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CIFAR-OBI Neuroscience Accelerator workshop: *Autism* Ivey ING Leadership Centre, Toronto, February 19-21, 2013

On February 19 - 21, 2013, CIFAR, in partnership with the Ontario Brain Institute, brought together international experts from diverse areas of neuroscience for a high-level meeting in Toronto. Researchers shared their latest research findings and knowledge of autism to elucidate new ways of thinking and cutting-edge approaches that would lead to a better understanding of the root causes of this life-long brain disorder.

SESSION I: AUTISM SPECTRUM DISORDER – OVERVIEW

Session Chair: Sir Michael Rutter, King's College London
Clinical and genetic perspectives: prospects and challenges

Dr. Peter Szatmari, McMaster University: *Between complexity and parsimony; the ASD phenotype from a developmental perspective*

SESSION SUMMARY: Autism spectrum disorder (ASD) is currently reported to occur in roughly 1% of the human population, with a strong male sex bias. ASD is highly heterogeneous and is characterized by a core set of behavioural phenotypes. However, ASD is not just a collection of behavioural traits, and cognitive dysfunction is frequently seen in ASD patients. Despite progress in identifying a small number of high risk ASD susceptibility genes through genome-wide association studies (GWAS), no common genetic variants have definitively been linked with ASD. The development of effective early diagnostic techniques for the majority of ASD cases remains elusive. The large degree of phenotypic overlap between ASD and other mental disorders – as well as overlap in susceptibility genes for these disorders – indicates a lack of diagnostic specificity. Additionally, success of treatment methods is highly variable between autistic individuals, and pharmacological treatment of ASD is ineffective. In this introductory session, Dr. Rutter and Dr. Szatmari discussed the implications of these trends and suggested that ASD is not a single modular social cognitive deficit. As such, effective clinical diagnosis and treatment of autism requires a neurocognitive designation. Improved clinical outcomes for treating autism will stem only from an improved understanding of the biology of ASD.

Although autism is clinically well-established as a disorder, an understanding of its etiological basis is lacking. Diagnosis of autism is based on a set of core phenotypes, known as the autistic triad, which include: impairment in social reciprocity; impairment in verbal and non-verbal communication; and preference for repetitive

and stereotyped behaviours. The expression of these behavioural traits varies greatly from one autistic individual to another. Additionally, orphan phenotypes such as challenging behaviours, IQ deficits, anxiety and sleep problems, and epilepsy co-occur with the core autism phenotypes. This enormous phenotypic heterogeneity has led autism researchers and clinicians to state that if you have met one person with autism, then you have met one person with autism.

Adding to the complexity of autism, this disorder often co-occurs with a variety of dysfunctions in cognitive traits, such as intellectual disability, intellectual deterioration, and savant skills. The overlap between different mental disorders is also reflected at the level of the gene. Genetic influences that have been associated with autism are also seen at high frequencies in cases of attention-deficit hyperactive disorder (ADHD) and learning disorders. Enormous overlap in phenotypic outcomes and recognized genetic influences presents a daunting challenge to the diagnosis and treatment of individual cases of autism.

The current DSM 5 has replaced autism, PDD-NOS (pervasive developmental disorder not otherwise specified) and Asperger's syndrome with a single diagnosis: autism spectrum disorder (ASD). The rationale for this change was simply that no evidence exists demonstrating that these disorders have different etiologies or outcomes from autism. DSM 5 uses social communication and repetitive stereotyped behaviour in a two-factor model to diagnose ASD. Dr. Szatmari criticized this two-factor model for its failure to effectively capture the complex heterogeneity of ASD cases. As an alternative to this parsimonious two-factor model, Dr. Szatmari introduced a more complex two-factor, three-class model that incorporated individual differences in severity of symptoms as a means of identifying individual heterogeneity in ASD cases. This model was discussed further in the workshop's poster session by his graduate student, Stelios Georgiades (see Session VIII of this report).

Complex variation in the developmental trajectories of ASD patients also adds to the challenge of effectively diagnosing this disorder. Trajectories of core and orphan phenotypes may interact with one another to yield developmental outcomes that would not have been predicted by looking exclusively at only a subset of these phenotypes. While this trait has enormous implications for treatment of ASD patients on an individual basis, the current understanding of these complex interactions is inadequate to permit improved diagnostics. As a means of unraveling this complexity, both Dr. Rutter and Dr. Szatmari stated that more work needs to be done with individuals who have autism, as opposed to with groups of autistic individuals. An improved understanding of the etiological basis of ASD is essential for improving the quality of life of autistic individuals, as successful treatment outcomes are widely recognized as being dependent upon early life diagnosis.

Dr. Rutter concluded by presenting several points for the workshop attendees to consider throughout the following days' data presentations and discussions:

1. We need to recognize the lack of validating evidence for categorically distinct, mutually exclusive, diagnostic entities. 'Pure' disorders are the exception BUT not the rule. This needs to be taken into account in DSM-5 and ICD-11. It is possible that ASD will prove to be heterogeneous; so, do the diagnostic techniques work as they are now? Sub-categorization does not currently work, but the idea should not just be thrown out.

2. It is clear that early life neurodevelopmental impairment is characteristic of ASD, ADHD, and schizophrenia (as well as other disorders). So, don't just think about how these disorders are different, but also ask what do they have in common?

3. In addition, all three disorders are likely to involve several distinct biological pathways. How do these different biological pathways come together?

4. In searching for possible causal influences, it will be advantageous to consider neurodevelopmental disorders as a group, and not just individual diagnoses. How can we build in a way of responding to new biological findings as they come up without having to go through the process of redoing the entire classification?

SESSION II: DEVELOPMENT

Session Chair: Dr. Charles A. Nelson III, Harvard Medical School *A cognitive neuroscience approach to the early identification of autism*

Dr. Tom Boyce, University of British Columbia: *Young children sensitivity to social context*

Dr. Colin Studholme, University of Washington Medical Centre: *Studying human brain growth in utero using MRI*

Dr. Armin Raznahan, NIMH IRP, NIH: *Models of typical brain development as a critical framework for autism neuroimaging*

SESSION SUMMARY: Heterogeneity in both the nature and severity of ASD is thought to be reflective of a similar degree of variation in the developmental trajectories of its biology. The development of the central nervous system (CNS) is a focus for autism research, with the goal being to use abnormalities in CNS development as early biomarkers of ASD. However, the results of imaging efforts to characterize the influence of ASD on CNS development are strikingly inconsistent across studies. One key problem has been the absence of a reliable model of normal CNS development in humans. Dr. Studholme and Dr. Raznahan presented work conducted using magnetic resonance imaging (MRI) techniques to describe neuroanatomical changes that take place during normative brain development both in utero and in young children. These brain imaging models were used to emphasize the potential diagnostic power of using maturational coupling of developmental rates between different brain regions as a biomarker of ASD. Electrophysiological and neural metabolic properties of the developing brain also

present the potential of yielding early life biomarkers for diagnosing ASD, and Dr. Nelson described differences in these phenotypes between different ASD risk groups. The social context in which a child lives and matures is now recognized to bear great influence on the developmental trajectory of the CNS, as well as on adult health outcomes that include mental health disorders. Dr. Boyce discussed commonalities between context-sensitive children and individuals lying along the autism spectrum, stating that biological commonalities between these two groups may provide insight into the developmental basis of ASD. While the characterization of the genetic and environmental susceptibilities of individuals to developing ASD is as yet incomplete, the influence of gene by environment interactions (GEI) on the biology of ASD cannot be ignored.

While autistic behavioural phenotypes are thought to be a result of abnormal development and/or activity within the CNS, an accurate model of 'normal' brain development through gestation, childhood, adolescence and adulthood has yet to be developed. This model of normative development may provide an essential basis for comparison in early clinical screening for the diagnosis of ASD and other neuropsychiatric disorders.

Neuroimaging techniques using MRI technology construct neuroanatomical maps of the brain and its diverse functional regions. A major challenge for imaging studies is to obtain images from an immobile subject; movements of even fractions of a centimetre can blur the resultant image and greatly limit its diagnostic usefulness. Dr. Studholme has developed MRI techniques for imaging tissue growth in utero, and discussed their clinical application for ASD.

Dr. Studholme's solution to imaging a moving fetus was to capture a large number of images very quickly using 2D Multi Slice imaging and then stitch the images together in order to produce a 3D representation of the target tissue. This reconstruction-based motion correction of fetal MRIs has generated models of fetal CNS development over the course of weeks 20-32 of gestation (20-32GW) that recapitulate the results of post-mortem imaging studies. Dr. Studholme's research group has been particularly interested in characterizing the temporal-spatial patterning of tissue growth in developing fetal brains. Their studies have identified discrete time periods during which some regions of the brain develop more quickly than others, as well as differences in the rate of tissue growth in distinct brain regions. While their work has not specifically examined ASD cases yet, Dr. Studholme's imaging techniques have identified abnormalities in fetal ventricle growth in individuals with isolated mild ventriculomegaly (IMVM). This example demonstrated the potential of fetal neuroimaging as a means of not only modeling human CNS development in utero, but also as a means of diagnosing neurodevelopmental disorders before birth.

Models of normative brain development in children, adolescents and adults also have great clinical potential not just for neuropsychiatric diagnostic techniques, but also for assessing the efficacy of treatment. Dr. Raznahan reported that his group's efforts to construct a model of child brain development have identified distinct differences in tissue growth between brain regions and hemispheres. Enormous asymmetries in developmental rates between brain hemispheres have been identified. Additionally, the rates of development of some regions are tightly matched with other distinct regions, while yet other regions develop at a different rate over the course of maturation. These trends in the maturational coupling of distinct brain regions may have enormous implications for our understanding of the etiological basis of ASD: via a process of developmental dissemination, the effects of an abnormal developmental event that occurs at a discrete timepoint in one brain region may influence the development of other brain regions that are simultaneously undergoing change. Such a mechanism may help to explain the enormous heterogeneity of ASD phenotypic outcomes, and further work with longitudinal studies will be required to establish this as an early ASD diagnostic technique.

Neuroanatomical imaging technology is not alone in its potential for improving the success of early life ASD diagnoses. Dr. Nelson presented work from a project aimed at identifying the presence of neural signatures in infancy that distinguishes between the susceptibility of developing ASD in high and low risk children (HRC and LRC). This on-going longitudinal study has examined gamma activity in the frontal areas of the brain for evidence of reduced levels of neural integration in HRC, particularly during the first year of life. While substantial differences were reported between LRC and HRC gamma activity at 6 months of age, these differences were absent by 24mo.s and 36mo.s. Additionally, Dr. Nelson reported differences in brain hemisphere connectivity and specialization in face and language processing tasks between LRC and HRC groups. Between 6-12 months of age HRC showed poorer connectivity relative to LRC, as well as a right hemisphere bias for specialization in LRC and a left bias in HRC. These trends demonstrate functional differences in brain development between LRC and HRC during infancy.

Dr. Nelson also reported differences in neural metabolism between HRC and LRC groups. Near-infrared spectroscopy (NIRS) was used to monitor neuroanatomical oxy-hemoglobin responses in infants to images of a familiar (eg: mother) or strange person with a neutral or smiling expression. While differences in the patterns of oxy-hemoglobin response have been recorded in the right postero-lateral and orbitofrontal cortex, Dr. Nelson stated that they are as yet unsure of how these differences relate to ASD susceptibility and developmental outcome. Further work with these longitudinal cohorts is anticipated to identify changes in neural signatures that are predictive of the development of ASD.

These data have demonstrated early life variation in CNS developmental trajectories between brain regions within an individual as well as between individuals who are known or suspected to exhibit different developmental outcomes. These early life differences are anticipated to provide a means of diagnosing ASD so that treatment can begin earlier and be tailored to the individual. But what role could early life experience play in both the development and treatment of ASD?

Previous work has demonstrated the potential of early life social experience to perturb neurodevelopment and generate a diversity of maladaptive mental health

outcomes in both children and adults. Dr. Boyce presented the model of the context-sensitive child as an example of not just the influence of early life experience on development, but also of a role for natural genetic variation serving to modify individual sensitivity to the environment. Dr. Boyce's group has identified broad individual differences in stress reactivity between children in response to psychological challenge tests. In children with low stress reactivity, the social context (ie: stressful vs. supportive living conditions) did not influence individual response to stress tests. In highly reactive children, however, the social context matters: those reared in a positive, nurturing environment showed even lower reactivity to stress tests than low reactive children. When reared in a stressful environment, highly reactive children showed the highest levels of reactivity. These trends were postulated to represent a curvilinear response to early-life stress exposure, where low-reactive – or dandelion – children were exposed to moderate stress levels, and highly reactive – or orchid – children were exposed to high or low levels of stress. These phenotypic trends have been associated with a naturally occurring polymorphism in the gene encoding BDNF.

Highly reactive children display a number of phenotypes that are reminiscent of ASD phenotypes, such as social shyness, a need for routine in everyday life, increased mental health risk under adversity, and exaggerated sensory sensitivity. Dr. Boyce suggested that these similarities may be reflective of biological commonalities between orchid children and individuals who lie somewhere along the autism spectrum. Differential sensitivity to social context may contribute to generating alternate developmental trajectories in autistic individuals. Additionally, individual sensitivity to social environment may translate to responsivity to therapy.

SESSION III: NEURAL PERSPECTIVES

Session Chair: Dr. Takao Hensch, Harvard Medical School
Critical periods: molecular and neurophysical approaches

Dr. Ricardo Dolmetsch, Allen Institute for Brain Science:
Using stem cells and mice to look at autism

Dr. Geoffrey Hinton, University of Toronto: *Can neural network models help us understand autism?*

SESSION SUMMARY: The neural perspectives approach to studying ASD involves multiple levels of analysis, going from the level of the entire CNS down to the small scale of neurons, synapses and molecules (eg: neurotransmitters). By nature of the extraordinary complexity in sequence and timing of events that take place during neural development, it is clear that there are many levels at which developmental errors can occur and generate dysfunctional neurons and neural circuits. Dr. Hensch's laboratory has developed mouse models for critical windows of neural plasticity during which key developmental events must occur for the proper maturation of neural circuits. Dr. Hensch posits that autism may be a consequence of developmental mistiming of these sequential windows of opportunity/vulnerability, and that following such an event a cascade of neurodevelopmental defects may ensue. Dr. Dolmetsch described the use of pluripotent stem cells in the characterization of neural development and activity in vitro, and discussed the potential of this technique for phenotyping the neurodevelopmental events that occur in ASD. A key challenge to conducting neurodevelopmental phenotyping research is that it is impossible to monitor these events in vivo in humans. Dr. Hinton proposed the use of computer neural network modeling as another means of constructing models for autism research. Using human biological data, computer modelers construct representative models (ie: simulated programs) of neural networks in humans. Dr. Hinton proposed that this method could not only provide a means of describing the maladaptive consequences of perturbations during critical periods of neurodevelopment, but that they also have the potential to generate a more detailed characterization of ASD behavioural phenotypes.

The development of the nervous system is characterized by sequential windows of neural plasticity, which are best viewed as periods of opportunity and vulnerability for neurodevelopment. The timing of onset of these critical periods (CP) of plasticity in different brain regions is sequential, and any mistiming in their onset may subsequently lead to a cascade of defects in neurodevelopment. Dr. Hensch's research has previously described a mechanism whereby GABAergic (gamma aminobutyric acid) circuit maturation triggers neural plasticity in the visual cortex. Prior to onset of a CP, high levels of excitatory input and low levels of inhibition in GABAergic parvalbumin (PV)-positive basket cells prevent maturation of these circuits. Inhibitory activity surpasses excitatory input from PV cells during the CP; this excitatory-inhibitory (EI) imbalance stabilizes upon closure of the CP. Perturbations in the timing of onset of these CP are thought to give rise to neurodevelopmental disorders.

Using spatiotemporal patterns of large basket PV cell maturation (ie: changes in EI balance), Dr. Hensch suggested that it is possible to map the maturational time course of discrete brain regions throughout the CNS. PV-cell phenotypes have been implicated in ASD phenotypes in both humans and mouse models of ASD. Dr. Hensch is currently interested in examining ASD patients for evidence of specific circuit defects in EI balance at discrete timepoints during development, but the technology to examine this activity at the level of the cell in vivo is not yet available in humans.

Autism is highly heritable and the study of the genetic basis of ASD has seen the development of many mouse models in which to study the etiology of this disorder. With mouse models, the goal is to mutate ASD candidate genes and observe changes in behavioural and neurophysiological phenotypes. However, as Dr. Dolmetsch described from his experience with mouse models, it is far easier to phenotype behavioural traits in humans. Additionally, behaviour is multigenic, and the relative contribution of genetic background to human behaviour cannot be replicated in a mouse. Similarly, the neurophysiology of the mouse brain does not precisely

represent that of the human brain. However, recording from circuits in vivo in the human brain is impossible.

By reprogramming skin cells from patients with neuropsychiatric disorders into neural stem cells, it is possible to record neural activity in vitro from slices of human nervous tissue. This technique has been used successfully by Dr. Dolmetsch's group to characterize abnormal neural activity in Timothy Syndrome (TS; calcium defects) and Phelan McDermid Syndrome (reduced evoked postsynaptic excitatory currents) tissue slices. A screen of 1200 drugs demonstrated that roscovitine eliminated not only the dysfunctional phenotype seen in TS slice recordings, but also reversed the effects of TS on gene expression in neurons. Reintroduction of the SHANK3 gene into Phelan McDermid tissues rescued the observed defects in these slices; this is of interest for autism research as SHANK3 is an ASD candidate gene.

For a neural network modeler like Dr. Hinton, the question of interest in ASD research is that of how all of the symptoms of autism fit together. Furthermore, do all of these diverse symptoms merit being placed together as part of a single disorder? The general approach of neural network modeling to addressing these questions is to construct a model of the network using the best possible biological information. This working model of a normal network can then be disrupted in a specific way and the resultant effects used to provide insight into the mechanistic and etiological basis of neuropsychiatric disorders. Dr. Hinton described existing neural network models of ASD as being too simplistic: specifically, they fail to represent the complex connectivity of the one hundred billion neurons and one hundred trillion synapses of the human CNS. Although network modeling is now capable of constructing models with billions of connections, knowledge of the basic biology of ASD is now limiting the usefulness of network models. In addition to this potential for the development of neural network models of ASD, Dr. Hinton suggested that these models could also serve as a means of more effectively diagnosing ASD. By training a network model with videos of autistic behavioural phenotypes, it may be possible to develop an automated and unbiased means of diagnosing autistic patients more accurately.

SESSION IV: GENETIC, GENOMIC, EPIGENETIC PERSPECTIVES

Session Chair: Dr. Marla Sokolowski, University of Toronto

Dr. Stephen Scherer, The Hospital for Sick Children: *Challenges in ASD diagnosis and treatment*

Dr. Brendan Frey, University of Toronto: *Predicting phenotype from DNA sequence*

Dr. Declan Murphy, King's College London: *Genomic imaging: can it help develop new treatments?*

Dr. Rosanna Weksberg, The Hospital for Sick Children: *Etiology of autism: a role for epigenetics?*

SESSION SUMMARY: The search for common genetic variants underlying ASD has largely been abandoned in favour of studying rare, highly penetrant variants that cause ASD. One prominent trend that has appeared in studies of these rare genetic variants is the co-occurrence of ASD with other neuropsychiatric disorders. Significantly, no one single variant has been uniquely associated with autism. Insight gained into the influence of these rare penetrant risk loci on basic neural function can serve to illuminate the mechanistic and developmental bases of these disorders. Dr. Scherer discussed the role played in the etiology of ASD by rare genetic variants that are known to influence the functioning of neural connections, or synapses. Using a network modeling approach, Dr. Frey discussed the influence of novel variation in DNA sequence on gene expression as a means of explaining the development of some diseases. Presenting work from the European public-private research consortium EU-AIMS, Dr. Murphy discussed ongoing research into the development of ASD biomarkers. Epigenetic mechanisms (specifically, DNA methylation and histone modification) were discussed by Dr. Weksberg as mechanisms whereby environmental factors could putatively contribute to the development of ASD.

Rare genetic variants have been associated with between 0.1-1% of all documented ASD cases. These variants include rare chromosomal abnormalities, rare copy number variants (CNVs) and rare highly penetrant genes, and are usually associated with the incidence of other neuropsychiatric disorders. Analysis of these variants implicates neuronal synaptic genes in the etiology of ASD, and Dr. Scherer stated that 15-20% of all ASD cases can be associated with genetic variants that alter synaptic function and therefore neural communication. Indeed, synaptic spine volume is reduced in some ASD cases, and this has been hypothesized to reflect altered homeostatic regulation of neuronal proteins (ie: the distribution of synaptic proteins is imbalanced).

Dr. Scherer's research has identified a variety of rare genetic variants from ASD patients that result in altered synaptic function such as PTCHD1and SHANK1. Whole genome sequencing (WGS) techniques allow researchers to better identify variation in both coding and non-coding sequences and CNVs that underlie ASD. The results of these studies can be used to help people with family planning as well as to increase the efficacy of early life interventions for carriers of risk genes. These data have led Dr. Scherer to propose a model of relative genetic contribution to ASD risk, whereby mutations in risk genes contribute to the susceptibility of an individual to developing ASD. The total contribution of all mutant risk loci generates a diverse spectrum of heterogeneous phenotypic outcomes. In spite of the identification of risk genes for ASD, many questions remain. Why are so many genes seemingly involved in the etiology of ASD? Are any of these risk loci specific to ASD, or do they represent general neurodevelopmental genes? Are all ASD risk genes associated with a specific component of neural function (eg: synaptic development and plasticity)?

Autism research often looks at the association between variations in gene sequence and altered behaviour and neurophysiology. Dr. Frey's research uses neural

network modeling to investigate the impact of DNA sequence variation on the expression of genes known to have multiple splice variants. These splice variants each give rise to unique mRNA transcripts, and the presence or absence of a specific transcript in a given cell can generate developmental and/or functional consequences. Dr. Frey's model also allows for the manipulation of the cell environment in which a gene is expressed. In this model, the percent of transcripts containing a specific exonic sequence is denoted by psi (Ψ), and ΔΨ yields a measure of the phenotypic change in mRNA resulting from a specific genetic sequence variant. This model has been tested against clinical data for cases of spinal muscular atrophy associated with mutations of the SMN1 gene. Modeling of specific point deletions in SMN1 accurately predicted the transcript phenotypes that had been identified through clinical molecular analyses of SMN1 mutations. Dr. Frey suggested that this modeling approach has the potential to predict transcriptional phenotypic outcomes of mutations in ASD risk genes, particularly given that multiple splice variants are known to be produced by ASD risk loci.

Dr. Murphy discussed his involvement with EU-AIMS, a public-private consortium designed to bridge the gap between scientists and clinicians. This consortium's goals are to improve efficiency in the translation of cellular and animal model work to clinical and therapeutic practices, with a particular focus on the development of effective early life biomarkers of ASD. Through investigations of the developing CNS for developmental differences in white and gray matter growth between children with ASD, their research aims to identify ASD susceptibility based on cortical volume and surface area traits. As with Dr. Scherer's work, EU-AIMS is investigating proteins involved in mediating synaptic transmission, and aims to develop biomarkers of synaptic function that identify ASD before the onset of clinical symptoms.

Environmental contributions to ASD etiology have not been discussed thoroughly in this workshop's sessions largely because few – if any – studies have definitively demonstrated environmental influences on ASD. Epigenetic modifications provide a route whereby environmental influences can alter CNS development and generate ASD outcomes. Dr. Weksberg's presented research driven by the hypothesis that mutations in genes involved in epigenetic regulation give rise to ASD. Their work focused on the effect of fertility treatments (FT) because the timing of FT coincides with epigenetic programming events during the first trimester. Using Illumina 27k methylation arrays, Dr. Weksberg's group has identified changes in DNA methylation patterns at several loci that have previously been implicated as ASD risk genes. Their work is ultimately focused on developing means of modifying these methylation sites for the clinical treatment of ASD.

SESSION V: ANIMAL MODELS

Session Chair: Dr. Joel Levine, University of Toronto *Animal models of autism: what's the control?*

Dr. Jacqueline Crawley, UC Davis School of Medicine: *Mouse models of autism: behavioural phenotyping and treatment discovery*

Dr. Daniel Turnbull, New York University: *Imaging mouse models: MRI of the developing mouse brain*

Dr. Steve Suomi, NICDH/NIH: *Eye-tracking of faces in imitating and non-imitating Rhesus monkey neonates*

SESSION SUMMARY: Autism, as a neuropsychiatric disorder resulting in abnormal social phenotypes, is a uniquely human condition. An understanding of the etiological basis of ASD is complicated by the fact that diagnosis of this heterogeneous disorder is based almost entirely on descriptive behavioural phenotyping. The use of model organisms such as primate, mice and fruit flies in studies to tease apart the developmental basis of ASD allows researchers to investigate the genetic, molecular and cellular components of this disorder's etiology. The study of ASD candidate genes in non-human organisms requires the careful selection of appropriate controls and behavioural phenotypes that faithfully reflect human ASD behavioural phenotypes. Dr. Levine's work with fruit flies has revealed a hitherto unrecognized complexity underlying social interactions within groups of flies, and his lab's work has recently identified a genetic basis for these traits in flies. Dr. Crawley discussed her lab's work with mouse models for the ASD risk gene ENGRAILED 2, and Dr. Turnbull reported the use of Manganese-Enhanced MRI (MEMRI) to study the influence of this candidate gene on mouse brain development. Genetic and CNS-related phenotypes in Rhesus monkeys displaying autistic-like behavioural phenotypes were discussed by Dr. Suomi, who reported that a neo-natal facial imitation phenotype seen in both Rhesus monkeys and humans has the potential to serve as an early life screen for autism.

ASD is a highly heterogeneous disorder characterized by a host of social behavioural abnormalities. Key to effectively diagnosing and treating ASD is the ability to identify an autistic individual's position along this behavioural spectrum. Studies of social networks aim to identify patterns in the organization of social groups. Studies of human social networks have identified that the distribution of individuals in these networks is non-random. Dr. Levine's research has demonstrated the formation of non-random social networks in groups of fruit flies, and that genetic manipulations that impede communication confound the formation of these networks. This work has identified a genetic basis for social interactions within groups of fruit flies. Dr. Levine reported that mutations affecting various neurodevelopmental genes affect how a fly responds to its social context. This work has demonstrated that the genetically tractable fruit fly has a complex social structure and behavioural repertoire. Through the study of evolutionarily conserved genes, these traits make them useful as models for studying the genetic and molecular bases of human neuropsychiatric disorders that have social phenotypes.

Mouse models exist for a variety of ASD candidate risk genes. As a human disorder whose diagnosis is based largely on behavioural phenotyping, the study of ASD-like features is complicated in non-human organisms by the fact that human social behaviour is uniquely human: there is no such thing as an autistic mouse or fly. This demands that the question of which behaviours in mice reflect human ASD phenotypes be properly addressed. What are the appropriate bioassays for examining these behaviours? Dr. Crawley discussed this fundamental issue in the context of her group's work with mouse models for the ASD candidate risk gene, ENGRAILED-2 (En2).

En2 encodes a homeobox transcription factor that regulates embryonic brain development. Using a novel 3-chamber social behaviour assay, Dr. Crawley's group demonstrated a lack of sociability in mice mutant for En2 (ie: En2 -/-). This assay was designed so as to provide a means of analyzing a phenotype that had strong face validity to autistic features, specifically that of social interaction between children in novel situations. Treatment of En2 -/- mice with anti-depressants improved this social interaction phenotype. The ability of this treatment to restore some social function in En2 -/- mice prompted Dr. Crawley to suggest that there may yet be some hope of developing effective pharmaceutical interventions for ASD.

Dr. Turnbull discussed the use of manganese-enhanced MRI (MEMRI) microimaging to study the influence of En2 on the development of the mouse brain. Poor resolution of the neonatal brain by standard MRI techniques can be improved by the injection of manganese into a newly born pup. MEMRI may also provide a means of detecting neural activity in vivo. This provides greater contrast between different brain regions, and Dr. Turnbull has used this technique to construct a model of mouse brain development over the first two weeks of life. This longitudinal imaging work complements the data presented by Dr. Crawley by providing a means of establishing some neurodevelopmental basis for the autistic-like behavioural phenotypes of En2 -/- mice. MEMRI revealed an effect on cerebellar growth in En2 -/- mice specifically in the deep cerebellar nuclei (DCN). This is potentially an important finding for autism research, as cerebellar output to other brain regions occurs via the DCN: disruptions in cerebellar communication may underlie some ASD phenotypes.

While ASD is clinically a uniquely human disorder, autism research using animal models is made feasible typically through the study of evolutionarily conserved ASD risk genes in genetically tractable species like flies and mice. One concern with this gene-to-behaviour approach that was raised repeatedly during this session was that of how to identify behavioural abnormalities seen in these models as valid surrogates of human autistic behaviour. Dr. Suomi's work with Rhesus macaque monkeys has instead worked from the behavioural level to that of the gene, and has demonstrated the occurrence of autistic-like features in specific individuals within Rhesus troupe societies.

Rhesus macaque societies are based around a dominant matriarch, and every individual in the troop has a place within the social hierarchy. Dr. Suomi's research focus has been on monkeys within a troupe that have profound differences in personality. Roughly 20% of the monkeys studied demonstrate highly reactive responses to stressful situations; another 5% of individuals show highly impulsive and aggressive reactions within their social group. The first month of neonate life has been identified as highly influential for the development of a rhesus' social skills. During this time, mother-reared (MR) infants remain in physical contact with their mothers, and a tight infant-caregiver bond is formed. Dr. Suomi's work has demonstrated that infants removed from their mothers during the first 7-8 months of age and peer-reared (PR) form a hyperattachment to their peers. When returned to the troupe these PR monkeys show behavioural and social deficits, displaying either extreme social inhibition or aggression.

Relative to their MR counterparts, PR monkeys show lower brain serotonin activity as well as increased expression of genes related to inflammation, cell growth and transcriptional control. In contrast, the expression of genes related to immunoglobin production and Type 1 interferon response is decreased in PR monkeys; these patterns reflect what is seen in socially isolated humans. Another striking trend is that of DNA methylation differences, where about 25% of the Rhesus genome is differentially methylated between PR and MR monkeys of both sexes after 1month of age; this is striking, as after 2 years of age far fewer genes are differentially methylated in PR females as compared to males. This trend is associated with the onset of puberty, and this imbalance between sexes is reminiscent of male:female differences in the incidence of ASD in humans.

Dr. Suomi's group has recently discovered the phenomenon of neonatal facial imitation in rhesus monkeys, a trait that was once thought to be uniquely human. Neonatal facial imitation is thought to be integral to the proper formation of the infant-caregiver bond in humans, and in rhesus is a trait that disappears by the end of the first month of life. Rhesus infants that fail to imitate during the first week of life develop self-focused behaviours, a common trait in autistic children. This finding has prompted the development of the 'monkey avatar', a computer program of a monkey face which includes eye-tracking software that records where the infant rhesus' eyes focus on the computer screen. The monkey avatar software has revealed that monkeys which imitate during the first week of life focus visually on the eyes and the mouth of the avatar, whereas non-imitators focus on only the mouth. This defect is reminiscent of facial eye-tracking phenotypes of autistic individuals, who focus on different facial regions as compared to non-autistic peers. Dr. Suomi's research is now focused on developing interventions aimed at rescuing the eye-tracking phenotypes of PR monkeys to the 'normal' levels of their MR peers. Specifically: human caregivers will interact with the PR monkeys 2 hours/day; administration of oxytocin, and; attempts to bias a non-imitator to focus on the eyes and mouth of the monkey avatar. This research represents the first primate model of autistic-like behaviour, and may have identified neonatal success/failure of facial imitation as an early life screen for ASD.

SESSION VI: TRANSLATIONAL PERSPECTIVES

Session Chair: Dr. Evdokia Anagnostou, University of Toronto and Bloorview Research Institute *Therapeutics for the social deficits of ASD: the promise of neuropeptides*

Dr. Jane Foster, McMaster University: *Effects of gut micrbiota on the brain: a role in anxiety and stress reactivity*

Dr. Jason Lerch, The Hospital for Sick Children: *Examining autism through the lens of imaging multiple mouse models related to the disease*

Dr. Peter Kind, University of Edinburgh: *Cellular dysfunction in Fragile X Syndrome and related disorders*

SESSION SUMMARY: The translation of science to treatment is fundamental to the success of autism research. Only through proper communication between scientists and clinicians can the results of animal modeling studies be translated into clinical practice in a manner that allows for the proper development of therapeutic interventions. Ultimately, improved diagnostic and treatment success resulting from translational methods will enhance the quality of life for autistic individuals. In this session, Dr. Foster discussed her research into the gut microbiome and its contribution to behaviour in mice and humans. Dr. Lerch presented his lab's progress in characterizing CNS development in a variety of mouse ASD models. The role of the synapse in mediating autistic neurophysiological phenotypes has been a central theme of this workshop. Dr. Kind's research group has investigated the efficacy of an MgluR5 antagonist in treating synaptic and circuit dysfunction in an FXS mouse model. Dr. Anagnostou's contribution to this workshop represents Canada's first ever clinical trials network dedicated to the study of neurodevelopmental disorders. Dr. Anagnostou's research into a role for oxytocin (OXT) as a pharmacological intervention for treating autistic patients exemplifies the clinical aspect of the translation of animal model research into clinical applications.

The immune system provides an important route for the communication of environmental information to the developing brain, and gut microflora are essential to the development of the immune system. Dr. Foster presented research into the relation between the gut microbiome, immune function and the development of the CNS in 'germ-free' (GF) mice lacking gut microflora. In an elevated plus maze, GF mice displayed reduced anxiety-like behaviour relative to controls. This phenotype persisted in GF mice whose guts were conventionalized (ie: guts colonized with microflora) at 10-weeks of age. In contrast, this phenotype disappeared after conventionalization of GF mice just prior to adolescence (ie: 3-weeks of age). Anxiety-like behaviour is also altered in mice (TCR) deficient for T-cells, and these TCR mice show changes in hypothalamic brain volume. These data demonstrate that changes in the gut microbiome as well as inflammatory response can influence behaviour. Gastrointestinal (GI) disturbances are prevalent in autistic children and the number and severity of GI disturbances increases with the severity off ASD. Future work in this area will seek to characterize the influence of the gut microbiome on human CNS development in utero (from the mother) as well as during infancy.

Although ASD is now thought to result from altered CNS development, conflicting reports exist in the literature regarding the association between ASD and changes in amygdala and hippocampus volume. This is, perhaps, unsurprising given the vast heterogeneity of ASD phenotypes. With this in mind, Dr. Lerch postulated that it would be possible to associate differences in brain development with specific ASD risk gene models. Dr. Lerch reported that the results of MRI assays conducted on ten different mouse ASD gene models have identified general decreases in brain volume associated with ASD genes, particularly within the cerebellum and hypothalamus. These data were analyzed so as to cluster similar neuroanatomical changes together in three groups, and Dr. Lerch reported that the genes associated together within these clusters perform similar functions in the same brain regions. These data also demonstrated that changes in one specific brain region at a given time point were often associated with changes later in another specific brain region(s). This trend seems to parallel the model of cascading neurodevelopmental defects that was discussed by Dr. Hensch at this workshop (see Session III).

Neuronal synapses are a focus of ASD research. Synaptic connectivity, and plasticity of this trait, reflects the ability of the brain's different circuits and regions to communicate properly with one another. Dr. Kind's research is focused on the biochemistry of the synapse, and aims to understand how genes permit the developing brain to be modified by experience. Using mouse models, Dr. Kind's group studies the development of the primary somatosensory cortex, the brain region to which all axons extending from whiskers extend. Their research has previously identified a role for glutamate receptors in the post-synapse in modifying development of the somatosensory cortex, and focus on the MgluR5 receptor has stemmed from this. Using mouse models of Fragile X Syndrome (FXS), Dr. Kind's group has reported that MgluR5 antagonists can correct some FXS sensory problems. Investigations of circuit defects in FXS model mice (ie: Fmr1 gene knockout mice) have identified abnormalities in synaptogenesis, although abnormalities in dendritic spine density (a traditional hallmark of FXS) are subtle. However, recordings from thalamocortical slices have identified a delay in the timing at which long-term potentiation occurs in these neurons; this is indicative of a delay in the critical period of synaptic plasticity. In addition to this delay, signals generated from these neurons are not propagated properly across cortical networks. In Fmr1 mutant mouse thalamocortical circuits, neurons are more sensitive to activation and that the transmission of signals across the cortical sheet is impaired. Significantly, these trends indicate an excitatory-inhibitory imbalance in Fmr1 mutant neurons; this is reminiscent of the work discussed previously by Dr. Hensch in this workshop.

The autistic triad is clinically so varied that multiple pathways are likely to be involved. For treatment, specific pathways for each ASD case must therefore be targeted. Therapeutic approaches have involved borrowing medications from overlapping conditions; this is based on the rationale that overlapping phenotypes share a common etiological basis. However, this approach has not been very successful. Two major new proposals for drug development involve the translation of molecular targets

from genomic studies (see Dr. Scherer's work in session IV), as well as the translation of circuitry knowledge into therapeutics that target disturbed networks. Advances in these approaches were discussed further by Dr. Anagnostou.

Administration of the drug STX209 to FXS patients has seen success in treating the low sociability trait associated with this disorder. Oxytocin (OXT) treatment has also been demonstrated to ameliorate social deficits in animal neurodevelopmental models, as well as emotion processing in humans. Dr. Anagnostou reported that – while the data is not yet convincing – oxytocin deficits have been identified in ASD patients. While current studies have suggested that OXT treatment improves social interaction deficits as well as language comprehension, these studies have not followed patients over a long-term course of OXT administration. Dr. Anagnostou reported that her group is currently pursuing longitudinal studies to further examine the effects of OXT treatment on ASD. Their pilot work has demonstrated a large effect on improving eye motion detection and focus in ASD patients; however, no improvement in social interaction has yet been identified. While patients report a feeling of well-being, they cannot characterize this feeling. Dr. Anagnostou stressed that while this pilot data is by no means conclusive, it is promising for the development of more effective clinical treatment of ASD symptoms.

SESSION VII: WORKSHOP SUMMARY AND FUTURE PROSPECTS

Session Chairs: Dr. Evdokia Anagnostou and Dr. Marla Sokolowski *Future prospects, cross-disciplinary/collaborative opportunities, and novel research directions*

Dr. Nelson started the summary discussion by asking the workshop's attendees a series of questions:

- An extremely diverse collection of phenotypes are associated with ASD: is there some way to leverage this trait, or is it only complicating efforts to identify the etiological basis of ASD?
- What will it take to validate the contribution of human genes to ASD?
- How exactly are critical periods and excitatory-inhibitory balance involved in ASD?

For the validation of human genes, will in vitro analysis of human genes in cells (as discussed by Dr. Dolmetsch) or in vivo analysis of orthologs/homologs in mice be sufficient? Developmental and functional consequences may not be properly captured or represented by either of these two methods: this could cause researchers to miss identifying a key technique for treating ASD. For the development of drugs, you need something that will incorporate as much of the circuit involved as is possible, and this is impossible in vivo in humans.

De novo mutations seem to be strongly associated with ASD. Dr. Levine raised the issue of environmental contributions to ASD and suggested that perhaps novel environmental stressors are increasing the rate of these de novo mutations. How can genomic hotspots for de novo mutations be protected from these environmental effects? Increasing parental age may also be a contributing factor here. An important question that will need to be answered in this line of questioning is whether or not the rate of mutations has indeed increased in recent decades. Dr. Nelson suggested the use of sperm bank samples to address this point.

On the topic of phenotypic variation, Dr. Rutter mentioned that past efforts to focus on individual differences in behaviour has not paid off. Given that the three key features of ASD are not – strictly speaking – a biological category, how likely is it that genes identified in individuals and organized in this way will yield any useful information? An important question to ask is whether or not two children with the same ASD phenotype have the same disorder; are there multiple routes to the same developmental endpoint? Additionally, the biological pathway that carries a risk for ASD and schizophrenia is in all humans: what are the implications for how these disorders are studied?

Current efforts to improve diagnostic success through the association of a biological phenotype with ASD are focused on — among other regions — the synapse. The suggestion that research should be able to identify some circuit or excitatory-inhibitory endophenotype that serves as a biomarker for ASD was raised in this workshop. This prompted Dr. Hensch to state that he doesn't think that we can take the step from EI imbalance to explaining all of ASD without understanding how circuit abnormalities alter sensory perception. Dr. Hensch stressed that it is EI imbalance during critical periods of neural development that alters neuroanatomical and physiological properties. A resultant EI imbalance in the affected circuits then persists throughout life. For researchers, it is important to identify which 'E' and which 'I' is of interest, and then focus on a specific region of the brain and monitor how an EI imbalance in this and associated regions affects development. Significantly, different genetic mutations can have different effects on EI, and rescuing the effect of EI imbalance may depend on which CP, which kind of EI imbalance and which brain regions are all targeted. This putative approach to diagnosis and treatment reflects the extraordinary heterogeneity of ASD cases.

Although current research holds promise for improved diagnostic and therapeutic outcomes, Dr. Rutter stressed to the workshop attendees that it is imperative that the research community does not overstate its current ability to provide treatment for ASD patients. Discussions of a cure for autism are particularly to be avoided, as the idea of curing a disorder is contrary to how medicine works. While the concept of personalized diagnosis and treatment is fundamentally appealing from the perspective of ASD's clinical heterogeneity, current knowledge of the basic biology of ASD is incapable of providing this level of care. Even in the case of rare highly penetrant ASD risk genes, personalized treatment is not yet feasible. However, we do currently have both the knowledge and the ability to improve quality of life. Continued work with animal models will eventually provide a sufficient level of understanding of the basic biology of ASD to permit improved diagnosis and treatment.

Following on Dr. Anagnostou presentation, Dr. Kind asked whether or not current pharmaceutical trials are ineffective because the drugs do not work, or if their efficacy is dependent upon their being coupled with an appropriate behavioural or cognitive therapy. Dr Anagnostou's group has reported improvements in social functioning in children following oxytocin treatment, but that the children did not know what to do or how to interact. Citing unpublished research from Dr. Allison Fleming's group into maternal depression and oxytocin, Dr. Sokolowski suggested that Dr. Anagnostou collect history data (specifically for depression and abuse) from their test subjects' mothers.

Representatives from Autism Speaks were invited to join the workshop. Dr. Spoelstra of Autism Speaks addressed two key points that were missing from the workshop. The communication of research to the parents of autistic children can be improved, particularly with respect to those areas that show the most promise for improving quality of life for people with ASD. Improved communication is essential given the vast wealth of information – ranging from genuine scientific research to pseudoscience – available to public stakeholders. Great care must be made in not miscommunicating information with the public. Dr. Spoelstra's second point had to do with how little (ie: none) mention was made of adults living with autism. All research and therapeutic efforts are focused on children, but adults with autism are largely failing to be integrated into society. Dr. Spoelstra commended the workshop as the best example of integrative science that she had yet seen. She also encouraged the autism research community to suggest means by which parents of autistic children can learn to think more critically about the 'data' that filters through to the public domain.

PUBLIC LECTURE

In conjunction with this workshop, Autism Speaks, sponsored public event, *"Cracking the Autism Enigma"* on February 20, 2013, CIFAR and the Ontario Brain Institute hosted an evening in Toronto with Dr. Stephen Scherer who presented some of his latest research on Autism. The lecture was complimented with a discussion with Dr. Marla Sokolowski (Co-Director, CIFAR program in Child & Brain Development, formerly Experience-based Brain and Biological Development; Co-Director, Fraser Mustard Institute in Human Development, University of Toronto) and Dr. Evdokia Anagnostou (Clinician Scientist, Bloorview Research Institute; Assistant Professor, University of Toronto) moderated by OBI's President Dr. Donald Stuss.

Dr. Stephen Scherer, The Hospital for Sick Children:
Cracking the Autism Enigma

Autism spectrum disorder is highly heterogeneous and is associated with impairments in 3 domains of function: social impairment, verbal and non-verbal communication impairment, and repetitive/restrictive behaviours. Known as the autistic triad, impairments in these three domains of function show highly variable expression not only between individuals but also within an individual over time. Enormous variation in clinical presentation of ASD makes the description of a 'classical' autism case impossible. This phenotypic variation is reflected at the level of the gene by enormous variation in genetic factors now recognized and suspected to underlie ASD. However, variation in autistic phenotypes between monozygotic twin pairs demonstrates the significance of environmental contributions to ASD. In this public lecture, Dr. Scherer described the results of recent genomic, imaging and animal model research efforts that have contributed to unraveling the etiological basis of ASD. Clinical application of this research is aimed at improving the quality of life of autistic individuals, and Dr. Scherer discussed the potential of developing personalized therapeutic interventions from genomic studies.

The central nervous system is comprised of 100 billion neurons which are connected to one another by 100 trillion synapses, and roughly 75% of the 30,000 genes in the human genome are expressed over the course of the brain's development. ASD is thought to be a consequence of the developmental mistiming of key processes that occur during the growth and maturation of the CNS. In addition to the contribution of genetic factors, the development of the CNS is known to be highly sensitive to a host of environmental perturbations. Dr. Scherer stressed that while this extraordinary complexity makes unraveling the etiology of ASD a seemingly insurmountable task, modern imaging and genomic studies are providing the means of accomplishing this goal.

Magnetic resonance imaging (MRI) studies of the CNS have begun to shed light on putative mechanistic bases of autistic behavioural traits. These studies have associated the cerebellum and caudate nucleus with repetitive behaviours, amygdala with emotional processing, and the thalamus with communication between brain regions. Dr. Scherer briefly mentioned some of the data presented at the on-going workshop which described the development of models of normative brain development. Such models may help in the development of biomarkers for the identification of ASD neuroanatomical phenotypes and permit early life (or even pre-natal) diagnosis. He also mentioned the increasing interest in the role of the synapse as a target for autism research and clinical intervention. Dr. Scherer's genomic work has implicated the synapse as a target for ASD research.

Nearly 100 ASD candidate risk genes have been identified through genomic studies of autistic individuals, and many of these genes and their protein products function at the synapse. An example cited from Dr. Scherer's own work was that of SHANK2, which was associated with decreased synaptic spine volume in ASD patients. Mutations in synaptic genes such as SHANK2 produce imbalances in synaptic proteins: this results in altered neuronal homeostasis. This finding may lead to the development of improved pharmaceutical treatments for individual ASD cases that are known to be associated with abnormal synaptic phenotypes.

Dr. Scherer reported that 1 in 88 children are currently estimated to develop autism during their lives. This statistic combined with the fact that improved therapeutic outcomes are strongly associated with early life diagnosis makes the development of more effective screening methods essential. The behavioural traits of the autistic triad will always be the mainstay of ASD diagnosis. However, improved knowledge of the neuroanatomical and physiological features of the brain as well as of ASD risk genes will serve to increase the quality of early life diagnosis. Current trends in ASD research reported in this public lecture have prompted Dr. Scherer to predict that a new autistic triad – clinical description, the genome, and the brain – will be the future of improved diagnostic success, as well as of improved quality of life for ASD patients and their families.

SESSION VIII: POSTER PRESENTATIONS

Dr. Jacob Ellegood, Hospital for Sick Children: *Clustering multiple mouse models of autism based on neuroanatomy*

Dr. Ellegood presented research aimed at characterizing neuroanatomical variation between 27 different mouse ASD risk gene models. Using MRI, this work has identified regional differences between the models and clustering analysis revealed 3 distinct functional groupings of ASD risk genes. Additionally, these groups cluster in the same distinct brain regions, and this work has demonstrated that changes in volume in a specific region of the brain are often associated with volume changes in other regions.

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Dr. Anne Takesian, Children's Hospital Boston: *Lynx1 regulates a critical period for auditory thalamocortical plasticity*

ASD may be a consequence of developmental mistiming of critical periods (CP) of neural development. Dr. Takesian presented work describing a role for Lynx1 in regulating the opening and closing of CP in the mouse auditory cortex. This work will contribute to the molecular characterization of neurodevelopment, and will also serve to identify new means of clinical intervention for developmental disorders.

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Dr. Krissy Doyle-Thomas, Bloorview Research Institute/ University of Toronto: *Atypical functional connectivity during rest in ASD*

Dr. Doyle-Thomas's research uses functional magnetic resonance imaging to examine brain network function in discrete neural circuits. The preliminary results of these imaging studies suggest deficits in both local and long-range connectivity in the brains of ASD patients. Local over-connectivity between precuneus and occipital lobe brain regions was identified in autistic children; this is thought to interfere with the clarity of neural transmission.

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Dr. Irene E. Drmic, McMaster University: *Mental health in ASD: Improving treatment and identifying risk factors*

Mental health and anxiety disorders commonly co-occur with ASD, and the alleviation of these symptoms can greatly improve the quality of life of autistic individuals. Identification of early life factors that influence developmental trajectories in behavioural and emotional domains of functioning is the focus of this work. This research will help in the development of superior therapeutic practices for alleviating mental stress in ASD patients.

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Matthew Gazzellone, University of Toronto: *Cross-disorder genomic analysis identifies Gephyrin (GPHN) as a risk gene for ASD*

Genomic analysis across cohorts drawn from three mental health disorders (ASD, schizophrenia and epilepsy) has identified gephyrin (GPHN) as a novel risk gene for neurodevelopmental disorders. GPHN is a post-synaptic scaffolding protein and is known to interact functionally with ASD risk genes. Matthew Gazzellone reported the discovery of overlapping deletions of GPHN in six patients diagnosed with ASD, schizophrenia or epilepsy.

Stelios Georgiades, McMaster University: *Phenotypic heterogeneity in children with ASD*

New DSM 5 criteria for the clinical diagnosis of ASD are based on identifying social communication deficits (SCD) and fixed interests and repetitive behaviours (FIRB). Stelios Georgiades has developed a 2-factor/3-class model based on severity of symptoms in SCD and FIRB domains that more faithfully represents individual differences between autistic patients.

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Dr. Kieran J. O'Donnell, McGill University: *The early care environment, symptoms of inattention/hyperactivity and DNA methylation in childhood*

During childhood, epigenetic mechanisms guide neurodevelopmental processes such that the growing brain is ideally adapted to its environment. Dr. O'Donnell's research is particularly focused on the identification of patterns in DNA methylation that are associated with maladaptive neurodevelopmental outcomes later in life. The goal of this research is to develop a means of identifying individuals who are high at risk of developing neuropsychiatric disorders, and to develop improved clinical interventions for these individuals.

Patrick Steadman, University of Toronto: *The importance of structure in autism: the cerebellum's morphology in three genetic mouse models*

Through the use of MRI, Patrick Steadman has demonstrated the existence of volume differences in the cerebella of three mouse ASD risk gene models: Neuroligin 3 R451C, MECP2 and Integrin-β 3. These patterns were discussed with respect to the cerebellum's known regulatory roles in mediating repetitive and social behaviours, and cognitive function.

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Dr. Ryan Yuen, The Hospital for Sick Children: *Detection of clinically relevant genetic variants in autism spectrum disorder using whole genome sequencing*

Dr. Yuen reported the use of whole genome sequencing to identify de novo as well as rare inherited genetic variants predicted to be associated with the incidence of ASD in 32 families. This approach detected genetic variants known or suspected to be involved in the development of ASD or related clinical symptoms. This approach may help in early life detection of ASD, which will lead to improved therapeutic outcomes and quality of life for autistic patients.

For more information on the Neuroscience Accelerator Workshop: Autism or CIFAR/OBI Knowledge Outreach events, contact:

Amy Cook, CIFAR Director, Knowledge Outreach:
acook@cifar.ca
Tel: 416-971-4885

Kirk Nylen, OBI Director, Outreach:
knylen@braininstitute.ca
tel: 647-872-1213