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International Society for Autism Research

2019

ANNUAL MEETING

PRESS BOOK

All abstracts and interviews EMBARGOED until
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INSAR 2019 PRESS BOOK

Abstracts of Highlighted Papers and Keynote Addresses

HIGHLIGHTED STUDY ABSTRACTS

Page

**Names of press conference presenters in bold*

R. A. Luna[1,2], T. Savidge[1,2], R. P. Goin-Kochel[1,2], C. M. Powell[3], C. Redel[1,4], K. C. Williams[5] and J. Versalovic[2,6], (1)Baylor College of Medicine, Houston, TX, (2) Texas Children's Hospital, Houston, TX, (3)Neurobiology, UAB School of Medicine, Birmingham, AL, (4)Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, (5)Nationwide Children's Hospital, Columbus, OH, (6)Pathology & Immunology, Baylor College of Medicine, Houston, TX

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A. Zitter[1], R. Solorzano[2], S. Turnacioglu[2], J. S. Miller[3], V. Ravindran[4], **J. Parish-Morris**[1] and J. McCleery[5], (1)Center for Autism Research, Children's Hospital of Philadelphia, Philadelphia, PA, (2)Floreo Virtual Reality, Washington DC, DC, (3)Center for Autism Research, The Children's Hospital of Philadelphia, Philadelphia, PA, (4)Floreo, Inc., Washington DC, DC, (5)The Center for Autism Research, The Children's Hospital of Philadelphia, Philadelphia, PA

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KEYNOTE ADDRESSES

Whole Genome Sequencing in Autism

Included in Panel Session: Genetic & Genomic Discovery in Autism: From SNPs, to Exomes & Genomes

ABSTRACT:

Whole Genome Sequencing in Autism

S. W. Scherer, The Hospital for Sick Children, Toronto, ON, Canada

Background: Autism Spectrum Disorder (ASD) is heterogeneous, both phenotypically and in its genetic architecture. There are now hundreds of genes found associated with ASD, with risk contributed by multiple types of rare and common genome-wide variation. Some individuals carry single rare (de novo or inherited) penetrant gene alterations. Others have multiple variants, and for these and others with ASD, a whole host of (poly)-genic risk factors may be involved.

Objectives: Whole genome sequencing (WGS) technology has been launched worldwide by large-scale projects to study thousands of families from ASD cohorts and biobanks (e.g. AGRE, SFARI). The goal of this research is to decode entire genome sequences including all their genetic variants, link to available phenotype data, and make these massive genomic/phenotypic datasets available for scientific study. Before this, to find the complete spectrum of variants has required the incremental technologies of karyotyping, microarray, panel-sequencing and exome-sequencing. With WGS, an experiment costing about US$1000 can complete the task in a single comprehensive step.

Methods: WGS is usually performed on DNA from whole blood (or sometimes other tissues), typically using 'short-read' sequencing technologies. Other useful data are arising from 'long-read' technologies. Bioinformatic pipelines are applied to raw sequence data to enable the robust identification of constitutional single nucleotide variants (SNVs), small insertion/deletions (indels), as well as copy number variants (CNVs), structural variants (SV; including short repeats), and mitochondrial variants. New algorithms further differentiate mutations occurring somatically from those present in all cells. Following approval of a Data Access Committee, primary and processed genomic data are then placed into different cloud- and web- based formats, to be accessible to the community.

Results: WGS sequencing has identified new variants in protein-coding and non-coding (e.g., lncRNA, regulatory) regions, in or near genes missed by other technologies. A more complete view of the entire genome can increase the yield of findings relevant for ASD or its co-morbidities and provide context for their interpretation. Smaller CNVs and more complex SVs, often missed by other technologies, also contribute significantly in the etiology of ASD. Approximately 100 gene and CNV regions currently have value for testing in ASD diagnostics. Through data consistent across studies, we find genes involved in synaptic and neural adhesion, neural transcriptional regulation, and RNA processing to be involved in ASD, offering new entry points for drug development. Hundreds of scientists from around the world are using WGS data to enable their research studies.

Conclusion: WGS data with accompanying phenotype information can greatly enable basic and clinical research in ASD. As the costs continue to decrease and WGS eventually moves into the diagnostic setting - supplanting microarray and exome-testing - thousands of additional genomes will become available for comparative analysis. The presentation will provide an overview of results of the major published studies, the data and resources available, and the most significant scientific advances, all based on WGS.

Complete Disruption of Autism-Susceptibility Genes By Gene-Editing Predominantly Reduces Functional Connectivity of Isogenic Human Neurons

ABSTRACT:

Complete Disruption of Autism-Susceptibility Genes By Gene-Editing Predominantly Reduces Functional Connectivity of Isogenic Human Neurons

Included in Panel Session: Stem Cell Based Technologies in Autism Research

E. Deneault[*1]; S. H. White[2];D. C. Rodrigues[3];J. Ross[4];M. Faheem[3];K. Zaslavsky[3];Z. Wang[3];R. Alexandrova[3];G. Pellecchia[3];W. Wei[3];A. Piekna[3];G. Kaur[3];J. Howe[3];V. Kwan[2];B. Thiruvahindrapuram[3];S. Walker[3];A. C. Lionel[3];P. Pasceri[3];D. Merico[5];R. K. Yuen[3];K. K. Singh[2];J. Ellis[3] and **S. W. Scherer**[3], (1)McGill University, Montreal, QC, Canada, (2)McMaster University, Hamilton, ON, Canada, (3)The Hospital for Sick Children, Toronto, ON, Canada, (4)University of Prince Edward Island, Charlottetown, PE, Canada, (5)Deep Genomics, Toronto, ON, Canada

Background: Familial clustering of autism spectrum disorder (ASD) and related subclinical traits has been described, and with sibling recurrence risk estimates ranging from 8.1 to 18.7, a significant amount of familial liability is attributed to genetic factors. Genomic microarray and sequencing studies have identified that ~10% of individuals have an identifiable genetic condition, and there are over 100 genetic disorders that can exhibit features of ASD, e.g., Fragile X and Rett syndromes. Dozens of additional penetrant susceptibility genes have also been implicated in ASD, some being used in clinical testing. Genetically-identified ASD-risk genes are enriched in broader functional groups consisting of synapse function, RNA processing, and transcriptional regulation. Importantly, so far, each risk gene or copy number variation (CNV) implicated in ASD accounts for <1% of cases, suggesting significant genetic heterogeneity. Even within families, siblings can carry different penetrant mutations. Common genetic variants may also contribute to ASD-risk.

Objectives: To determine the role of specific ASD-risk genes in neuronal function, we use gene editing to knockout their expression in induced pluripotent stem cells (iPSCs) that are used as a model in vitro. Patient-specific iPSCs provide a newfound ability to study developmental processes, and functional characteristics, directly. Importantly, differentiation of human iPSCs into forebrain glutamatergic neurons are used to recapitulate early molecular events in the trajectory of ASD development.

Methods: We devised a precise clustered regularly interspaced short palindromic repeats (CRISPR)-based strategy to efficiently generate complete knockout (KO) of any ASD-relevant gene, with all mutations made in the same “isogenic” (identical genetic background) human control iPSC line. We used the CRISPR/Cas9-mediated double-strand break (DSB) mechanism coupled with error-free single-stranded template repair (SSTR) pathways to introduce an all-reading-frame premature termination codon, named “StopTag”, into a specific exon of a target gene, designed to prevent stable RNA/protein product from being made. We then explored excitatory neuron functional differences relevant to ASD for 10 different successfully-edited genes (AFF2/FMR2, ANOS1, ASTN2, ATRX, CACNA1C, CHD8, DLGAP2, KCNQ2, SCN2A, TENM1). Directed induction into excitatory neurons was achieved with high efficiency using transient ectopic expression of the transcription factor NGN2.

Results: Our results indicate that some ASD-risk genes display reduced synaptic activity between NGN2-derived excitatory neurons implying that ASD genes from different classes can present the same general cellular

phenotype in vitro. RNAseq revealed convergence of several neuronal networks. Using both patch-clamp and multi-electrode array approaches, the electrophysiological deficits measured were distinct for different mutations. However, they culminated in a consistent reduction in synaptic activity, including reduced spontaneous excitatory post-synaptic current frequencies in AFF2/FMR2-, ASTN2-, ATRX-, KCNQ2- and SCN2A-null neurons.

Conclusions: Despite ASD susceptibility genes belonging to different gene ontologies, isogenic stem cell resources can reveal common functional phenotypes, such as reduced functional connectivity.These results also indicate that aberrant functional connectivity is a frequent phenotype in human neurons with ASD candidate gene null mutations. Overall, given the heterogeneity involved in ASD, we believe that this type of CRISPR-isogenic KO system may be essential for step-wise controlled cellular phenotyping experiments.

Genetic Mechanisms Connecting Autism with Sleep & Circadian Rhythms

SUMMARY:

O. Veatch, University of Pennsylvania School of Medicine, Philadelphia, PA

Sleep and circadian rhythm disorders are common in individuals with ASD. Disturbed sleep is shown to exacerbate core symptoms of ASD. Sleep problems may also intensify expression of other serious ASD comorbidities, such as epilepsy. Sleep has strong, neuronal-specific effects on the function of molecular, cellular and network mechanisms of neuronal plasticity. Further, studies in model systems indicate that sufficient sleep promotes proper neurodevelopment. In addition, mistimed sleep (i.e. mismatch between endogenous circadian rhythms and preferred sleep/wake schedule) is associated with a number of negative health outcomes and has been observed to disrupt physiological rhythms and circadian regulation of the transcriptome. Given the observations that disturbed sleep relates to more severe symptoms in ASD and that sleep is important to neuroplasticity, it is likely there is a crucial window during neurodevelopment where the quality of sleep has a lasting impact on neurological function. As such, the need for effective treatments for sleep disorders in ASD is profound. Understanding the causes and consequences of sleep disturbances in children with ASD is an important step toward mitigating these symptoms. It is possible that ASD symptoms drive disturbed sleep or that expression of ASD symptoms with comorbid sleep disturbances are modified by convergent genetic risk factors. Notably, the known biological functions for recurrently implicated genes in ASD suggest involvement of convergent molecular mechanisms. Evidence also indicates many of these convergent mechanisms overlap with those associated with risk for sleep disorders and expression of circadian rhythms. This suggests that pleiotropic genetic effects contribute to sleep and/or circadian disorders in some individuals with ASD. Understanding the genetic architecture underlying the relationship between ASD and expression of sleep and circadian disturbances may provide evidence useful toward optimizing more effective, personalized treatments in this population. This presentation will offer a broad overview of key findings from genetic studies of ASD, sleep traits, and circadian rhythm regulation highlighting shared genetic mechanisms that may underlie expression of sleep and circadian rhythm problems in ASD.

Leveraging Developmental Trajectories of Broadband Screening to Detect Autism Risk in Primary Care

ABSTRACT:

Leveraging Developmental Trajectories of Broadband Screening to Detect Autism Risk in Primary Care

W. Guthrie[1], R. T. Schultz[2] and J. S. Miller[1], (1)Center for Autism Research, The Children's Hospital of Philadelphia, Philadelphia, PA, (2)Center for Autism Research, Children's Hospital of Philadelphia, Philadelphia, PA

Background: The gap between the typical onset of autism symptoms and the average age of diagnosis remains wide, demonstrating the need for novel screening methods that detect ASD more reliably and at younger ages. Infant-sibling studies suggest that many children later diagnosed with ASD show developmental deceleration in the first two years of life, sometimes before clear autism symptoms emerge. However, this has not yet been demonstrated in low-risk samples so its screening value is unknown. This study leveraged routine developmental screening in primary care to examine whether developmental deceleration is an early indicator of ASD that can contribute to universal screening.

Objectives: Test the hypotheses that (1) developmental deceleration can be detected in a subset of low-risk primary care patients and (2) this pattern confers elevated risk for ASD.

Methods: The Children's Hospital of Philadelphia has conducted universal screening for 10+ years across 31 primary care sites. The Survey of Well-Being in Children (SWYC) Milestones (Sheldrick & Perrin, 2013) is administered at 9, 18, and 24-30 months, according to American Academy of Pediatrics (AAP) guidelines. All patients with at least one SWYC screening and follow-up diagnostic data at ≥4 years were included in this epidemiological cohort, identified from electronic health records (N=32,280). The ASD prevalence rate in this cohort was 2.4%.

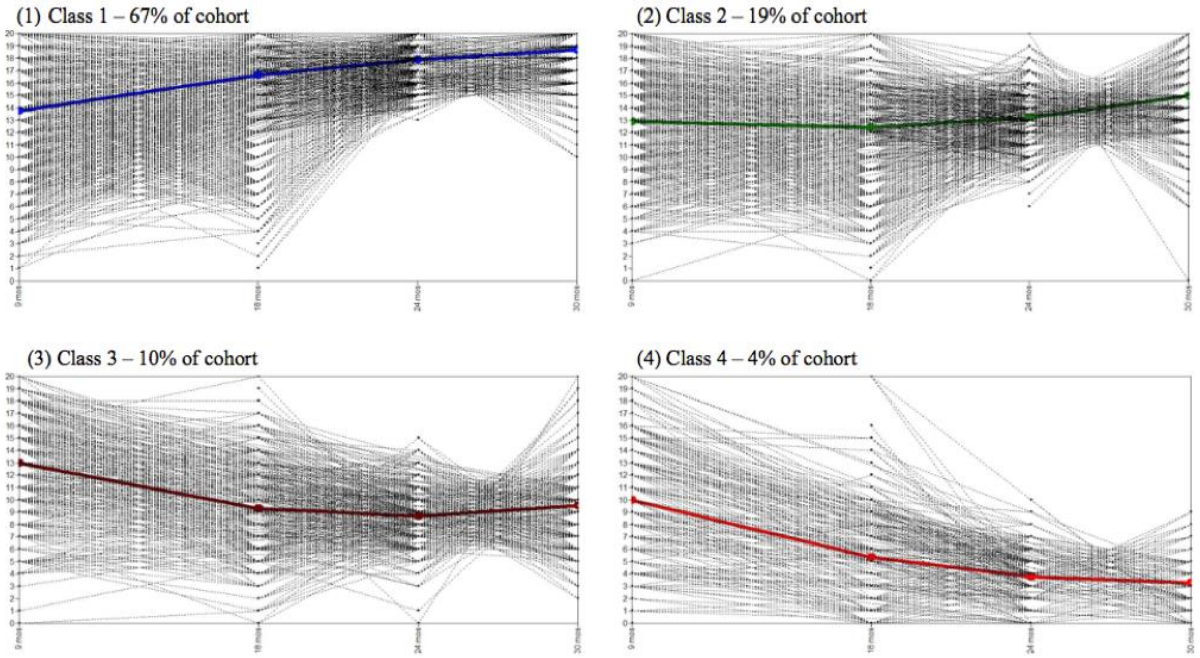
Results: Growth mixture models identified distinct developmental trajectories of SWYC scores from 9-30 months; a four-class model provided the best fit. Class 1 (67% of the cohort) had 9-month scores that met age expectations and significantly increased from 9-30 months. This class (average posterior probability [APP]=.92) had a lower probability of a later ASD diagnosis (0.5%) compared to the entire cohort (2.4%). Class 2 (19%, APP=.78) also met age expectations at 9 months, but showed a more modest increase from 9-30 months; the rate of ASD in this class was 1.6%.

In contrast, Class 3 (10%, APP=.81) showed developmental deceleration from 9-30 months and had an elevated rate of ASD (7.1%). Class 4 (4%, APP=.89) had lower 9-month scores and more significant developmental deceleration, with a very elevated rate of ASD (27.0%). Two-thirds of children with ASD were classified into Class 3 or 4 (i.e., sensitivity=74%). Specificity of these developmental profiles was 88%, positive predictive was 13%, and negative predictive value was 99%. Additional analyses will combine SWYC developmental trajectories and M-CHAT/F results to determine if the combination yields more accurate screening than either alone.

Conclusions: These data demonstrate that clear developmental deceleration is detectable through routine developmental screenings, and when this pattern is present, it confers elevated risk for ASD. As such, screening for developmental deceleration in the first two years of life may improve the status quo of universal screening in

primary care. One important benefit of this approach is that it leverages tools pediatricians are already administering as a part of routine clinical care. Though this study used screenings from 9-30 months (given guidelines for screening at these ages), developmental deceleration may be detectable even earlier than 24-30 months with more repeated developmental screenings.

Figure 1. Developmental Trajectories of SWYC Scores from 9-30 Months



Gut Feelings: Linking Gastrointestinal Multi-Omic Profiles with Complex Phenotypes in Pediatric Autism Spectrum Disorder

ABSTRACT:

Gut Feelings: Linking Gastrointestinal Multi-Omic Profiles with Complex Phenotypes in Pediatric Autism Spectrum Disorder

R. A. Luna[1,2], T. Savidge[1,2], R. P. Goin-Kochel[1,2], C. M. Powell[3], C. Redel[1,4], K. C. Williams[5] and J. Versalovic[2,6], (1)Baylor College of Medicine, Houston, TX, (2)Texas Children's Hospital, Houston, TX, (3)Neurobiology, UAB School of Medicine, Birmingham, AL, (4)Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, (5)Nationwide Children's Hospital, Columbus, OH, (6)Pathology & Immunology, Baylor College of Medicine, Houston, TX

Background: Chronic gastrointestinal (GI) issues are a significant co-morbidity in autism spectrum disorder (ASD), and behavioral challenges, such as self-injurious and aggressive behaviors as well as sleep disruption, have been associated with the manifestation of GI symptoms. It is especially important to establish a way to identify when GI issues, such as abdominal pain, are present in autistic individuals who may be unable to directly communicate the location or source of their discomfort, where behavioral changes may be the only indication in these cases. While the role of the gut microbiome in human health is now well established, alterations in the composition of the gut microbiota in patients with neurodevelopmental disorders have been shown to correlate with clinical symptoms such as functional GI disorders (FGIDs).

Objectives: This study represents the largest, most well-controlled exploration of the gut microbiome and metabolome in pediatric ASD. Autistic children, unaffected siblings, and unrelated typically developing controls were compared. Comprehensive clinical data, including behavioral and GI phenotypes, have been analyzed in parallel with microbiome and metabolome results to create novel multi-omic profiles.

Methods: Extensive clinical history was obtained as well as data from several behavioral surveys (Sensory Profile-2, the Repetitive Behavior Scale-Revised, Aberrant Behavior Checklist, Social Responsiveness Scale, and the Child Behavior Checklist) and a two-week diary detailing diet, stooling pattern (Bristol stool ratings and stool frequency), and GI pain. Stool specimens were collected from pediatric subjects with ASD (n=145), unaffected siblings (n=48), and unrelated typically developing children (n=219). The QPGS-Rome III questionnaire was also utilized for the identification of FGIDs across all three groups. Microbiome and mycobiome characterization and global metabolomics were performed. Multiple bioinformatics and biostatistical approaches were utilized to identify individual organisms (both bacterial and fungal) and metabolites of interest.

Results: Differences in both microbial composition and diversity were observed across groups. The greatest shifts in the gut microbiome were associated with GI pain, with distinct differences noted in the ASD group that reported pain. Statistically significant differences ($p<0.05$) were observed in the relative abundances of several organisms that were previously reported as associated with pediatric ASD. These organisms were also associated with specific behavioral patterns and overall severity as well as with a variety of metabolites, including metabolic pathways associated with glutamate and tryptophan.

Feasibility and Safety of Immersive Virtual Reality as a Tool to Improve Police Safety in Adolescents and Adults with Autism Spectrum Disorder

ABSTRACT:

Feasibility and Safety of Immersive Virtual Reality as a Tool to Improve Police Safety in Adolescents and Adults with Autism Spectrum Disorder

A. Zitter[1], R. Solorzano[2], S. Turnacioglu[2], J. S. Miller[3], V. Ravindran[4], **J. Parish-Morris**[1] and J. McCleery[5], (1)Center for Autism Research, Children's Hospital of Philadelphia, Philadelphia, PA, (2)Floreo Virtual Reality, Washington DC, DC, (3)Center for Autism Research, The Children's Hospital of Philadelphia, Philadelphia, PA, (4)Floreo, Inc., Washington DC, DC, (5)The Center for Autism Research, The Children's Hospital of Philadelphia, Philadelphia, PA

Background: Individuals with Autism Spectrum Disorder (ASD), are at an elevated risk of poor outcomes when interacting with police officers. Approximately 1 in 5 adolescents with ASD will be stopped and questioned by an officer before the age of 21 (Rava, Shattuck, Rast, & Roux, 2016), and individuals with disabilities, including ASD, are 5 times more likely to be incarcerated than individuals without disabilities (Bronson, Maruschak, & Berzofsky, 2015). Additionally, civilian injuries and fatalities during police interactions are disproportionately common among people with disabilities (Perry & Carter-Long, 2016). Therefore, it is critical to develop interventions that foster safe and effective communication between individuals with disabilities and police officers. Here we report the results of an NIMH-funded Phase I trial to test the safety and feasibility of using immersive virtual reality (VR) to teach police safety behaviors to adolescents and adults with ASD.

Objectives: Assess the safety and feasibility of an immersive VR-based Police Safety Module (PSM) developed by Floreo, Inc. for verbally fluent adolescents and adults with ASD.

Methods: Sixty individuals aged 12-60 years (Mean=16.9, 52 male) with ASD completed 1-3 visits during Phase I of the present study. IQ was estimated at the beginning of the study (Weschler Abbreviated Scale of Intelligence; WASI-II) to ensure that all participants met a minimum verbal and overall IQ of ≥ 75 (Mean VCI=104, Mean FSIQ=104.5). During each visit, participants engaged in four 2-minute interactions with virtual police officers. Safety was assessed through direct experimenter observations, participant questionnaires, and a qualitative interview that inquired about potential adverse side effects. System usability was indexed via participant ratings on the System Usability Scale (Brook, 1996), adapted for adolescents and adults with ASD.

Results: Scores on the revised version of the System Usability Scale ranged from 52.5-100, with the average score exceeding a minimum acceptable score of 70 (Mean=85.3, SD=3.54). Ninety-eight percent of participants completed the entirety of the PSM. Five participants reported mild effects after usage (such as slight headache or disorientation) and no serious adverse events occurred. Eighty percent of participants reported that they would like to use this VR again, suggesting that this program is feasible in verbally fluent adolescents and adults with ASD.

Conclusions: This first-of-its-kind study demonstrated that using immersive VR to teach police safety skills in adolescents and adults with ASD is safe and feasible, with no serious adverse effects and acceptable usability scores. Phase II, beginning spring 2019, includes a randomized control trial to test the efficacy of Floreo PSM on behavior while interacting with live police officers.

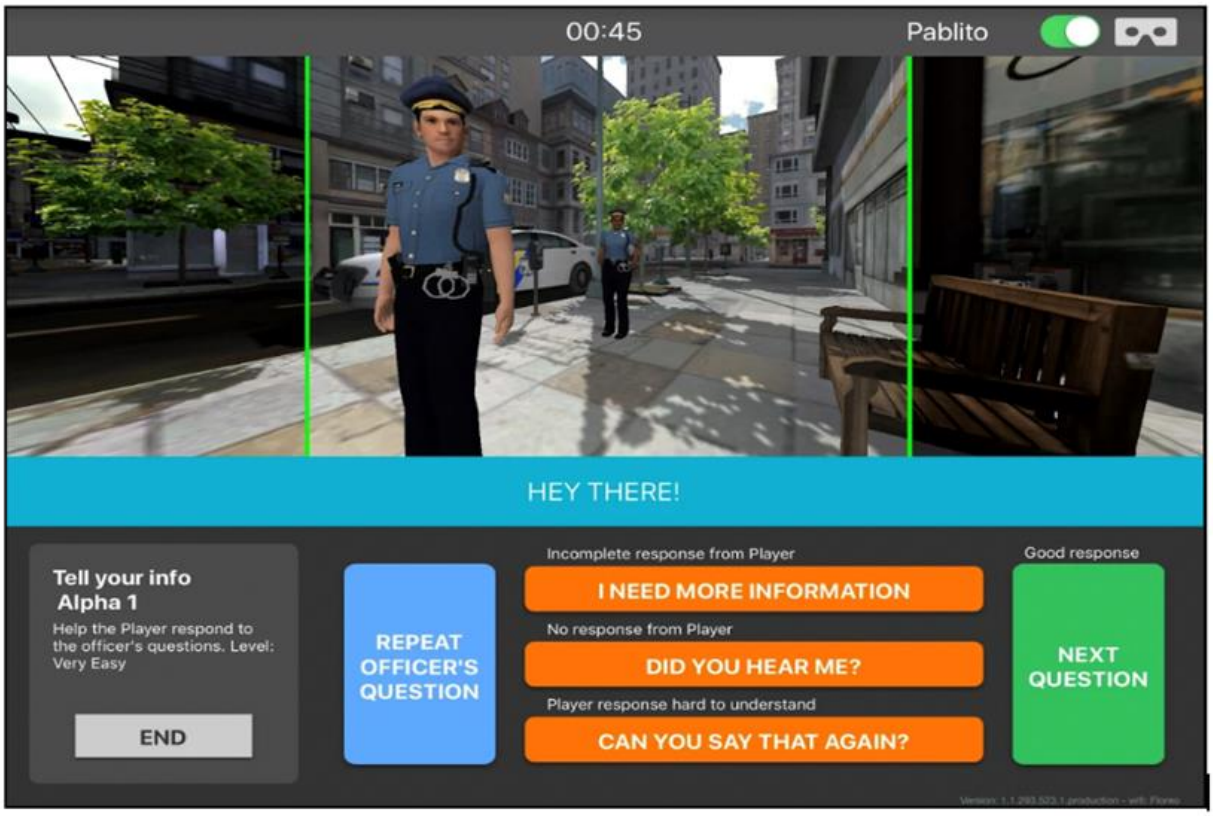


Figure 1. Example screen shot of the Floreo PSM virtual environment and control panel.

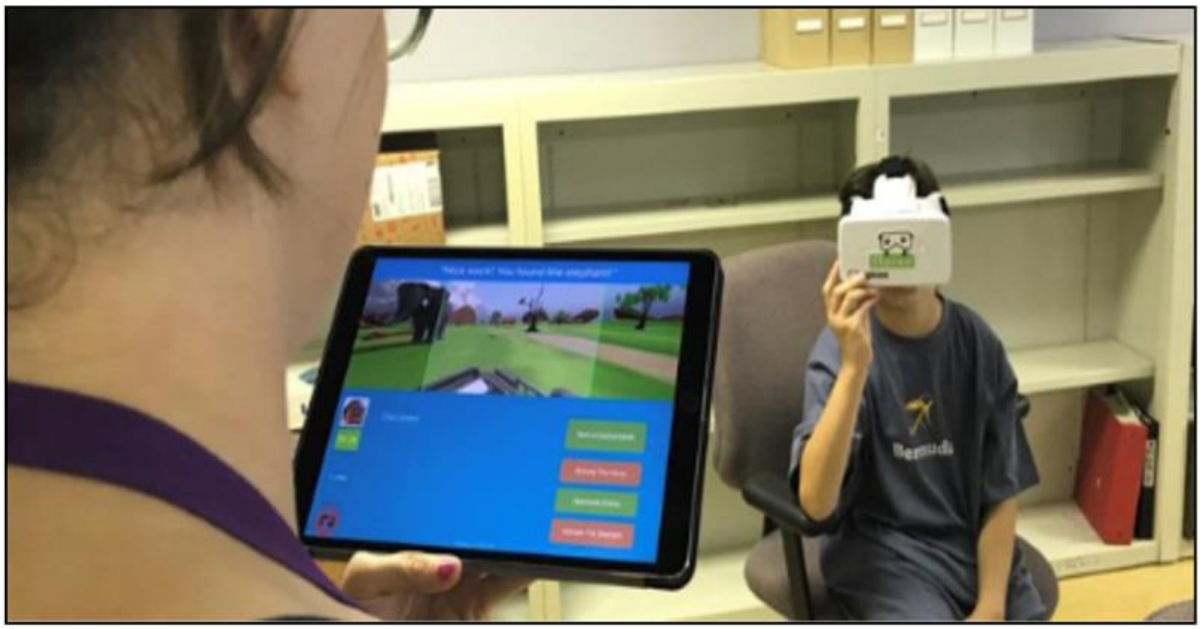


Figure 2. Example of virtual reality interaction experience.

KEYNOTE ADDRESSES:

De novo Variation in Coding and Noncoding Regions: What We Can Learn from the Data About Etiological Pathways

Kathryn Roeder, PhD

Thursday May 2, 2019: 9:00 a.m. – 10:00 a.m.

Kathryn Roeder has developed statistical and machine learning methods in a wide spectrum of areas, including high dimensional data problems. Her work focuses on statistical genetics and the genetic basis of complex disease. Recently her group developed tools for identifying autism risk genes from de novo mutations as well as associated gene networks. She is one of the leaders of the Autism Sequencing Consortium, an international organization dedicated to discovering the genetic etiology of autism. Roeder is the UPMC Professor of Statistics and Life Sciences in the Departments of Statistics & Data Science and Vice Provost for Faculty at Carnegie Mellon University. She received the COPSS Presidents' Award and the COPSS Snedecor Award for outstanding work in statistical applications, two of the most prestigious awards in her field.

Of Many Autisms or One Neurodevelopmental Disorder

Jason Lerch, PhD

Friday May 3, 2019: 9:00 a.m. – 10:00 a.m.

Jason P. Lerch, Ph.D. is the Director of Preclinical Imaging at the Wellcome Centre for Integrative Neuroimaging (WIN) at the University of Oxford and an Adjunct Scientist at the Mouse Imaging Centre (MICe) of the Hospital for Sick Children and an Associate Professor in Medical Biophysics at the University of Toronto. Jason joined WIN in March of 2019; prior to that he completed his Ph.D. in 2005 in the Department of Neurology and Neurosurgery at McGill University and a post-doctoral fellowship at MICe from 2005-2008 with Dr. Mark Henkelman and Dr. John Sled. He received his B.A. in 1999 in Anthropology and Social Studies of Medicine from McGill University. His Ph.D. research, under the supervision of Dr. Alan Evans, was on in-vivo measurements of cortical thickness from MRI. His current research focus is on detecting neuroanatomical changes due to behavioural and genetic manipulations in tightly controlled mouse models, primarily related to neurodevelopmental disorders, and to relate these findings to sadly not so well controlled human subjects. As an antidote to these academic pursuits, he likes to leave the city and hike in the woods, whenever possible.

From Clinics to Communities: Addressing Global Disparities in Autism Care

Vikram Patel, MBBS, PhD

Friday May 3, 2019: 5:30 p.m. – 6:30 p.m.

Vikram Patel is The Pershing Square Professor of Global Health and Wellcome Trust Principal Research Fellow at the Harvard Medical School. His work spans the areas of mental health problems, child development and adolescent health in the global health context, in particular the use of community resources for assessment, prevention and recovery. He co-founded Sangath, an Indian NGO which has won the MacArthur Foundation's International Prize for Creative and Effective Institutions and the WHO Public Health Champion of India award. He co-founded the Movement for Global Mental Health and is a Fellow of the UK Academy of Medical Sciences. He was named in the TIME 100 most influential persons of the year in 2015 and is the 2019 laureate of the John Dirk Canada Gairdner Award in Global Health.

Transcending Barriers to Development of Targeted Treatments for Fragile X Syndrome

Elizabeth Berry-Kravis, MD, PhD

Saturday May 4, 2019: 9:00 a.m. – 10:00 a.m.

Elizabeth Berry-Kravis MD, PhD is a Professor of Pediatrics, Neurological Sciences, and Biochemistry at Rush University Medical Center in Chicago. She established the Fragile X Clinic and Research Program in 1991, through which she provides care to over 600 patients with fragile X syndrome (FXS). She has studied medical issues, epilepsy and psychopharmacology in FXS, and translational research in FXS including outcome measures and biomarkers, natural history, newborn screening, and clinical trials of new targeted treatments in FXS. Her laboratory studies the cellular role of fragile X mental retardation protein (FMRP), relationship between FMRP and clinical function, and optimization of genetic testing methods. More recently she has expanded clinical and translational work to other neurodevelopmental disorders including autism spectrum disorders, and single gene models of ASD in addition to FXS, including Phelan McDermid syndrome, Rett syndrome and Angelman syndrome. She also is working on translational research in rare neurogenetic disorders including Niemann-Pick type C, Battens disease, pantothenate kinase-associated neurodegeneration, and creatine transporter deficiency. She is on Advisory Boards for the FRAXA Research Foundation and the National Fragile X Foundation.

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