Symposium Title: From biology to behaviour: modelling cause and intervention for problem behaviours

Chair: Caroline Richards[1]

Discussant: Frank Symons[2]

Overview: Whilst there have been significant advances in understanding problem behaviours in individuals with intellectual and developmental disabilities (IDD), these behaviours still present significant clinical challenges. Description of biological pathways to self-injurious and aggressive behaviours remains limited, and implementation of risk-informed intervention strategies is hindered by inconclusive predictive models. Application of evidence-based interventions is often restricted by practical constraints on the availability of expert therapists. In this symposium we present data from cutting edge biological studies, exploring the aetiology and biological contributors to self-injury and aggression. Longitudinal studies are used to explore early risk markers for self-injury, and through the application of machine learning, predictive models of problem behaviour are presented. Finally, we consider technological enhancements to facilitate the delivery of interventions for problem behaviour via tele-health. To foster the discussion and encourage interaction between these differing approaches, we have adopted a data-blitz style symposium which provides a unique opportunity to highlight the diversity of active problem behaviour research programs. This will lead to increased opportunities for interdisciplinary collaboration and translational research in IDD. Each presentation is designed to highlight the key underlying concept and approach and the novel data resulting from their combination.

Paper 1 of 5

Paper Title: Preliminary evidence for self-injury associated with possible failure of age-dependent decrease in epidermal nerve fiber innervation

Authors: Frank Symons[2], Brian McAdams[2], Chantel Barney[3], Shawn Foster[2], George Wilcox[2], & William Kennedy[2]

Introduction: In one biologically-oriented line of research investigating peripheral biomarkers of sensory function and self-injury, we made a series of observations specific to epidermal nerve fiber innervation in the skin that may be relevant to the sub-clinical markers for biological vulnerability and SIB risk (2, 3, 4). A self-injurious behavior (SIB) subtype associated with a specific pattern of peripheral biomarkers was characterized initially in adults with IDD. This pattern of differences was characterized by the density of small-diameter unmyelinated sensory nerve fibers and quantity of substance P (SP) containing fibers, a neuropeptide relevant to nociceptive (i.e., 'pain') signaling. Subsequent observations were extended to and replicated in pediatric samples with IDD. There is limited normative data, however, specific to epidermal nerve fiber density (ENFd). The only report documenting ENFd values in a 'healthy' (no disability) pediatric population suggested that innervation was dense and age-dependent – ENFd values decrease with age (1). Whether such a pattern would also apply to children with developmental delays is unknown. The purpose of this study was an exploratory investigation of ENFd in young children with global developmental delay with and without parent-reported self-injury.

Methods: Following IRB approval and informed parental consent, children (N=25) with global developmental delays (76% male; mean age = 58 months, 24-96) were consecutively recruited through a tertiary developmental pediatric clinic from a large children's specialty rehabilitation hospital and a large primary care clinic. The Repetitive Behavior Scale –Revised (RBS-R; [5]) was used as the primary measure of self-injurious behavior (SIB). All children failed to meet typical developmental milestones in two or more developmental domains (e.g., motor, language, etc) and were being evaluated diagnostically. Epidermal skin biopsies

---

[1] University of Birmingham
[2] University of Minnesota
[3] Gillette Children's Specialty Healthcare, Saint Paul

were obtained painlessly while the child was under general sedation for an indicated procedure (MRI). Specimens were obtained from the postero-medial calf - an area that had no pre-existing skin damage and no history of SIB among the SIB cases. The biopsy was made with a 3 mm punch tool (Acupunch; Acuderm; Fort Lauderdale, FL) and processed as described previously (1-4). All processing and reviews of microscopy images were 'blind' to child status with respect to whether or not they self-injured. The primary outcomes measured for this preliminary analysis were ENF density (ENF count/mm) and p set at 0.10 for small N exploratory analyses.

Results: SIB grouping was empiric – a histogram revealed two 'severity' groups – 'severe SIB' and 'minor/no SIB' (RBS-R scores > 3; RBS-R scores 0-2). Based on this grouping, mean ENFd values for the 'minor/no SIB' were 90.6 ENF/mm (sd = 31; N=13) and 78.8 ENF/mm (sd = 32.7, N=12) for 'severe SIB' (ns diff) although median values were trending different (minor/no SIB > severe SIB; 88 > 76 ENF/mm, respectively; Chi-Square = 1.99; p = 0.08). Linear regression analyses indicated that ENFd values were relatively stable in the 'severe SIB' group whereas they were decreasing in the 'minor/no SIB' group; Interaction: F = 2.527, p = .13; main effect of SIB: F = 3.17, p = .089; main effect of age: F = 0.075, p = .79.

Discussion: Based on these analyses with the largest sample yet specific to peripheral innervation and children with global developmental delays, we have initial evidence that developmentally regulated peripheral processes may be impaired in children with severe self-injury (as reported by parents). The expected age-dependent decrease in ENFd may be disrupted which may, in turn, have functional consequences specific to sensory function relevant to the initial emergence of SIB in this vulnerable group. A major concern remains, though, that as far as we and others know (A. Oaklander, personal communication; S. Beggs, personal communication), there are no published referent values for typically developing children from birth through five years of age.

References/Citations:
1. Panoutsopoulou IG, Luciano CA, Wendelschafer-Crabb G, Hodges JS, Kennedy WR. (2015) Epidermal innervation in healthy children and adolescents. *Muscle Nerve*. 51(3):378-84. doi: 10.1002/mus.24329
2. Symons, F. J., Tervo, R. T., Barney, C. Damerow, J., Wendelschafer-Crabb, G., & Kennedy, W. (2015). Is peripheral innervation density a risk factor for SIB in children with global developmental delay? *Journal of Child Neurology*. Nov;30(13):1722-7. doi: 10.1177/088307381557970
3. Symons, F. J., Tervo, R. T., Gilles, E., Wendelschafer-Crabb, G., & Kennedy, W. (2015). Skin and self-injury: A possible link between peripheral innervation and immune function? *Developmental Medicine & Child Neurology*. 57, 677-680. doi: 10.1111/dmcn.12580.
4. Symons, F. J., Wendelschafer-Crabb, G., Kennedy, W., Hardrict, R., *Dahl, N., & Bodfish, J. W. (2008). Evidence of altered epidermal nerve fiber morphology in adults with self-injurious behavior and neurodevelopmental disorders. *Pain, 134*, 232-237.
5. Bodfish, J. W., Symons, F. J., Parker, D. E., & Lewis, M. H. (2000). Varieties of repetitive behavior in autism: Comparisons to mental retardation. *Journal of Autism and Developmental Disorders, 30*, 237-243.
6. Supported, in part, by NICHD Grant No. 44763

Paper 2 of 5

Paper Title: Problem behaviours in autism: a longitudinal prospective cohort study over ten years

Authors: Catherine Laverty[1] Chris Oliver[1], Jo Moss[4], Lucy Sinclair-Burton[1], Georgie Agar[1], Lisa Nelson[1] & Caroline Richards[1]

Introduction: Aggression and self-injury are common and highly deleterious in individuals with neurodevelopmental disorders. Whilst these behaviors are evidently detrimental to the individual and those around them, limited epidemiological data exist delineating the developmental trajectory over time. Current literature suggests the stability of behaviors over the lifespan (Dimian et al., 2017; Totsika & Hatsings, 2009), however much research focusses solely on clinically derived samples (Baghdadli et al., 2008; Cooper et al., 2009; Oliver, Murphy & Corbett, 1937). There is a considerable paucity of research detailing the

---

[4] School of Psychology, University of Surrey, Guildford, Surrey GU2 7XH, UK.

naturalistic change over time for aggression and self-injury specifically within non-clinical populations. In this three wave longitudinal study, we investigated self-injury and aggression in a cohort of individuals with autism over 10 year period.

Methods: Caregivers of autistic individuals completed questionnaires relating to the presence of aggression and self-injury, as well as a battery of behavioral measures at three separate time points over a ten year period. Analyses examined the presence, persistence, and predictive value of putative correlates of aggression and self-injury.

Results: Self-injury was persistent in 44% of individuals over the 10-year period while aggression was persistent in 30% of individuals. Behavioral characteristics of overactivity and impulsivity were identified as a potential risk marker for persistent behaviors. A predictive model of self-injury was derived from LASSO analysis, with baseline impulsivity, interest and pleasure, stereotyped behavior, social communication and adaptive functioning predicting self-injury over 10 years.

Discussion: In this unique longitudinal investigation into the persistence of aggression and self-injury in a non-clinical sample of individuals with autism over a 10 year period, we have identified a novel, robust and stable profile of behavioral characteristics associated with behaviors. Findings support an early intervention strategy targeted towards individuals identified to be at a higher risk of developing behavior's known to be persistent and deleterious over prolonged periods of time.

References/Citations:

- Baghdadli A, Picot MC, Pry R, Michelon C, Burzstejn C, Lazartigues A, et al. What factors are related to a negative outcome of self-injurious behaviour during childhood in pervasive developmental disorders? J Appl Res Intellect Disabil. 2008;21(2):142–9
- Cooper SA, Smiley E, Allan LM, Jackson A, Finlayson J, Mantry D, et al. Adults with intellectual disabilities: prevalence, incidence and remission of self-injurious behaviour, and related factors. J Intellect Disabil Res. 2009;53(3):200–16
- Dimian AF, Botteron KN, Dager SR, Elison JT, Estes AM, Pruett JR, et al. Potential risk factors for the development of self-injurious behavior among infants at risk for autism spectrum disorder. J Autism Dev Disord. 2017;47(5):1403–15.
- Oliver C, Murphy GH, Corbett JA. Self-injurious behaviour in people with mental handicap: a total population study. J Intellect Disabil Res. 1987;31(2):147–62.
- Totsika V, Hastings RP. Persistent challenging behaviour in people with an intellectual disability. Current Opinion in Psychiatry. 2009;22(5):437–41.

Paper 3 of 5

Paper Title: Predicting self-injurious behavior at age three among high-risk infant siblings

Authors: Adele Dimian[2], Brittany Pennington[2], Kelly Botteron[5], Stephen Dager[6], Annette Estes[6], Heather Hazlett[7], Robert Schultz[8], Joseph Piven[7], & Jason Wolff[2] for the IBIS Network

Introduction: Existing research suggests that self-injurious behavior (SIB) is a relatively common behavior disorder that can occur across the lifespan of individuals with autism spectrum disorder (ASD). Repetitive behavior is also a core diagnostic feature of ASD, but few empirical longitudinal studies have examined SIB specifically in the early years of life. We previously reported potential risk factors for SIB using psychosocial variables from 12 months of age to predict SIB at 24 months among a preschool sample of children at high familial risk for ASD (Dimian et al., 2017). In the present study, we extend these findings and examine SIB occurrence and associated potential risk factors at 36 months. Our aims were the following: 1) Extend our previous models

[5] Washington University in St. Louis
[6] University of Washington
[7] University of North Carolina at Chapel Hill
[8] Children's Hospital of Philadelphia

on early potential risk factors with 12 months predictors of SIB occurrence at 24 months to predicting SIB occurrence at 36 months among toddlers at high familial risk for ASD; 2) investigate if sensory experiences and subtypes at 12 months of age predict SIB occurrence at 36 months, and 3) explore how topographies of SIB and stereotypy change across 12, 24 and 36 months of age.

Methods: Participants were from a longitudinal study of infants at familial risk for ASD. The present sample included 149 high-risk infants (65.8% male) who completed the following assessments at ages 12, 24, and 36 months: MSEL, Vineland-II, Sensory Experiences Questionnaire, and Repetitive Behavior Scales-Revised (RBS-R). The RBS-R was used to identify SIB and stereotypy. Descriptive analyses and binary logistic regression models were utilized to examine 12 month predictors for SIB at 36 months.

Results: SIB was reported for 22% of participants at age 36 months and the risk of engaging in SIB was 4.05 times higher among children who received a diagnosis of ASD compared to children with no diagnosis. The first logistic regression model replicated Dimian et al. and included sex, MSEL and Vineland composite scores, and SIB and stereotypy from the RBS-R at 12 months. The overall model significantly predicted 36 month SIB. Of individual predictors, Mullen composite score and stereotypy at 12 months were significantly predictive of SIB at age 36 months. A second model including Sensory subtype scores was evaluated and the overall model was significant with hyper and hypo responsiveness predicting SIB at follow up. Topographies of SIB and stereotypy changed in overall frequency over time and most children tended to engaged in hitting self against a surface.

Discussion: SIB was more prevalent among those children who received a diagnosis of ASD. Logistic regression results were mixed but the best fitting model indicated that presence of SIB, stereotypy, hyper and hypo responsivity, and lower intellectual functioning at age 12 months significantly predicted the occurrence of SIB at 36 months. These findings have implications for potential early intervention targets that could help inform prevention programming in the future, but more research is warranted.

References/Citations:

- Dimian, A. F., Botteron, K. N., Dager, S. R., Elison, J. T., Estes, A. M., Pruett, J. R., ... & Ibis Network. (2017). Potential risk factors for the development of self-injurious behavior among infants at risk for autism spectrum disorder. *Journal of autism and developmental disorders*, *47*(5), 1403-1415.

Paper 4 of 5

Paper Title: Development and validation of prediction models of risk for challenging behaviour in individuals with developmental delay.

Authors: Laura Groves[1], Louise Daniel[1], Louise Handley[1], Chris Oliver[1], Caroline Richards[1]

Introduction: Challenging behaviour is shown by approximately 10% of children with developmental delay. Severe challenging behaviour is persistent and associated with a marked impact on quality of life and wellbeing. Thus, early intervention targeted to children at the greatest risk of developing challenging behaviour is essential. Putative risk makers for challenging behavior are identified in previous literature, however no study has yet used these to build predictive models of risk to inform the delivery of early interventions. Machine learning approaches have been employed in physical health research (e.g. Liu et al., 2019) to build prediction models of risk with promising results. The aim of this study was to use machine learning to develop a predictive model, identifying individuals at low, moderate and high risk of challenging behaviour. A secondary aim was to assess the validity of these models to predict future levels of challenging behaviour.

Methods: Caregivers of individuals with developmental delay (n=732) completed the Self-injury, Aggression and Destruction Screening Questionnaire (SAD-SQ; Davies & Oliver, 2016). The SAD-SQ is a short, accessible screening measure of person and behavioural risk markers known to be associated with challenging behaviour, with good reliability and validity. Individual

predictive models were generated for self-injurious behaviour, aggression, destruction of property and a composite "any challenging behaviour". Regression analyses were conducted to identify the most predictive variables for each behaviour type from which models of level of risk (categorised as low, moderate and high risk) were developed using machine learning.Variables weighted by the regression coefficients were inputted to a random forest classifier with 512 (70%) randomly selected participants used to train the models and the remaining 220 (30%) used as the testing sample. To prevent overfitting, a maximum depth of 10 for each tree and a minimum of six individuals per node were set. To address the second study aim, the predictive models were validated on a separate longitudinal dataset. For this, caregivers of individuals with suspected or confirmed developmental delay completed the SAD-SQ at Time 1 (n=325) and 12 months later (Time 2). Level of risk for participants were calculated on Time 1 data and compared to reported challenging behaviour at Time 2.

Results: The sensitivity and specificity of the predictive models for classifying level of risk (low, moderate or high) for self-injurious behaviour, aggression, destruction of property and "any challenging behaviour" was found to be good.

Discussion: This study highlights that robust, sophisticated statistical analysis approaches such as machine learning may be applied to behavioural research in individuals with developmental delay, to model risk for challenging behaviour specifically. Further research is required to refine these models incorporating novel risk markers to increase their sensitivity and specificity. Identification of the level of risk for challenging behaviour is critical for parents and professionals to provide tailored, effective early interventions to those individuals at the highest risk.

References/Citations:

- Davies, L. E., & Oliver, C. (2016). Self-injury, aggression and destruction in children with severe intellectual disability: Incidence, persistence and novel, predictive behavioral risk markers. *Research in developmental disabilities, 49*, 291-301.
- Liu, X., Faes, L., Kale, A.U., Wagner, S.K., Fu, D.J., Bruynseels, A., … Denniston, A.K. (2019). A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis. *The Lancet Digital Health, 1*(6), 271-297. doi.org/10.1016/S2589-7500(19)30123-2

Paper 5 of 5

Paper Title: A Randomized Controlled Trial of Telehealth-Enabled Behavioral Treatment for Problem Behaviors Exhibited by Boys with fragile X syndrome

Authors: Scott Hall[9], Katerina Monlux[9], Arlette Bujanda[10] & Joy Pollard[10]

Introduction: Over the past few decades, studies have demonstrated that behavioral treatments based on the principles of applied behavior analysis (ABA) can effectively ameliorate problem behaviors commonly exhibited by children with developmental disabilities. Unfortunately, many children with rare genetic disorders such as fragile X syndrome (FXS) have limited access to much-needed behavioral treatment. To remediate health access disparities, telehealth has successfully been leveraged as a service delivery model to bring behavioral treatment to families in their home. In a previous study, we showed that caregivers of children with FXS could be successfully coached to administer behavioral treatments via telehealth in their home. However, the effectiveness of this intervention has not been evaluated using a randomized controlled design. We therefore conducted the first randomized controlled study to examine the effectiveness of telehealth-enabled behavioral treatment for problem behaviors in FXS.

Methods: Participants included 57 boys with FXS, aged 3 to 10 years, who were reported to exhibit problem behavior on at least a daily basis. Participants were randomized to one of two groups: 1) telehealth-enabled behavioral treatment or 2) treatment as

---

[9] Stanford University
[10] Behavior Change Institute

usual. Parents of participants in the treatment group were coached in their homes via telehealth to implement function-based behavioral treatment with their child by a Board Certified Behavior Analyst over 12 weeks. Participants in the control group continued to receive any treatments they would usually receive over 12 weeks. To examine treatment maintenance, a 4-week follow-up was conducted for both groups. The primary outcome measure was the score obtained on the *irritability* subscale of the Aberrant Behavior Checklist- Community (ABC-C) every 4 weeks. We also measured parent fidelity of treatment implementation and treatment acceptability every 4 weeks.

Results: Participants randomized to the treatment group evidenced a 42.6% decrease in mean score on the *irritability* subscale of the ABC-C (from 20.72 ± 9.97 at baseline to 12.0 ± 8.47) whereas the control group evidenced a 9.13% decrease (from 17.77 ± 8.64 to 16.15 ± 7.23) (Cohen's d = 0.65, p<.001) at 12 weeks. The treatment group also showed significant decreases on the *hyperactivity* subscale of the ABC-C (d = 0.58, p=.005) as well as on the *stereotypy* subscale of the ABC-C (d = 0.34, p=.042) compared to the control group. Scores obtained on the Treatment Acceptability Rating Form - Revised (TARF-R) indicated that treatment acceptability remained high during the 12-week treatment period and at the 4-week follow-up.

Discussion: These data provide strong evidence in support of implementing function-based behavioral treatments via telehealth for children with FXS aged 3 to 10 years*.* Telehealth also appears to be an acceptable, efficient and cost-effective method for coaching parents to implement behavioral strategies with their child in their home. The advantages and disadvantages of implementing behavioral treatments via telehealth will also be discussed.

References/Citations:

- Monlux, K.D., Pollard, J.S., Bujanda-Rodriguez, A.Y. & Hall, S.S. (2019). Telehealth delivery of function-based behavioral treatment for problem behaviors exhibited by boys with fragile X syndrome. *Journal of Autism and Developmental Disorders*, 49(6), 2461-2475.