



Prader-Willi Syndrome Mental Health Research Strategy Workshop

March 1-3, 2015

Bethesda, MD

ABSTRACTS OF POSTER PRESENTATIONS

Diagnosing Autism in Prader-Willi Syndrome: ADOS Only Part of the Puzzle?

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Introduction: Prader-Willi syndrome (PWS) is caused by the lack of paternally derived imprinted material on chromosome 15q11–q13 and is characterized by hyperphagia, hypotonia, and mild to moderate intellectual disabilities. The PWS phenotype also consists of many well documented behavioral features that are similar to those behaviors noted in individuals with Autism Spectrum Disorder (ASD) or Autism. These features include repetitive and compulsive behaviors, insistence on routine or sameness, rigid and concrete thinking, tantrums, irritability, and social deficits. Relatively few studies have been conducted that examine the relationship between PWS and ASD though the current literature suggests that nearly 40% of persons with PWS caused by mUPD and 15-18% of persons with PWS due to paternal deletion have a comorbid occurrence of ASD (for review, see Dykens, 2007). Based on the available information, it is difficult to make generalizations across studies as they had relatively small sample sizes and did not utilize the same instruments to assess the occurrence of ASD and Autism. This study examines the relationship between the diagnosis of ASD and Autism based on the ADOS cutoff criteria and the diagnosis provided by a trained clinician. In an effort to distinguish typical PWS behaviors from those that indicate a co-occurrence of ASD, this study also examines differences among those individuals whose assessment diagnosis and clinical diagnosis do not match.

Methods: Participants included 163 (72 males; 91 females) individuals with genetically confirmed PWS between the ages of 4 and 55 years ($M = 16.43$, $SD = 9.95$). Most participants (60.4%) had paternal deletions (Type 1 DEL = 30, Type 2 DEL = 58, Unique DEL = 11), and 34.1% had mUPD. Less than 5% of the participants had more rare subtype profiles (imprinting mutation = 7, Translocation = 1). The participants were assessed by a consistent, trained clinician using Module 3 of the Autism Diagnostic Observation Schedule (ADOS) as part of a larger, longitudinal research project. The ADOS was used to examine the occurrence of ASD and Autism among people with PWS. The ADOS protocols were scored based on the Revised Algorithms published by Gotham, Risi, Pickles and Lord (2007) and severity scores were assigned. At the time of assessment, the clinician (along with trained consensus clinician) also provided her own clinical diagnosis of non-spectrum, ASD, or Autism based on the DSM diagnostic criteria. Primary caregivers of the participants also completed the Vineland Adaptive Behavior Scales – II (Sparrow, Cicchetti, & Balla, 2005), Kaufman Brief Intelligence Test-2 (KBIT-2; Kaufman & Kaufman, 2004), Social Communication Questionnaire (SCQ; Rutter et al., 2003), Repetitive Behavior Scale (RBS-R; Lam & Aman, 2007), and the Scale of Prodromal Symptoms (SOPS; McGlashan et al., 2001).

Results: Preliminary results indicate that, based on ADOS severity scores alone, 76.2% ($n=125$) of those with PWS did not have any indication of ASD, 11% ($n=18$) had a severity score of 7-8 indicating ASD diagnosis, and 12.2% ($n= 20$) had severity scores of 9 or higher indicating an Autism diagnosis. In contrast, clinician classification showed that 87.8% ($n=144$) were Non Spectrum, 7.9% ($n=13$) were ASD, and only 3.7% ($n=6$) were considered to have a comorbid diagnosis of Autism. While the ADOS rating was positively correlated with the clinician rating ($r = .594$, $p = 0.00$), it is clear that many discrepancies still exist between the two methods of classification. The ADOS has often been cited as the “gold standard” tool used to assess ASD, however, it is not a replacement for clinical judgment and corroborating information to distinguish ASD features from psychiatric and developmental issues that are common in those with PWS. Using the ADOS and ADI-R alone may lead to an over diagnosis of ASD in persons with intellectual disabilities.

An in vitro model of cerebral cortex development and function in Prader-Willi syndrome

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Abstract: Using methods developed in our group for directed differentiation of human pluripotent stem cells to cerebral cortex neurons, we are modelling cortical development in Prader-Willi syndrome in vitro. This approach allows us to study multiple aspects of cerebral cortex development, from neurogenesis to neural network assembly and function. To date, we have generated iPSCs from individuals with maternal uniparental disomy of Chr15 and paternal deletions of Chr15. We have successfully differentiated those lines to cerebral cortex neurons and have initiated detailed analyses of neurogenesis, neuronal differentiation and synaptic function in individuals of each genotype. Data will be presented on the use of these systems to model neurodevelopmental disorders, using our ongoing work on the developmental neurobiology of Down syndrome as an example.

Social Cognitive Processes in Play among Children with Prader-Willi Syndrome
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Introduction: The processes involved in pretend play are associated with the positive development of cognitive, emotional, and social skills in children (Russ, 2004). Deficits in play have been identified in children with various developmental disorders, including autism spectrum disorder (ASD). Play deficits in ASD have been shown to be related to delayed social, language, affective, and creativity development. Specifically, children with ASD can express very high rates of repetitive behaviors, which cause their play to be rigid, stereotyped and lack divergent thinking. Although research suggests individuals with Prader-Willi syndrome (PWS) have social deficits and repetitive behaviors similar to that of ASD, play patterns have not been well studied. While hallmark characteristics of PWS include hyperphagia, obsessive-compulsive symptoms, and cognitive delays, understanding social and emotional risk factors for individuals with the disorder is important for planning intervention and increasing quality of life. The purpose of this research is two-fold. In study one, we examined pretend play ability in children with PWS in direct comparison to children with ASD in order to further characterize the PWS social phenotype (Zyga et al., 2014). Currently, in study two, we are examining play ability within PWS subtype, mUPD or DEL, to better understand social cognitive processes across genetic subtype.

Methods:

Study One: 14 children with PWS (mean age = 10.27) and 10 children with ASD (mean age = 10.39), matched for age and IQ, underwent the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2006) as part of a larger, ongoing research project. The ADOS sessions were video recorded and play abilities were assessed by scoring the “Make-Believe Play” activity from ADOS modules 2 and 3 using a modified Affect in Play Scale (APS; Russ, 2004). The modified APS scored participants on scaled measures of comfort, imagination in play, organization of storyline, affective expression in play, frequency of symbolic versus functional play versus no play acts, and number of repetitive actions. In addition, the “Make-Believe Play” activity included both individual and joint play periods, where the child would play with a trained psychologist.

Study Two: Secondary data analyses was conducted on ADOS data collected at two sites (CWRU, Vanderbilt) on 74 children with PWS (mUPD = 29, DEL = 45, mean age = 9.56). The ADOS “Make-Believe Play” sessions were coded using the modified APS scale explained above.

Results & Discussion:

Study One: Results showed that during the individual play period, the PWS group exhibited reduced play ability in comparison to normative data on all five of the original measures within the APS: Comfort (M = 2.07, SD = 0.92), Imagination (M = 1.14, SD = 0.36), Organization (M = 1.14, SD = 0.53), Affective Frequency (M = 0.71, SD = 1.49), and Affective Categories (M = 0.36, SD = 0.63). In relation to the modified scores, the PWS group spent 65% (SD = 28) of time in No Play, 31% (SD = 24) of time in Functional Play, and 3% (SD = 8) of time in Symbolic Play. Further, the PWS and ASD groups did not significantly differ in play abilities within both individual and joint play periods and, overall, all original scores within the APS increased during the joint play period and time spent in No Play activities decreased in both groups. Within the PWS group, all original APS scores significantly increased with the addition of a play partner.

Study Two: Preliminary results suggest that the mUPD and DEL subtypes have similar deficits across the domains of imagination, organization of the narrative, comfort in play, affective expression, and variety of affect expressed during the play period. However, results showed that the mUPD subtype showed significant improvements in Affective Frequency (t = -2.637, p = 0.019), Affective Categories (t = -3.467, p = 0.003), Organization (t = -3.162, p = 0.006), and Comfort (t = -4.392, p = 0.001) from individual to joint play, which is similar to the gains the ASD group made within study one. Conversely, the DEL subtype showed gains in Organization (t = -2.920, p = 0.013), Comfort (t = -3.950, p = 0.002), and Imagination (t = -2.889, p = 0.014), and not in affective expression abilities. Overall, these results suggest that play facilitation allowed for increases in affective domains within the mUPD subtype, which is similar to the findings in ASD, however, in the DEL group, this same facilitation allowed for increases in domains relating to more cognitive processes, specifically imagination.

Social communication skills in children with Dup15q syndrome
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Background: Duplication of 15q11.2-q13.1, or Dup15q Syndrome, is one of the most common copy number variations (CNV's) associated with autism spectrum disorders (ASD). The Dup15q phenotype is characterized by social communication deficits, intellectual disability, impaired speech, hypotonia, motor delays, and epilepsy (Battaglia, Parrini & Tancredi, 2010). Most studies have focused on diagnostic categorization of this cohort rather than performing a deeper characterization of the social communication, cognitive, and language profiles of these children. As a result, to date, there has been no research on targeted behavioral interventions for this population. An potential intervention model for the specific deficits found in Dup15q syndrome is JASPER (Joint Attention, Symbolic Play, Engagement and Regulation). JASPER is a play-based intervention focused on joint engagement in play routines with the therapists as a platform for developing play and communication skills (Kasari, 2006; 2014).

Objectives: To determine whether there are distinctive features of the social- communication deficits found in children with Dup15q syndrome and, if so, whether these characteristics could guide more targeted interventions for population. A subset of the children enrolled in this characterization study also participated in JASPER intervention sessions, to evaluate the feasibility and effectiveness of JASPER in a pilot sample of children with Dup15q syndrome.

Methods: In this ongoing study, children ages 18 months to 10 years with Dup15q syndrome are recruited from the Dup15q Alliance registry as well as the national Dup15q clinics, and they undergo a comprehensive, developmentally informed clinical phenotyping battery. We compare cognition, expressive and receptive language, social communication, play, and motor ability in this cohort (both intersitial and isodicentric cases) to that of an age matched cohort of children with non-syndromic ASD drawn from several existing studies in our UCLA Center for Autism Research and Treatment (CART). Measures include: Autism Diagnostic Observation Schedule (ADOS), Mullen Scales of Early Learning and/or Stanford- Binet Intelligence Scales, Early Social Communication Scale (ESCS), and the Vineland Adaptive Behavior Scales. A subset of these children also received JASPER intervention sessions. Intervention participants received 16 JASPER intervention sessions over 8 weeks. Sessions were 30-45 minutes in length and occurred twice per week.

Results: Thus far, 11 children with Dup15q syndrome have undergone comprehensive phenotyping. Age range is 22 months to 19 years, 5 males . 10/11 had isodicentric 15q [idic(15)], 11/11 had global developmental delay and/or intellectual disability. 9 children had developmental levels appropriate for ADOS testing and all of these children (9/9) met criteria for ASD on the ADOS. Common, consistent characteristics that distinguished this group from those with non-syndrome ASD included: Expressive language delays greater than receptive language delays, verbal IQ lower than nonverbal IQ, significant gross motor delays (>2 standard deviations from normal), limited eye contact but consistent use of facial expressions directed to the examiner during the ADOS, *failure to initiate* joint attention on the ADOS and ESCS, and consistent *evidence of response* to joint attention on the ADOS and ESCS. To date, 4 participants have completed the pilot JASPER sessions. All participants made meaningful gains in the amount of time spent engaged from the first session compared to the last session, as well as increased communication bids.

Conclusions: A distinctive social communication profile is emerging in children with Dup15q syndrome, with impairments in motor function, visual attention, and initiation of engagement that may prevent the development of appropriate language and social communication behaviors. Targets for intervention include expressive language, initiation of joint attention, and overall attention to social cues in the environment. Our efforts in the identification of social-communication patterns in genetically defined subgroups can be expanded to the investigation of other related syndromes, in order to identify and design targeted, personalized interventions for these children.

Human-centred design of 'TASTER', a cognitive training game for children with Prader-Willi syndrome.

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Abstract

Resistance to change in individuals with PWS, which often triggers temper outbursts, has been linked to deficits in task switching. The TASTER project aims to develop a prototype video game to train task switching in children with PWS. The game is being designed using a human-centred design process involving 10 children with PWS (7 to 15 years). Initial telephone interviews were conducted with parents to determine the current gaming habits of the children. 15 games were then selected, representing a range of gameplay types, control systems and graphical styles. Children play tested these games over a period of 14 days, recording their progress by completing web-based questionnaires. Initial results suggest a preference for the following: puzzle games, particularly shape-based puzzles; games with a clear, simple goal; touch-based control systems; visual cues rather than written instructions. A domain analysis of task switching mechanisms in video games was carried out. Influenced by research in cognitive neuroscience, this analysis focused on action games, which some studies have shown are particularly effective in training task switching. Future work will use the insights gathered – both from the human-centred design process and from the research-led domain analysis – to inform the development of the prototype game. The gameplay, user interface, graphics, control system, and distribution platform of TASTER will all be directly influenced by the children's feedback, thus maximising the role played by them in the design. Behavioural and physiological indices that have been linked to increased learning transfer will be measured during play testing sessions, for both design and validation purposes. The design process is ongoing, and the game will be engineered in a highly modular fashion so that design changes can be made throughout development. As such, design and implementation are not viewed as two discrete activities, but as simultaneous processes.

MRI study of neural endophenotypes in Prader-Willi Syndrome (PWS).

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Beyond the core features of appetite dysregulation, hypotonia, and growth and sex hormone deficiency, PWS is associated with mild to moderate intellectual disability, and a range of social and behavioural difficulties, including temper tantrums, a need for routine, repetitive and ritualistic behaviours, and impaired social functioning, as well as propensity to specific psychiatric disorders. These diverse characteristics suggest widespread atypical brain development and functioning in PWS and aberrant activity across distributed neural networks.

Advances in magnetic resonance imaging (MRI) offer the opportunity for detailed study of the neural architecture and connectivity of the brain. Multiparameter mapping (MPM) MRI sequences can be used to consider both macrostructure and tissue microstructure across the whole brain, and provides quantitative measures which can afford insight into myelin and iron content in neural regions. Greater understanding of the integrity of connections in the brain, as indicated by diffusion tensor imaging (DTI), is possible when these methods are combined. Resting state fMRI can further inform such investigations, looking at functional connectivity across the brain.

Participants with a genetic diagnosis of PWS, aged between 18-28 years, took part in tests of cognitive ability, including the WAIS-IV (providing indexes of verbal comprehension, perception reasoning, processing speed and working memory) and tests of Theory of Mind (ToM) and set-shifting. Each participant underwent one scanning session lasting approximately one hour, comprising 3 MRI sequences: MPM, DTI and a multiecho EPI resting-state functional MRI. Data relating to genetic subtype, behaviour, and social functioning and psychiatric state were also collected, including from informants (parents and carers). The neuroimaging data will be compared to that obtained from a group of similarly aged typically developing young adults. To date 25 participants with PWS have been recruited to the study. Recruitment is ongoing.

The approach to analysis will consider the connectivity of neural circuits relevant to the difficulties experienced by many individuals with PWS, informed by investigations in the typically developing control population. This will enable further exploration of the effects of differences in this circuitry on phenotypic variation in PWS. The aim is to use this data to design interventions that are built around a detailed understanding of underlying mechanisms and to be able to use these techniques to investigate the effectiveness of pharmacological, psychological or other interventions aimed at reducing problem behaviours.

Learning by Observation but not Learning by Doing is impaired in Prader-Willi syndrome

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Background. New competencies may be learned through active experience (*learning by doing*) or observation of others' experience (*learning by observation*). Both learning processes involve sequencing abilities, planning, working memory, response inhibition, cognitive flexibility and attentional abilities, with the only exception of the social component required by the observational learning. Observing another person performing a complex action accelerates the observer's acquisition of the same action and limits the time-consuming process of learning by doing, thus it represents a powerful learning mechanism. We compared learning by observation and learning by doing in individuals with Prader-Willi syndrome (PWS), in the hypothesis that PWS individuals could show more difficulties to learning by observation than to learning by doing because of their specific difficulty in effectively interpreting and using social information.

Methods. The performance of twenty-four PWS individuals was compared with that of mental age- and gender-matched twenty-eight typically developing (TD) children on tasks of learning a visuo-motor sequence by observation or by doing. To determine whether the performance pattern exhibited by PWS participants was specific to this population or a non-specific intellectual disability effect, we compared the PWS performances with those of a third mental age- and gender-matched group of individuals with Williams syndrome (WS).

Results. PWS individuals were severely impaired in detecting a sequence by observation, were able to detect a sequence by doing, and became as efficient as TD children in reproducing an observed sequence after a task of learning by doing. Interestingly, the learning pattern of PWS was reversed in comparison to that of WS individuals.

Conclusions. The observational learning deficit in PWS individuals may be rooted, at least partially, in their incapacity to understand and/or use social information. The characterization of their cognitive phenotype may allow for targeted interventions aimed at stimulating and improving learning performances.

A Mindfulness-Based Intervention for Self-Management of Verbal and Physical Aggression by Adolescents with Prader-Willi Syndrome

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Abstract

Many children and adolescents with Prader-Willi Syndrome (PWS), a neurodevelopmental genetic disorder, exhibit a wide range of maladaptive behaviors including impulsivity, excessive stubbornness, temper tantrums, verbal and physical aggression, skin picking, moodiness and irritability, and emotional lability, among others. There is a dearth of clinical and research literature on the treatment of maladaptive behaviors in adolescents with PWS. We evaluated the effectiveness of a mindfulness-based intervention, *Meditation on the Soles of the Feet* (SoF), in enabling three adolescents with PWS to manage their verbal and physical aggression. These adolescents learned to rapidly shift the focus of their attention from the aggression-triggering event to a neutral place on their body, the soles of their feet. When compared to baseline levels, verbal aggression decreased to minimal levels following mindfulness-based practice and physical aggression was virtually eliminated. Follow-up data showed that gains were maintained for at least a year. Our results indicate that the SoF procedure was effective with these three adolescents with PWS and may be equally effective with others.

Appetite-modulated homeostatic, reward, and prefrontal circuitry activity associated with obsessive-compulsive, perseverative, and food-related problem behavior in individuals with Prader-Willi syndrome

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Background: In the psychological profile of Prader-Willi syndrome (PWS), common characteristics include those viewed largely as unrelated to hyperphagia [obsessive-compulsive behavior and related repetitive/ritualistic behaviors (stereotypical behavior, self-injurious behavior); difficulty changing behaviors in response to feedback (perseverative errors)], as well as significant maladaptive behaviors specifically associated with food and hyperphagia. Previous studies in non-PWS populations (i.e., OCD, autism) suggest the former are supported by deficits in key neural circuits encompassing the caudate and orbitofrontal cortex (OFC), while our recent studies suggest hyperphagia in PWS involves dysfunction in the balance between homeostatic (hypothalamus)/reward (nucleus accumbens, amygdala, hippocampus, medial prefrontal cortex) and prefrontal inhibitory (OFC, dorsolateral prefrontal cortex) regions. However, the extent to which these seemingly disparate phenotypic profiles (OCD-like; food-related) might be associated, and brain circuitry involved in these relationships, have not been explored. In this preliminary study, we explored relationships between caregiver-reported obsessive-compulsive, repetitive, and food-related problem behavior, perseverative behavior during a computerized neuropsychological task, and brain activity in response to food images in individuals with PWS.

Methods: Participants included individuals with PWS ($n=14$; 2M, 12 F; mean age = 24.3; mean BMI = 32.1) and their caregivers. Caregivers completed a set of standardized questionnaires [Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Repetitive Behavior Scale (RBS), Food-Related Problem Questionnaire (FRPQ)]. Individuals with PWS completed a computerized version of the Object Alternation Task, a neuropsychological measure of perseveration. Individuals with PWS were also scanned using functional magnetic resonance imaging (fMRI) to measure blood-oxygen-level-dependent (BOLD) activity in response to food and non-food images before (*premeal*) and after (**postmeal**) a 500 kcal meal. ROIs were: hypothalamus (HYPO), nucleus accumbens (NAc), amygdala (AMYG), hippocampus (HIPPO), medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC). Anatomic overlays were used on the statistical maps of each individual to acquire signal change values across specific ROIs based on activation clusters within ROIs, significant at the voxel-level, family-wise error (FWE)-corrected. Values indicated the degree of change in BOLD signal detected between food and nonfood images, and are expressed in terms of percent signal change (PSC). Average PSC values (beta weights averaged across all voxels within an anatomical region) were obtained using the REX toolbox for SPM8 and exported to SPSS for correlational analysis using Pearson correlations (statistical threshold: $p<0.05$, unless otherwise noted).

Results: Caregiver-reported repetitive behavior (total number of repetitive behaviors on the RBS) was negatively related to *premeal* food-cue elicited brain activity in the HYPO ($r = -0.63$), NAc ($r = -0.54$), and AMYG ($r = -0.54$), while obsessive-compulsive behavior severity (subscale scores on the Y-BOCS) was positively related to **postmeal** food-cue-elicited brain activity in the NAc ($r = 0.64$), AMYG ($r = 0.76$), MPFC ($r = 0.62-0.67$), and OFC ($r = 0.62-0.70$). Perseverative errors were positively correlated with **postmeal** food-cue-elicited brain activity in the HIPPO ($r =$

0.67) and OFC ($r = 0.52$, $p=0.058$). Caregiver-reported food-related problem behavior (FRPQ composite negative behavior subscale) was positively associated with **postmeal** food-cue-elicited brain activity in the HYPO ($r = 0.74$), NAc ($r = 0.51$, $p=0.07$), AMYG ($r = 0.65-0.80$), and DLPFC ($r = 0.57$).

Conclusions: These findings provide evidence of strong associations between non-food-related phenotypic behaviors (OCD-like, repetitive/stereotypic, perseverative) and activity in brain regions involved in energy balance, reward, and inhibitory control in individuals with PWS. These associations appear to be modulated somewhat by internal appetitive state (premeal hunger, postmeal satiety), and collectively suggest that postmeal deficits in satiety in PWS may potentiate non-food-related maladaptive behaviors. Future studies should include larger samples of individuals with PWS, as well as BMI-matched controls without PWS, in order to achieve adequate power to detect relationships and determine specificity of associations to the PWS psychological profile. Additionally, studies measuring brain activity using fMRI during behavioral/cognitive paradigms (in addition to a food-cue task), ideally measured prospectively in the context of a randomized control trial of a novel pharmacologic, lifestyle, or neuromodulation therapy for PWS, would offer insight into dual circuitry involved in food- and non-food-related behaviors in PWS, and neural plasticity in this circuitry response to treatment.

Mood and behavioral activation associated with SSRI medication in children, adolescents and young adults with PWS

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Background: Mood and behavioral activation (MBA) is a known risk factor associated with the use of antidepressant medications of the selective serotonin reuptake inhibitor (SSRI) type. At starting doses of medication in PWS persons, there may be transient improvement in symptoms. Then, the first indication of MBA in PWS is increased intensity of typical excessive/repetitive behaviors, including food acquisition, perseveration, tantrums and picking behaviors. Mistaking early signs of mood activation as the recurrence of target symptoms, prescribers often increase medication dose, which in turn exacerbates symptoms. More severe symptoms of MBA include episodic impulsive suicidal, homicidal, self-injurious, or aggressive behaviors. In the extreme, MBA can be associated with psychosis. The treatment of choice for MBA is the discontinuation of the iatrogenic agent. Here, the serum half-life of these agents determines how fast the medication can be tapered safely, because abrupt discontinuation of SSRI's can precipitate a withdrawal syndrome characterized by further mood instability. MBA can occur at any age, although it is more common among adolescents and young adults with PWS.

Methods: This presentation is informed by literature review and the authors' longitudinal clinical experience in outpatient, inpatient and residential treatment settings. Chart review informs the clinical data.

Results: Among the 25 individuals with PWS (8 UPD; 9 DEL; 4 subtype undetermined; 1 atypical), ages 11-27 years, who displayed symptoms of mood activation associated with SSRI treatment, decreasing the medication resulted in improvement. However, in the referred population, very few individuals remained medication free. The majority of individuals (23/25) went onto require mood stabilizers and/or atypical antipsychotic medication to manage mood and behavior. In several cases, depressive symptoms were successfully treated with low doses of SSRI medication (equivalent of fluoxetine 5 mg or citalopram 10 mg). Neither age, gender, nor genetic subtype predicted mood activation, withdrawal emergent effects, or ongoing mood instability.

Discussion: Despite the growing awareness of mood activation associated with SSRI use as a problem in young patients, the authors continue to see this phenomenon as a reason for psychiatric deterioration, crises and hospitalization in PWS. In addition, prescribing or recommending these medications seems to be done without an adequate description of the behaviors associated with mood activation in PWS. Because behavioral changes can come on gradually and begin weeks or months after the initiation or increase in dose, families commonly fail to connect the behavioral changes with the medications and may suffer many months of crisis before the association is made. This relationship is further masked by the symptoms being an increase in intensity of syndromic behaviors. Psychiatrists familiar only with the symptoms of mood activation in typical persons do not necessarily recognize increased food seeking, increased rectal picking and increased perseveration as early signs of MBA. Communicating these risks to families and carers will enhance early recognition and management of these adverse treatment emergent effects.

A proposed mechanism of mood and behavioral effects in PWS individuals receiving selective serotonin reuptake inhibitors (SSRI's)

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BACKGROUND: The neurochemical mechanisms underpinning the etiology of the complex psychiatric/behavioral phenotype associated with PWS are not yet known, but abnormalities in the serotonin and GABA systems are suspected. Faulty editing of the serotonin 2C receptor (HTR2C) and a decrease in GABA_A receptors have been reported. SSRI's have been used with variable outcome to manage the repetitive and ritualistic behavior, skin picking, temper outbursts, anxiety and mood disturbances associated with this phenotype. Mood and behavioral activation (MBA) is a serious consequence of SSRI treatment that increases psychiatric morbidity and level of service.

Selective serotonin reuptake inhibitors (SSRI's) have distinct pharmacological mechanisms at low and typical doses. *Low doses* of SSRI decrease anxiety through INDIRECT, fast action by stimulating glutamatergic neurons to synthesize and release the neuro-steroid, allopregnanolone (ALLO). ALLO selectively activates GABA_A receptors which, in turn, inhibit glutamatergic neurons resulting in anti-anxiety, anti-aggressive and mood stabilizing effects. *Typical doses* of SSRI have a DIRECT action on serotonin transporter and receptors resulting in increased levels of serotonin or activation of inhibitory GABA_A receptors. Serotonin receptors are G-protein coupled, working through second messengers, which in turn affect transcription factors. It takes 4-6 weeks to experience the full effects of SSRI treatment. Treatment with high dose SSRI's carries risk for MBA in all populations.

RESULTS: SSRI's increase serotonin with differential effects on receptors, HTR2A (activation)>HTR2C (inhibition) as a function of age. During the developmental period, serotonin receptors HTR2A and HTR2C come "on-line" at different times, as measured in post mortem studies by normalized mRNA expression in the human prefrontal cortex. HTR2A is expressed in excitatory (glutamatergic) pyramidal neurons; HTR2C is expressed in inhibitory (GABAergic) interneurons. Recommended starting doses of SSRI can cause mood and behavioral activation during the developmental period due to an imbalance of availability of HTR2A (activating) > HTR2C (inhibitory) serotonin receptors whose timing of expression is genetically programmed with a peak disparity in adolescence and young adulthood. In neurotypical individuals, there is a bias toward activation. In PWS, abnormal editing of HTR2C receptors may lead to diminished efficacy, so there is an overwhelming bias toward activation that may persist outside the developmental period. Further, there is a decrease in GABA tone in PWS that results in inadequate inhibitory feedback resulting in MBA.

DISCUSSION: Low dose SSRI medication may have a beneficial effect on some of the characteristics of the PWS phenotype that are related to underlying anxiety and behavioral dyscontrol. An optimal clinical response may occur at low doses of SSRI that are mediated through effects at the GABA_A receptor and not through the serotonin system. Typical doses of SSRI's may precipitate MBA in PWS due to the dysequilibrium of serotonin receptor effects on already diminished inhibitory GABA_A action. Clinical studies suggest that MBA is managed by reducing the dose of SSRI, blocking excitatory serotonin receptor (HTR2A) with an atypical neuroleptic (second generation antipsychotic), and/or initiating treatment with GABA agonists, such as anticonvulsants or lithium. The antiepileptic action of anticonvulsants is related to their GABAergic effects. More research is needed into the role of GABA in PWS and the efficacy of GABA agonists in managing aspects of the PWS phenotype.

The nature of temper outbursts in PWS

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Background

Compared to parents of children with other developmental disabilities parents with a child with PWS report higher rates of parental control, worry, anger and marital conflict and lower levels of parental consistency (1). The increased stress (2) and cost (3) associated with caring for a person with a disability correlates positively with the level of behavioural problems.

Up to 97% of people with PWS experience temper outbursts (4). A significantly higher rate than is seen in the typically developing population or in people with an intellectual disability of mixed or unknown aetiologies (4,5).

Unfortunately, there are no interventions of established efficacy to manage these behaviours. Rather families often have to adjust their life to accommodate outbursts. Although there have been a number of descriptive studies, there have been few that have investigated the pathogenesis of PWS outbursts.

Understanding the nature of temper outbursts, particularly the provocations or antecedents, may help elucidate possible causal mechanisms.

A factor analysis of PWS symptomatology showed hyperphagia to load separately to temper outbursts, suggesting the causal mechanisms for these behaviours may not be directly related. One way to investigate this is to examine the age of onset of these two behaviours. If they occur concurrently than it may be that outbursts are derivative of hyperphagia. Alternatively, if they occur independently of one another than it is likely that they have arisen from different causal mechanisms.

Aims

- 1. To investigate possible shared qualities in the nature of PWS temper outbursts including: provocations, behaviours and setting events.**
- 2. To determine whether the onset of PWS outbursts and hyperphagia occur concurrently or independent of one another.**

Method

Participants: 103 caregivers of a person with PWS aged 1 to 64 years.

Measure: Based on findings from a pilot study. A survey was designed for the purpose of this study and included questions pertaining to the frequency, duration, provocations, behaviours and management of outbursts.

Statistical analysis: A cross-sectional design and non-parametric analyses were employed to investigate changes in the frequency and duration of PWS outbursts over the course of development. Descriptive analysis was used for provocations, behaviours and management.

Results

86% of caregivers reported that temper outburst and hyperphagia onset occurred independently of one another: 68% reported outbursts occurred before hyperphagia, 18% reported hyperphagia occurred before outbursts and 14% reported the two behaviours occurred around the same time. People with PWS due to UPD display more outbursts than those with deletion. Children displayed temper outbursts more frequently than other age groups, though adolescents displayed outbursts for a longer duration and caregivers reported adolescence to be a time of heightened outburst severity.

The most effective behavioural interventions were those that allowed the individual space and time to calm down, while the least effective were those that tried to intervene with the individual whilst upset or angry.

Provocations can be grouped in to three categories: food insecurity, difficulty with changes and esteem, independence or injustice.

Commonly reported setting events included: Being tired or ill, celebrations such as Christmas, times of transitioning and developmental stages of independence (e.g. discovering rights, wanting to move out)

The most commonly reported behaviours during a temper outburst were: raising voice, arguing, crying, screaming, stomping off, slamming doors and talking out loud to self.

Conclusion

Even though food is a common provocation to PWS temper outbursts our findings suggest that the physiological causal mechanisms may be different.

It appears that temper outbursts decrease in frequency though increase in duration with age, with adolescence being a time of heightened outbursts.

Some of the most commonly reported provocations to and behaviours displayed during PWS temper outbursts are consistent with those seen before and during temper tantrums displayed by typically developing (TD) toddlers.

In relation to behavioural interventions, PWS caregivers most commonly reported that there are no effective ways to reduce the likelihood of a PWS outburst once a person becomes upset or angry and any attempts made to intervene with the individual are more likely to be ineffective than effective, rather it is better to give the person time and space to calm down. We hypothesise that this is because people with PWS have a discrepancy between cognitive function and emotional maturity with emotional maturity being much more delayed than cognitive function.

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Reduced GABA in PWS is associated with internalising problems: A 1H-MRS study

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Background

A recent trial of exogenous OT on PWS behaviours found the only effect OT had on any PWS behaviour was an increase in temper outbursts, suggesting there is a physiological abnormality that predisposes individuals with PWS to temper outbursts. Within the typically developing population, impulsive aggression occurs when there is an imbalance between the “top-down” control modulating or suppressing aggressive behaviours and excessive “bottom-up” “drives” triggered or signalled by limbic region (1).

In line with this, an fMRI study found that during a task-switching activity individuals with PWS did not display activation or deactivation in the anterior region of the ventromedial prefrontal cortex, as is commonly seen in the typically developing population. The authors suggested that the lack of activation in this region might be associated with dysfunction of the default mode network (DMN) (2).

The DMN is a group of brain regions that are active when a person is awake but not actively perceiving information from the outside world. When an emotional stimulus is perceived activity in the DMN reduces as Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the central nervous system increases (3). This suggests that when a person switches from resting state to perceiving emotional input GABA increases in the DMN, inhibiting activity in this region.

Based on these findings, it may be that people with reduced GABA levels have more difficulty deactivating the default mode network in order to take in new information, leading to difficulty in task switching.

The PWS critical region (15q11-q13) contains GABA-A subunit gene clusters.

Though these gene are biallelically expressed within the typically developing population, there appears to be a paternal expression bias of GABRB3 in Prader Willi syndrome.

GABA-A receptors bearing benzodiazepine-binding sites are reduced in the cingulate, frontal and temporal cortices and insula in adults with PWS (4).

Plasma GABA levels are increased in people with PWS compared to ID and obese control groups(5)

The anterior cingulate cortex (ACC) links the hippocampus to the prefrontal cortex. After finding hypofusion in the anterior cingulum (6) and cingulate gyrus (7), Mantoulan and colleagues hypothesised that these regions may be associated with deficits in emotional liability and control, theory of mind and empathy in PWS (6).

Aim: The present study aimed to use 1H MRS to investigate the concentration levels of GABA in the brains of individuals with PWS. It is hypothesized that GABA will be reduced in people with PWS compared to typically developing controls. In addition, we will explore glutamate levels given it is the major excitatory neurotransmitter of the brain and a precursor of GABA.

Method

Participants: 13 people with PWS and 14 age- and gender-matched controls

Measures:

- Wechsler Abbreviated Scale of Intelligence (WASI)
- Developmental Behaviour Checklist Adult (DBC-A) and Primary Carer versions (DBC-P)
- ¹H MRS: Metabolites were acquired using a 3 x 3 x 3 voxel within the ACC.

Statistical analysis:

- 2 x MANOVA's were conducted to compare individuals with PWS to controls and individuals with PWS with clinically significant behaviour problems to controls on 2 metabolites: GABA and glutamate.
- Pearsons correlation was used to investigate the association between GABA levels and DBC total, DBC subscale mean item scores and temper tantrums.

Results

- There was no significant difference between individuals with PWS and controls for GABA or glutamate
- GABA was significantly lower in PWS participants with clinically significant behavioural problems compared to PWS participants without clinically significant behavioural problems ($P=.16$) and compared to typically developing controls ($P=.04$).
- There was a negative correlation between GABA and DBC Total Behaviour Problem Score ($r=-.62$; $P=.17$) and GABA and two DBC subscales: depression ($r=-.68$; $P=.15$) and social relating ($r=-.82$; $P<.01$).
- There was no association between GABA and tantrums.

Conclusion

The results from this study suggest that GABA may be associated with behaviour problems in PWS, specifically depression and social relating.

Higher rates of depression than psychosis in PWS (8)

Several studies have found reduced GABA in the ACC of individuals with depression(5, 9, 10). Our findings support and extend this hypothesis into the PWS population.

While, there was no association between GABA and tantrums there was a negative association between GABA and the social relating subscale of the DBC, suggesting that reduced GABA in the ACC may be play a role in the social difficulties commonly seen in PWS.

Though, GABA-A receptors have been found to be reduced in the ACC of people with ASD, there are no known studies to date that have investigated GABA concentration levels in the ACC of people with ASD.

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Developmental trajectory of temper outburst and aggression in PWS

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Background

Aggression is one of the most common forms of challenging behaviour displayed by people with an intellectual disability (1). It can lead to serious injury (2), reduced access to community support and participation (3), social isolation (4) and decreased quality of life. Temper tantrums and aggression are sometimes considered interchangeable during childhood. However, we distinguish these behaviours in the following way: aggressive behaviours are directed toward others or objects, whereas temper tantrums do not necessarily involve actions directed toward others. Up to 97% of people with PWS experience temper outbursts (5). A significantly higher rate than is seen in the typically developing population or in people with an intellectual disability of mixed or unknown aetiologies (6-8). Compared to typically developing children and children with other developmental disabilities, children with PWS display more rapid onset of outbursts in early childhood more severe outbursts and continue displaying outbursts to a later age (9) To date there are no known studies that have evaluated the developmental trajectory of temper outbursts or aggression in PWS.

Method

Participants: 51 with PWS and 433 with an intellectual disability due to other causes.

Measures: The Developmental Behaviour Checklist (DBC) [(10, 11)] was used to measure: Temper tantrums (e.g. stamps feet, slams doors); Verbal aggression (e.g. abuse, shouts at others); Physical aggression (e.g. kicks, hits others).

Statistical analysis: Locally Weighted Scatterplot Smoothing (LOWESS) was used to graphically present the mean trajectories with increasing age of the three aggression-indicating DBC item scores.

Random effects (repeated measures) regression was used to model these trajectories within the two groups as functions of age-defined stage of development (childhood, age 4 to 12 years; adolescence, age 12 to 19 years; young adulthood, age 19 to 30 years; older adulthood, age above 30 years).

Results

Compared to the control group, the PWS group scored significantly higher on tantrums, verbal and physical aggression. For the control group physical aggression and tantrums decreased with age, while verbal aggression remained constant. For the PWS group physical aggression and tantrum scores did not change overtime with age and verbal aggression was higher in adolescence than in childhood. For the PWS group, there was a trend toward an increase in tantrums from childhood and a decrease in later years, however this was not significant.

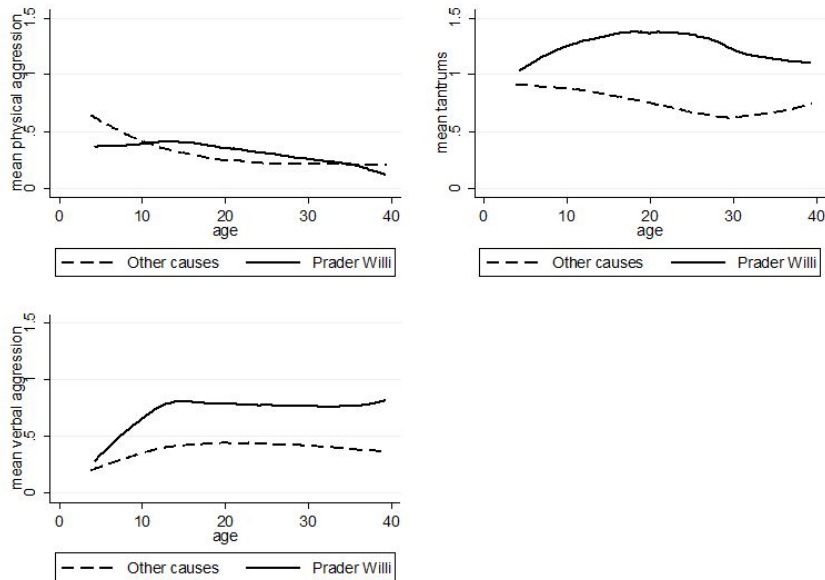


Figure 1: Lowess mean curves for physical aggression, verbal aggression and tantrums with age.

Conclusion

Our findings suggest that temper outbursts displayed by people with PWS are distinct from those seen in other populations with intellectual disability. Unlike the ID due to other causes groups, physical aggression and temper tantrums did not decline over the course of development for people with PWS and verbal aggression increased from childhood to adolescents. The lack of decline in tantrums and physical aggression is likely to be associated with the lifelong temper outbursts or rage attacks seen in this population (7).

It is likely that there is a physiological abnormality that arises from the PWS genotype and predisposes individuals with PWS to these behaviours. We have previously hypothesized that people with PWS have a discrepancy between emotional development and mental age, with emotional development being within similar range to a typically developing 2–3 year old and it is this delay in emotional development that predispose individuals to lifelong outbursts.

In line with previous findings, the LOWESS curve suggests that, for people with PWS, temper tantrums increase from childhood, peaking in early adulthood and possibly decline from then on (5, 12)

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Behavioral treatment of obsessive-compulsive symptoms in youth with Prader-Willi Syndrome

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Abstract:

Prader-Willi Syndrome (PWS) is a genetic disorder characterized by dysfunctional food behaviors (e.g., hyperphasia, food hoarding), motor and speech impairments, delayed puberty, and cognitive delays. In addition to the physical and cognitive symptoms, individuals with PWS often exhibit psychiatric symptoms such as behavioral outbursts, emotional lability, aggression, stubbornness, anxiety, and obsessive-compulsive symptoms. The latter can be particularly prominent in many individuals with PWS, and often lead to significant impairment. Despite this, there are no standardized treatment protocols for treating obsessive-compulsive symptoms in youth with PWS.

Pharmacological treatment is often partially effective, but can lead to significant and unpredictable tolerability issues and side effects. Cognitive-behavioral therapy (CBT) is effective in treating obsessive-compulsive symptoms in typically developing youth. However, its effectiveness for youth with PWS has not been sufficiently demonstrated.

In this study, we tested the application of a CBT protocol adapted for treating anxiety and obsessive-compulsive symptoms in youth with PWS. Participants were three youth with PWS and obsessive-compulsive symptoms. After receiving 12 sessions of CBT, all participants displayed significant improvement in obsessive-compulsive symptoms, as well as behavioral issues and anxiety. Implications of findings, treatment recommendations, and well as avenues for further research are discussed.

***MAGEL2*-associated disorder, a Prader-Willi-like syndrome with high prevalence of autism spectrum disorder**

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MAGEL2 is one of the protein coding genes in the Prader-Willi syndrome (PWS) domain on chromosome 15q11.2. Truncating point mutations of the paternal copy of *MAGEL2* cause a disorder that is best described as Prader-Willi-like, but occasionally may meet full clinical criteria for PWS. Here, we summarize the clinical features of 10 individuals with truncating *MAGEL2* mutations. We will discuss the clinical overlap with PWS, but also highlight those features that appear to be specific to either PWS or *MAGEL2*-associated disorder. Nine of the ten individuals with truncating *MAGEL2* mutations have been diagnosed with autism spectrum disorder, and one is reported to have autistic features. Detailed information about these individuals' behavioral and autistic phenotypes has not been assessed to date.

Understanding the molecular network of MAGE-L2 protein may provide us with a list of candidate genes for related neurodevelopmental and behavioral disorders. We will discuss new, unpublished findings of a protein that is part of the MAGE-L2 protein complex. We identified seven individuals with *de novo*, loss-of-function mutations in the respective gene. Affected individuals manifest a high prevalence of developmental delay/intellectual disability, hypotonia, autism spectrum disorder, aggressive behaviors, and epilepsy.