2021 Gatlinburg Conference Symposium Submission

EXAMPLE

Symposium Title: Novel approaches to behavioural phenotype research in genetic syndromes associated with intellectual disability

Chair: Jane Waite

Discussant: Jane Roberts

Overview: Improved cytogenetic analysis in recent years has led to an exponential increase in the number of research publications exploring gene-behaviour relationships in rare genetic syndrome groups associated with neurodevelopmental difference. Such behavioural phenotype research has to date provided us with a breadth of research that describes 'commonalities' in behaviour across syndrome groups (e.g. ADHD characteristics) and specific typographies of behaviour within syndrome groups (e.g. 'cat-like' cry in Cri du Chat syndrome; Hodapp & Dykens, 2001). However, to fully explore the complexity of behaviour beyond the descriptive, taking into account indirect relationships and gene-behaviour-brain associations, behavioural phenotype research needs to be theoretically driven, developmentally orientated, and multimethod in its approach to understanding the multifaceted aetiology of behaviours in rare syndrome groups (Hodapp & Dykens, 2005). The presentations in this symposium have adopted a developmental focus using novel methodologies to detail salient aspects of behaviour, sociability, cognition, sleep and autism profiles associated with genetic syndromes. The first presentation outlines the use of informant-report measures with enhanced specificity to explore behaviours in children and adults with SATB2-associated syndrome beyond subscale level. The second presentation details the novel use of radio frequency identification technology to study the social profile of poor sleep in Angelman and Smith-Magenis syndromes. The third presentation explores behavioural variability between individuals with fragile X syndrome at the genotype level via single nucleotide polymorphisms variant analysis. The fourth and fifth presentations evaluate core features of social-cognition (gaze following and overimitation) via the use of eye tracking and direct behavioural tasks in order to further understand atypical patterns of autism in children with fragile X syndrome and Cornelia de Lange syndrome. Together, these presentations highlight the need for innovative research strategies to uncover the behavioural nuances associated with rare syndrome groups, with a view towards implementing effective and appropriate behavioural interventions.

Hodapp, R. M. & Dykens, E. M. (2001). Strengthening behavioral research on genetic mental retardation syndromes. American Journal on Mental Retardation, 106(1), 4-15.

Hodapp, R. M. & Dykens, E. M. (2005). Measuring behavior in genetic disorders of mental retardation. Mental Retardation and Developmental Disabilities Research Reviews, 11(4), 340-346.

Paper 1 of 5

Paper Title: The behavioural phenotype of SATB2-associated syndrome: A cross-syndrome comparison with Angelman syndrome and autism

Authors: Stacey Bissell[1], Chris Oliver[1], Jo Moss[2], Mary Heald[3], Jane Waite[4], Hayley Crawford[5], Vishakha Kothari[1], Lauren Rumbellow[1], Grace Walters[1], & Caroline Richards[1]

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Introduction: SATB2-associated syndrome (SAS) is a multisystem neurodevelopmental disorder characterised by intellectual disability, speech delay and craniofacial anomalies (Zarate & Fish, 2017; Zarate et al., 2017). Although the physical and clinical characteristics of SAS are well-documented, a variable SAS behavioural profile is evident in the literature; with high levels of sociability (e.g. 'jovial personality') and autistic behaviours (e.g. 'repetitive movements') both previously described (Zarate et al., 2017). The present study aimed to detail the behavioural phenotype of SAS via comparisons to two well-delineated associated neurodevelopmental disorders: Angelman syndrome (AS) and autism.

Methods: Informant-report behavioural questionnaire measures were completed on behalf of 63 individuals with SAS (median age = 7.07 years; 31 male), who were matched according to age and level of ability to 63 individuals with AS and 63 individuals with idiopathic autism from an existing dataset. Between-group analyses and Social Communication Questionnaire (SCQ) item-level analyses are reported (significant group differences at $p < .01$).

Results: Between-group analyses revealed lower levels of stereotyped behaviour in SAS compared to autism ($p = .001$, $BF_{01} = .028$), but no significant differences between SAS and autism in relation to compulsive behaviour ($p = .406$, $BF_{01} = 5.031$) and insistence on sameness ($p = .043$, $BF_{01} = 1.109$). When measuring positive affect, SAS and AS groups both obtained higher mood (SAS: $p = .001$, $BF_{01} = .289$; AS: $p < .001$, $BF_{01} = .000$) and interest and pleasure (SAS: $p < .001$, $BF_{01} = .000$; AS: $p < .001$, $BF_{01} = .000$) subscale scores than individuals with autism. At SCQ item-level, individuals with SAS evidenced relative difficulty compared to individuals with autism on items pertaining to facial expressions, interest in others and social approach, but relative strengths in imaginative play and peer group interaction.

Discussion: There is a well-established literature that the presentation of autistic behaviours in genetic syndrome groups may differ to the behavioural profile seen in idiopathic autism (Moss & Howlin, 2009). This study highlights the importance of behavioural comparisons to well-delineated groups and fine-grained item-level analyses to elucidate potential nuances in the autism profile of recently recognised syndrome groups. Such a detailed approach is necessary when considering which autism behavioural interventions may be effective in rare syndrome groups with purported associations with autism.

References/Citations:

- Moss, J. & Howlin, P. (2009). Autism spectrum disorders in genetic syndromes: Implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. Journal of Intellectual Disability Research, 53(10), 852-873.
- Zarate, Y. A. & Fish, J. L. (2017). SATB2-associated syndrome: Mechanisms, phenotype, and practical recommendations. American Journal of Medical Genetics Part A, 173(2), 327–337.
- Zarate, Y. A., Kalsner, L., Basinger, A., Jones, J. R., Li, C., Szybowska, M., … & Everman, D. B. (2017). Genotype and phenotype in 12 additional individuals with SATB2-associated syndrome. Clinical Genetics, 92(4), 423–429.

Paper 2 of 5

Paper Title: Overnight parent-child proximity in relation to poor sleep in children with Angelman and Smith-Magenis syndromes

Authors: Georgie Agar[1], Chris Oliver[1], Caroline Richards[2]

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Introduction: Poor sleep is common in individuals with Angelman syndrome (AS) and Smith-Magenis syndrome (SMS). Typical explanations for poor sleep in individuals with intellectual disability are drawn from operant theory, with behavioural techniques often used in sleep interventions (Priday et al., 2017). Despite the known

preference for adult interaction and high rates of challenging behaviour and caregiver stress noted in both groups (Adams et al., 2011; Wilde et al., 2013; Arron et al., 2011; Goldman et al., 2012), no empirical data has directly considered parent-child interactions overnight or the implications of these for understanding and treating poor sleep in AS and SMS.

Methods: Nineteen children aged 4-15 years (8 with AS, 11 with SMS) took part in a week-long at-home assessment of sleep and overnight parent-child proximity. Sleep parameters were recorded using the Philips Actiwatch 2 and proximity data were recorded using custom-built radio frequency identification watches. These data were plotted together and visual inspection employed to consider patterns of parent-child proximity overnight. Additionally, standardised definitions of 'wake' and 'interaction' were applied to analyse the number of actigraphy-defined wakings which resulted in an objectively-defined episode of parent-child interaction. The relative risk of having a parent-child interaction at waking given a parent-child interaction when settling to sleep was analysed.

Results: Visual inspection revealed three patterns of proximity data between parent-child dyads overnight – 'checkers' (6 in the AS group, 5 in the SMS group), 'co-sleepers' (4 in the SMS group) and those who had 'no proximity' overnight (2 in the AS group, 2 in the SMS group). In the AS group, 25.45% of actigraphy-defined wakes resulted in a parent-child interaction. In the SMS group, 39.34% of wakes identified by actigraphy resulted in a parent-child interaction. However, children who interacted with their parents when settling to sleep were not significantly more likely to have an interaction at waking.

Discussion: Overall, the results suggest that the novel application of radio frequency identification technology is a feasible method of studying overnight parent-child proximity in two syndromes associated with poor sleep and preference for adult interaction. The findings demonstrate a variable profile of proximity between participants, even within the same syndrome group, providing an initial challenge to operant understanding of poor sleep in these groups. The data also highlight the level of demand experienced by some caregivers and the variability in approaches taken by parents in interacting with their children overnight. These results have significant implications for our understanding of the aetiology of poor sleep and the application of behavioural sleep interventions in children with AS and SMS.

References/Citations:

- Adams, D., Horsler, K., & Oliver, C. (2011). Age related change in social behavior in children with Angelman syndrome. American Journal of Medical Genetics Part A, 155(6), 1290-1297.
- Arron, K., Oliver, C., Moss, J., Berg, K., & Burbidge, C. (2011). The prevalence and phenomenology of self-injurious and aggressive behaviour in genetic syndromes. Journal of Intellectual Disability Research, 55(2), 109-120.
- Goldman, S. E., Bichell, T. J., Surdyka, K., & Malow, B. A. (2012). Sleep in children and adolescents with Angelman syndrome: association with parent sleep and stress. Journal of Intellectual Disability Research, 56(6), 600-608.
- Priday, L. J., Byrne, C., & Totsika, V. (2017). Behavioural interventions for sleep problems in people with an intellectual disability: a systematic review and meta-analysis of single case and group studies. Journal of Intellectual Disability Research, 61(1), 1-15.
- Wilde, L., Silva, D., & Oliver, C. (2013). The nature of social preference and interactions in Smith–Magenis syndrome. Research in Developmental Disabilities, 34(12), 4355-4365.

Paper 3 of 5

Paper Title: Self-injurious and aggressive behaviour in males with fragile X syndrome: genetic modifiers and persistence over time

2021 Gatlinburg Conference Symposium Submission

EXAMPLE

Authors: Hayley Crawford[1], Andrew Beggs[2], Efthalia Karakatsani[3], Joseph McCleery[4], Joanna Moss[5], Pria Sandhu[3], Gaia Scerif[6], Lauren Shelley[7], Gusharan Singla[3], Chris Stinton[1], Joanne Stockton[2], Chris Oliver[3], Lucy Wilde[8]

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Introduction: Self-injurious and aggressive behaviours are phenotypic of fragile X syndrome (FXS) but vary in severity and frequency across individuals (Arron et al., 2011). Despite the detrimental impact of these behaviours on individuals with FXS and their caregivers, little is known about a) how they change over time and behavioural risk markers for their persistence, and b) genetic risk markers that account for variation across individuals. We address this gap in knowledge across two studies. First, we explore the persistence of self-injurious and aggressive behaviours, and whether behavioural characteristics associated with autism spectrum disorder (ASD) and attention-deficit-hyperactivity disorder (ADHD) are associated with, and can predict, persistence of these behaviours. Second, we examine relationships between three single nucleotide polymorphisms (SNPs), selected a priori (5-HTTLPR, MAOA, COMT) with a range of clinically-relevant behaviours including self-injurious and aggressive behaviour.

Methods: In Study 1, data on standardised informant measures of behavioural characteristics were collected at three time points spanning eight years from 79 (M_{age} = 17.64 years at Time 1) males with FXS. In Study 2, 64 males, from whom behavioural data were collected during at least one of the time points across the eight year data collection period, provided saliva samples to identify 5-HTTLPR, MAOA and COMT genotypes. Behavioural data were compared between each SNP genotype.

Results: Results of Study 1 showed 77% and 69% persistence rates over eight years for self-injurious and aggressive behaviour, respectively. Baseline levels of repetitive behaviour predicted persistent self-injurious behaviour. Chronological age and baseline measures of impulsivity and overactivity were associated with persistent aggressive behaviour but only impulsivity *predicted* persistence of this behaviour. Results of Study 2 showed that the COMT AA genotype was associated with reduced risk for property destruction, stereotyped behaviour and compulsive behaviour.

Discussion: Study 1 identifies early risk markers of impairing behavioural features, which paves the way for targeted early intervention. Study 2 suggests that common genetic variation in the COMT genotype affecting dopamine levels in the brain may contribute to the variability of challenging and repetitive behaviours in this population. Together, these studies offer novel insights into the behavioural phenotype of fragile X syndrome and associated risk factors.

References/Citations:

- Arron, K., Oliver, C., Moss, J., Berg, K., & Burbidge, C. (2011). The prevalence and phenomenology of self-injurious and aggressive behaviour in genetic syndromes. Journal of Intellectual Disability Research, 55(2), 109-120.

Paper 4 of 5

Paper Title: Gaze following in fragile X syndrome

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Introduction: Autism is highly prevalent in fragile X syndrome (FXS; Richards et al., 2015). A distinct syndromal profile of autism characteristics is typically reported (Hall et al., 2010; Moss et al., 2013), indicating that there may be differences in the underlying social-cognitive features that contribute to the development of autism characteristics in this group, relative to individuals with non-syndromal autism. In this study, we evaluated whether children with FXS show similar attentional responses to shifts in eye gaze compared to autistic children. The impact of high vs. low social demand on attentional responses was also evaluated.

Method: Children with FXS (N=10; Mage = 8 yrs), autistic children (N= 21; Mage = 8 years) and neurotypical children (N=32; Mage = 6 yrs), comparable for receptive language participated. Participants were presented with a passive viewing paradigm, similar to that developed by Senju and Csibra (2008). Videos were presented in which a central cue (ball/cartoon face/human face) directed attention towards one of two objects. Spontaneous gaze patterns were recorded using eye-tracking.

Results: Data collection is ongoing. Preliminary analyses indicate that children with FXS and autistic children generally paid less attention to all central cues than neurotypical children ($p<.001$). Autistic children were just as likely as neurotypical children to follow directional cues to look at the target object ($p=.683$), whereas children with FXS followed these cues less often ($p=.030$). When they did follow them, children with FXS showed a preference for facial cues ($p=.035$), as did neurotypical children ($p=.002$), whereas autistic children responded similarly to all cues ($p=.553$).

Discussion: Autistic profiles in FXS are subtly different to most autistic individuals. This may result from differences in underlying social-cognitive abilities. Understanding the social-cognitive features that contribute to the development of atypical patterns of autism in FXS can inform earlier diagnosis and support the development of more tailored interventions for individuals with FXS and their families.

References/Citations:

- Hall, S.S., Lightbody, A.A., Hirt, M., Rezvani, A., & Reiss, A.L. (2010). Autism in fragile X syndrome: a category mistake? Journal of the American Academy of Child & Adolescent Psychiatry, 49(9), 921-933.
- Moss, J., Oliver, C., Nelson, L., Richards, C., & Hall, S. (2013). Delineating the profile of Autism Spectrum Disorder characteristics in Cornelia de Lange and fragile X syndromes. American Journal on Intellectual and Developmental Disabilities, 118, 262-283.
- Richards, C., Groves, L., Jones, C., Moss, J., & Oliver, C. (2015). Prevalence of autism spectrum disorder phenomenology in genetic disorders: a systematic review and meta-analysis The Lancet Psychiatry, 2, 909-916.
- Senju, A. & Csibra, G. (2008). Gaze following in human infants depends on communicative signals. Current Biology, 18, 668-71.

Paper 5 of 5

Paper Title: Overimitation in Cornelia de Lange and fragile X syndromes

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Introduction: Although individuals with Cornelia de Lange (CdLS) and fragile X syndromes (FXS) show high levels of autistic traits, the profiles of these behaviours differ between one another and non-syndromic autism (Moss, Oliver, Nelson, Richards & Hall, 2013). Differences in core social skills, such as imitation skills, may contribute to the different profiles of autistic traits observed in these groups. Typically developing (TD) children 'overimitate' irrational actions that are not instrumental in achieving a particular goal. Overimitation is considered to be a socially motivated behaviour aimed to facilitate social relatedness and social learning (Hoehl et al., 2019). Autistic children show reduced rates of overimitation, which may reflect difficulties in social engagement and social motivation (Marsh, Pearson, Ropar & Hamilton, 2013). In this study, we investigated overimitation in children with CdLS and FXS, using AUT and TD children as comparison groups.

Method: Participants currently include 20 TD children, 19 AUT children, 11 with CdLS and nine with FXS, comparable on receptive language ability. Participants took part in five overimitation trials adapted from procedures used by Marsh and colleagues (2013, 2019) and Vivanti, Hocking, Fanning and Dissanayake (2017). In each trial, children watched an experimenter retrieve an object from a transparent box using two rational actions (e.g. unclipping the lid, removing the box lid) and one irrational action (e.g. tapping the top of the box). Children were then given the same materials and told to "Get the [object] as quickly as you can". Following these trials, the experimenter redemonstrated the actions and after each one asked the child whether each individual action was 'sensible' or 'silly' (rationality discrimination task). Data collection is ongoing.

Results: Preliminary findings indicate that 85% of TD children and 89% of children with FXS overimitated at least once, compared to 64% of children with CdLS and 53% of AUT children. Of those children who overimitated, the TD (median=3.33) and AUT children (3.30) overimitated on more trials than the CdLS (1.00) and FXS groups (1.00). TD children (3.00) discriminated between rational and irrational actions in more trials than the CdLS (2.00), AUT (1.50) and FXS (1.00) groups.

Discussion: Children with CdLS and FXS show different patterns of performance to TD and AUT children, which may indicate differences in social motivation. High rates of rationality discrimination in TD children suggests high rates of overimitation are driven by motivation to affiliate with the demonstrator. Low rationality discrimination performance in AUT indicates those who overimitate inferred that the irrational action is casually meaningful to the goal rather than for social affilitation.

References/Citations:

- Hoel, S., Keupp, S., Schleihauf, H., McGuigan, N., Buttelmann, D., & Whiten, A. (2019). 'Over-imitation': A review and appraisal of a decade of research. Developmental Review, 51, 90-108.
- Marsh, L., Pearson, A,., Ropar, D., & Hamilton, A. (2013). Children with autism do not overimitate. Current Biology, 23(7), 266-268.
- Marsh, L., Ropar, D., & Hamilton, A. (2019). Are you watching me? The role of audience and object novelty in overimitation. Journal of Experimental Child Psychology, 180, 123-130.
- Moss, J., Oliver, C., Nelson, L., Richards, C., & Hall, S. (2013). Delineating the profiles of autism spectrum disorder characteristics in Cornelia de Lange and fragile X syndromes. American Journal of Intellectual and Developmental Disabilities, 118(1), 55-73.
- Vivanti, G., Hocking, D. R., Fanning, P., & Dissanayake, C. (2017). The social nature of overimitation: Insights from autism and Williams syndrome. Cognition, DOI: 10.1016/j.cognition.2017.01.008