was 75.38 (SD=17.77) assessed using Kaufman Brief Intelligence Test-2 (K-BIT-2; Kaufman & Kaufman 2004). The two genetic subtype groups did not differ in age, IQ, body mass index (BMI), or reported hyperphagia severity.

Parents/guardians of participants provided written informed consent, and individuals with PWS indicated their assent for all study procedures. The study was conducted with approval from the Institutional Review Board of Vanderbilt University Medical Center.

Hyperphagia Evaluation

Parents of each participant completed the 11-item Hyperphagia Questionnaire (Dykens et al., 2007), which uses a Likert-type scale to evaluate hyperphagic behaviors, drive, and severity in people with PWS (e.g., persistence in food seeking, emotional reactions to food restriction). Higher scores index more severe hyperphagia. Parents based their responses on behaviors demonstrated by the person with PWS across different environmental settings (e.g., at home, at school, in the community) during the week preceding the assessment.

Visual Exploration Task (VET)

The task was adapted from an eye tracking paradigm previously used to examine restricted interests in individuals with autism (Sasson et al., 2008, 2011).

Stimuli.

Color images representing common foods (high and low calorie options), animals (in non-aggressive poses), and household objects (e.g., furniture, clothes, small appliances) served as the stimuli. All individual images occupied comparable physical space. The 72 possible images (3 categories x 24 exemplars) were grouped into 12 arrays presented on colored background, each consisting of 24 images representing two categories (e.g., food+animals, food+objects, animals+objects; see example in Figure 1). The number of images from each category within an array varied from 4 (17%) to 12 (50%) to 20 (83%).

Eye tracking data acquisition.

Eye tracking data were collected using a table-top device (Tobii x50). Tobii's eye-tracking technology utilizes corneal reflections and does not require any head-mounted equipment or physical constraints. Ambient lighting was reduced to increase salience of the stimulus screen. Stimulus presentation was controlled using ClearView v 2.1.

A 5-point calibration procedure (included in Tobii software) was implemented prior to collecting VET data. The procedure took on average ~30 sec and could be repeated as needed to achieve adequate data quality. Each of the 12 visual arrays was presented for 10 sec each with 1 sec inter-trial interval marked by a white fixation point presented in the center of a black screen. Participants viewed one of three possible sequences of the arrays and were instructed to watch the screen "like TV". When necessary, their gaze was directed to the screen using gestures and other nonverbal cues. No image-specific instructions were

provided. The entire acquisition procedure, including calibration, lasted between 4–7 minutes. All eye tracking sessions were completed between 9–11:15 am (after breakfast) except for two participants whose data were acquired at 1pm and 1:30pm (after lunch).

Data Analysis

Using ClearView software analysis tools, each participant's eye gaze data were automatically scored for 24 regions of interest corresponding to the individual items in each visual array. A fixation was defined as having a radius of at least 50 pixels (visual angle of approximately 2.5°) and the minimum duration of 100 msec. For the purpose of the current study, only data from the 6 arrays containing pictures of foods were included in analyses. Visual attention to food items was quantified in the context of other high-interest (animals) and low-interest stimuli (household objects) as the number of items looked at within each category, total duration of fixations, and the number of gaze returns to a particular item after looking away (see Table 2 for summary data). The resulting three dependent measures were analyzed separately using repeated measures ANOVA with Stimulus (2: food vs. objects/animals) x Contrast Type (2: high interest, low interest) as the within-subject factors and Genetic Subtype (2: Deletion, mUPD) as the between-subject factor. Preliminary analyses identified no sex differences for any of the dependent measures, therefore sex was not included as a factor. Significant interactions were followed up with pairwise t-tests and one-way ANOVAs with Bonferroni correction for multiple significance testing. Pearson correlations were used to examine the associations between the eye tracking variables and behavioral characteristics of the participants (age, IQ, BMI, hyperphagia).

Results

Total Number of Items Explored

There was a main effect of Contrast Type, $F(1,40)=7.663$, $p=.009$, $\eta_p^2=.161$, and a Stimulus x Contrast Type interaction, $F(1,40)=4.881$, $p=.033$, $\eta_p^2=.109$. Follow-up analyses found a greater number of food items explored compared to the household objects (low-interest contrast), $t(41)=2.650$, $p=.011$, $d=.41$. The number of fixations on food items was also greater in the low-interest than high-interest arrays, $t(41)=4.287$, $p<.001$, $d=.66$. There were no significant differences in the number of fixations on food vs. animal images ($p=.891$).

Total Duration of Fixations

The analysis revealed a Stimulus x Contrast Type interaction, $F(1,40)=5.919$, $p=.020$, $\eta_p^2=.129$. Follow-up analyses revealed longer duration of fixations on food items presented with the low-interest than high-interest items, $t(41)=4.182$, $p<.001$, $d=.65$.

Number of Gaze Returns

A main effect was found for Contrast Type, $F(1,40)=8.064$, $p=.007$, $\eta_p^2=.168$, as well as the interactions of Stimulus x Contrast Type, $F(1,40)=4.837$, $p=.034$, $\eta_p^2=.108$, and Stimulus x Contrast Type x Genetic Subtype, $F(1,40)=9.798$, $p=.003$, $\eta_p^2=.197$. Follow-up analyses revealed group differences for the low-interest stimulus contrast, where a greater number of returns to food items presented in the arrays with household objects was recorded in participants with the mUPD versus deletion subtype, $F(1,40)=7.538$, $p=.009$. An opposite

trend was observed for the high-interest arrays (food items presented with animals), where persons with the deletion subtype evidenced greater number of gaze returns to food compared to participants with the mUPD subtype, $F(1,40)=4.025$, $p=.052$. Within-subtype analyses revealed no significant differences in gaze returns for the deletion group, while persons with the mUPD subtype demonstrated more gaze returns to food presented with low-interest compared to high-interest items, $t(41)=7.483$, $p<.001$, $d=2.08$.

Correlations Between Eye Tracking and Behavioral Measures

Increased scores on the hyperphagia questionnaire were associated with greater number of fixations on food images, and greater number of gaze returns to these items, but only when presented along with the high-interest animal stimuli, $r=.351$, $p=.023$ and $r=.347$, $p=.024$, respectively (Figure 2). The same pattern of correlations was present within each genetic subtype. There were no significant correlations between the eye tracking variables and age, IQ, or BMI.

Eye-Gaze Data Quantity

To be included in analyses, each participant had to provide gaze data for at least 50% of the stimulus arrays. The relatively low threshold setting was motivated by the characteristics of the participant population, primarily intellectual disabilities and inattention. When we repeated the analyses for the 27 participants who provided gaze data for 100% of the stimulus arrays, the same overall pattern of results was found. Additionally, there was a nearly two-fold increase in the strength of correlations between the eye tracking measures of visual attention to food images and the hyperphagia scores (number of fixations: $r=.667$, $p<.001$; duration of fixations: $r=.577$, $p=.002$; number of gaze returns: $r=.631$, $p<.001$).

Test-retest reliability

As a part of a different study, a subset of 9 participants with PWS (6 deletion, 3 mUPD) completed the VET task a second time, two days after the initial testing (all retests were conducted at 9:30am). These participants were enrolled in a pharmacological treatment study and randomized into a placebo group, thus they were not expected to change their visual exploration behavior across the two test sessions. The two data sets were analyzed using the procedures above, except the repeated measures ANOVA included Test Time (2: test, retest) as an additional within-subject factor along with Stimulus (2: food vs. objects/animals) x Contrast Type (2: high interest, low interest). The genetic subtype was not included in this analysis due to the small sample size of this subgroup. The results revealed no significant main effect of Test Time or any interactions with this factor. Intraclass correlation analysis of the eye tracking measures for the high-interest arrays noted good reliability for the number of food items fixated (ICC $r=.801$) and the number of gaze returns to food items (ICC $r=.742$), but not for the total duration of fixations (ICC $r=.340$). Reliability of the three eye tracking measures for the animal stimuli was low (ICC $r<.280$).

Discussion

The goal of this study was to examine whether gaze data obtained during spontaneous visual exploration of complex stimulus displays containing images of food and other high- and

low-interest items could inform about hyperphagia in PWS. Importantly, our results demonstrated the feasibility of collecting informative eye tracking data in children and adults with PWS. In line with the expectation of increased visual attention to food than non-food stimuli, the data revealed greater number of items explored, longer looking time, and greater number of gaze returns for the food images, but only when presented in the arrays with the low-interest household objects. The lack of similar attentional effects for the high-interest arrays combining food and animal images suggests that visual salience of food items may not necessarily exceed that of other stimuli that persons with PWS find interesting.

Also in accordance with our predictions, we observed a positive association between caregiver reports of hyperphagia and the number of food items explored, as well as the number of gaze returns to previously seen food pictures. However, these correlations were only present for the high-interest arrays composed of food and animal pictures. Thus, when studying food-related interests in PWS, the broader attentional context needs to be considered: increased focus on food at the expense of concurrently presented other salient stimuli may be particularly informative in regard to hyperphagia. Additionally, our study provided preliminary evidence of test-retest reliability for the eye tracking measures indexing visual attention to food. This is an important first step toward establishing gaze data in a VET task as a marker of hyperphagia in PWS.

Our current findings also contribute to the accumulating evidence of genetic subtype differences in food-related attention in PWS. The exploratory analysis revealed that the two subgroups varied in the number of gaze returns to previously looked at food images. In particular, while the mUPD subgroup was more likely to repeatedly fixate on food stimuli presented among the household objects, the deletion subgroup more frequently revisited food images presented in the context of other high-interest stimuli (animals). Previous studies employing other physiological measures also found differences in food-related information processing across genetic subtypes. Using fMRI, Holsen et al. (2008) noted increased activation of the reward system during food picture viewing in participants with the deletion subtype compared to the mUPD. Using event-related potentials, more typical perceptual processing of food pictures was reported in participants with the mUPD than the deletion subtypes of PWS, with the former focusing on the suitability for consumption while the latter examined quantity of food (Key & Dykens, 2008). Thus, our eye tracking data strengthen the evidence for possible distinct genetic contributions to the salience of food stimuli in PWS.

Interestingly, genetic subtype differences were not observed for the informant-based Hyperphagia Questionnaire. No such differences have been noted in previous studies using the same measure either (Dykens et al., 2007, Key & Dykens, 2008). To date, caregivers have been the main source of data regarding food-related behaviors in PWS. Although informative, the questionnaire may be less sensitive to subtle genetic subtype differences than more direct physiological measures. Such discrepant findings across methodologies highlight the need to further explore associations between caregiver reports and other physiological measures of food interests and hyperphagia in PWS.

While yielding novel findings, this study presents several limitations. First, our sample included a wide age range. Even though we did not observe any significant correlations between age and the eye tracking variables, it is possible that the pattern of associations between visual exploration and hyperphagia symptoms could be different in children compared to adults with PWS. While hyperphagia is a life-long concern in PWS, different age groups may represent varied nutritional phases (Miller et al., 2011), and food-related problem behaviors may wax and wane in response to life transitions, or internal or external factors (e.g., move to a group home, distress). Thus, systematic examination of food-related visual exploration patterns in persons of different ages or life conditions will help refine our understanding of hyperphagia in PWS.

Another limitation is the overall amount of gaze data: the threshold for inclusion in the analyses was gaze data availability for at least 50% of the stimulus arrays. However, most participants (64%) provided complete data sets, and although associations between gaze data and hyperphagia scores were stronger in that group, inclusion of individuals with missing data did not alter the overall pattern on findings. Increasing the amount of eye tracking data may increase precision, but our current findings suggest that even with some missing individual gaze data, overall results are representative of participants with PWS. Future studies will need to establish the empirical criteria for the minimal amount of gaze data that would be considered meaningful and reliable in PWS.

In conclusion, this study demonstrates that brief, low-cost eye tracking measures collected during free visual exploration of complex displays can yield direct, objective markers of hyperphagia in PWS. Assessments based on eye tracking offer a number of advantages that complement and extend informant-based reports of food-related behaviors. In particular, data are collected directly from the participant, and due to minimal behavioral and/or cognitive demands, the procedures can be completed across a wide range of ages and intellectual ability. Eye tracking tasks can also be administered repeatedly, allowing for objective evaluation of developmental trajectories using the same instrument across the life span. The passive nature of VET procedures makes it less likely to be affected by social desirability, and in the context of future treatment trials, by placebo effects. For persons with PWS this means that systematic evaluation of food-related interests could begin early in the developmental course, allowing better documentation of the emergence and progression of hyperphagia in cross-sectional as well as longitudinal studies. The correlations between gaze data and caregiver reports of hyperphagia, as well as the acceptable test-retest stability of food-related eye tracking variables, suggest that they could be suitable for use in clinical and research settings, including future treatment studies.

Acknowledgements

The authors have no financial interests or benefits arising from the direct applications of their research. We thank the participants and their families for their support of the study. We are grateful to Elizabeth Roof and Hailee Hunt-Hawkins for assistance in coordinating research visits and collecting hyperphagia data, and to Dorita Jones for help with eye tracking data acquisition.

This work was supported in part by EKS-NICHD Grants U54 HD083211 to the Vanderbilt Kennedy Center (VKC) and R01 HD035684 (EMD). Requests for reprints should be sent to: Alexandra P. Key, Vanderbilt University, 230 Appleton Place, Peabody Box 74, Nashville, TN 37203. E-mail: sasha.key@vanderbilt.edu.

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Figure 1.

An example of a stimulus array, with regions of interest for each object marked by rectangles. Circles and connecting lines depict the visual scan path and distribution of fixations for a single subject.

Figure 2.
The associations between eye tracking measures and hyperphagia severity.

Table 1.

Participant demographic characteristics.

	Deletion		mUPD		Total	
	M	SD	M	SD	M	SD
n (F/M)	29 (12/17)		13 (10/3)		42 (22/20)	
Age (years)	15.33	6.22	15.77	7.61	15.47	6.59
IQ	71.90	17.62	83.15	16.12	75.38	17.77
Hyperphagia	29.21	11.16	27.54	13.48	28.69	11.78
BMI	24.05	6.92	24.72	6.75	24.25	6.79

Table 2.

Summary of the eye tracking data.

	High-Interest Contrast				Low-Interest Contrast			
	Food		Animals		Food		Household Objects	
	M	SD	M	SD	M	SD	M	SD
Total Number of Items Explored								
Deletion (n=29)	22.55	8.11	20.21	11.47	26.34	9.36	23.00	13.19
mUPD (n=13)	19.46	6.54	25.54	13.49	32.69	12.20	27.54	11.45
Total (n=42)	21.60	7.71	21.86	12.22	28.31	10.60	24.40	12.72
Total Duration (ms)								
Deletion (n=29)	6,433.03	3,434.52	6,524.55	4,209.81	8,013.24	3,880.08	6,872.97	3,928.78
mUPD (n=13)	6,662.38	2,014.56	9,359.77	6,159.28	9,643.85	3,687.85	8,729.77	3,922.71
Total (n=42)	6,504.02	3,042.22	7,402.12	4,996.64	8,517.95	3,852.81	7,447.69	3,974.88
Number of Gaze Returns								
Deletion (n=29)	5.97	3.53	4.90	3.91	6.72	4.19	6.69	6.54
mUPD (n=13)	3.85	2.08	7.46	5.36	10.54	4.10	8.23	5.76
Total (n=42)	5.31	3.28	5.69	4.51	7.90	4.48	7.17	6.28