Course Materials
The purpose of these materials is to help provide an introduction to the Summer Institute session on brain function and structure. The materials were designed to prepare trainees who are unfamiliar with pharmacological treatment with the general background to get the most educational benefit from Dr. Veenstra-VanderWeele’s presentation. Toward this objective, we have prepared the following: (1) learning objectives for this session; (2) some key terms and concepts to become familiar with different methods of brain research; (3) some broad review articles that are recommended reading. These materials could be considered “prerequisites” in preparing for Dr. Veenstra-VanderWeele’s presentation.

In collaboration with Dr. Veenstra-VanderWeele, these materials were developed by the trainee group for this session: Kristina Cottle (graduate student at University of Utah; Kristina.cottle@utah.edu), Tom Rayner (medical student at University of Utah; Thomas.rayner@hsc.utah.edu), Kimberly Aldinger (research staff at Seattle Children’s Research Institute; Kimberly.Aldinger@seattlechildrens.org), and Susan Brasher (graduate student at University of Florida; suez7272@ufl.edu). Feel free to contact us with questions/comments.

Register for this course and other sessions in this series at http://sfari.org/summer
Learning Objectives

The Summer Institute for Autism Research was established in direct response to requests from early career researchers (graduate students, postdocs, etc), who asked INSAR and SFARI for greater training opportunities in multidisciplinary topics. In designing the Summer Institute, the priorities were: (1) to provide a multidisciplinary training platform for young scientists from various backgrounds; (2) allow international participation; and (3) make it freely available. Thus, the inaugural Summer Institute covers broad topics (which are geared to researchers outside the respective topic areas), is offered over a free web platform, and allows researchers from around the world to connect with the presenter. The overarching goal of the Summer Institute is to expose junior scientists to topics they are not currently engaged in, with the hope that basic scientists and clinical scientists could learn from each other to ultimately advance the understanding of autism spectrum disorders.

The current session, Pharmacological Treatments, is lead by Jeremy Veenstra-VanderWeele and a team of trainees who worked in tandem to prepare these materials and the web presentation. The learning objectives for attendees of this session include:

- Understand the process of moving from preclinical hypotheses to testing medications in ASD.
- Explain two pathways to developing new medications in ASD, one building from an understanding of risk factors contributing to ASD and one arising from an understanding of circuits important for social or repetitive behavior.
- Discuss the challenge of heterogeneity in relation to treatment in ASD, where individuals present with highly varying patterns of core and associated symptoms.
- Describe the current evidence for medications used in children with ASD.
Glossary of Terms / Key Concepts

- **Molecular genetics**: Molecular genetics is the field of biology that studies the structure and function of genes at the molecular level. [For more information: view the course materials and watch the replay of Session IV: Genetics, led by Matthew State: http://bit.ly/State_replay ]

- **Copy number variants**: Copy Number Variants (CNVs) are when stretches of DNA (arbitrarily defined as greater than 1000 base pairs) are present in different amounts between individuals. At most places in the genome, each person has two copies of DNA. There are some places in the genome that have fewer or more copies. These copies can be small and impact one gene or large and impact many genes. Some CNVs are part of the normal genetic variation between people and some of these changes contribute to disease. CNVs account for genetic risk in 5-7% of individuals with ASD.

- **Single-nucleotide variants**: A single-nucleotide variant (SNV) is a single base change in the DNA of a genome that arises naturally, usually caused by errors in the normal functioning of DNA replication machinery. SNVs can either be inherited from a parent or they may arise in an affected person for the first time, which is often referred to as spontaneous or de novo. SNVs can lead to changes in protein sequence, which may impact gene function and cause disease. This type of genetic variation is rare in the population. SNVs that impact gene function are predicted to account for genetic risk in at least 25% of individuals with ASD.

- **Heterogeneity**: Heterogeneity refers to diversity. Clinical heterogeneity refers to variability in participants, the types or timing of outcome measures, and intervention characteristics. Genetic heterogeneity is a phenomenon in which one phenotype can be caused by genetic changes in many genes. ASD is both clinically and genetically heterogeneous, which poses challenges for diagnosis and treatment.

- **Phenocopy**: A phenocopy is a phenotype (disease, symptom or trait) caused by different means among affected individuals.

- **Basics of pharmacological treatment**: The decision to prescribe a pharmacological treatment considers potential risks and benefits to each patient. Psychiatric disorders can be treated with either or both pharmacological and behavioral interventions for a pre-defined period of time following a detailed clinical assessment. Patients should be informed of possible side effects and possible interactions. Clear, comprehensive and individualized treatment plans may represent the best therapeutic approach. Pharmacological treatment may be used in children and adults with ASD in conjunction with other therapies to alleviate particular symptoms, such as seizures, aggression, irritability, agitation, inability to focus, depression, and excessive energy levels.

- **Off-label use**: Pharmaceutical drugs can be prescribed by physicians for uses other than what the FDA has approved. These “off-label” or unapproved features may be indication, age group, dosage or form of administration.

- **Antipsychotic medications**: Antipsychotic medications are a class of psychiatric medication used to treat symptoms associated with various mental disorders. Typical antipsychotic medications have been used in the treatment of psychosis and disordered thinking since the 1950’s, while atypical antipsychotic medications were developed later on. Both typical and atypical antipsychotic medications block dopamine receptors and have severe side effects including movement disorders, weight gain, and increased risk for cardiovascular disease. Atypicals also act on serotonin receptors. Two atypical antipsychotic medications, risperidone and aripiprazole, are FDA approved to treat symptoms of irritability, aggression, and agitation in children with ASD.
• **Peptide hormones:** Peptide hormones are a class of proteins composed of only a few amino acids that are secreted into the bloodstream and have an effect on the endocrine system.

• **Secretin:** Secretin is a naturally occurring peptide hormone that stimulates the pancreas to secrete alkaline pancreatic juice and the liver to secrete bile. Secretin regulates the pH of the gut by inhibiting the secretion of stomach acid and stimulating the production of bicarbonate from the pancreas. Secretin has been used to treat core symptoms in children with Autism Spectrum Disorder (ASD) despite clinical evidence showing no effectiveness.

• **Oxytocin and vasopressin:** Oxytocin and vasopressin are hormones made in the hypothalamus and stored and released by the pituitary gland. Oxytocin causes contraction of the uterus during labor and of the mammary glands during lactation. Oxytocin plays important roles in pair-bonding, including intimacy, sexual reproduction, and during and after childbirth by regulating neural processing of social signals and social attachment. Vasopressin has two primary functions: to retain water in the body and to constrict blood vessels. Oxytocin and vasopressin have a similar structure, they are located next to each other on the same chromosome, and they are expressed by neighboring neurons in the hypothalamus. A small series of trials that used oxytocin treatment to restore social deficits in ASD were not effective.

• **Glutamate:** Glutamate is the primary neurotransmitter and the major mediator of excitatory signals in the brain. It is involved in most aspects of normal brain function including communication between neurons, cognition, learning and memory. Glutamate is released by one cell and binds to receptors on an adjacent cell. There are two main types of receptors in the brain that bind glutamate to activate neurons. Ionotropic glutamate receptors activate neurons directly when glutamate binds, while metabotropic glutamate receptors activate neurons indirectly by initiating a signaling cascade. Ionotropic receptors transmit signals more quickly, while signals transmitted through metabotropic receptors can last longer. Glutamate receptors are implicated in many neurological conditions. Too much stimulation of glutamate receptors can cause cell death in the brain over time.

• **Metabotropic glutamate receptors:** Metabotropic glutamate receptors (mGluRs) are a family of glutamate receptors that modulate synaptic transmission through an indirect process that involves G proteins. Thus, mGluRs are referred to as G-protein coupled receptors. G proteins affect multiple biochemical pathways in the cell and can both increase or decrease cell signaling to produce a wide range of physiological effects. There are eight different types of mGluRs that are divided into three groups based on their structure and physiological activity. Group I mGluRs (mGluR1 and mGluR5) have been implicated in the pathogenesis of Fragile X syndrome (FXS), the most common inherited cause of intellectual disability due to loss of function of the fragile X mental retardation protein (FMRP). FMRP is normally involved in reducing mGluR5 activity and drugs that block (antagonists) mGluR5 alleviate some symptoms in mouse models. Clinical trials using mGluR5 antagonists to treat FXS did not show improvement over placebo in any outcome measures.

• **Criteria for validating animal models of psychiatric disorders:** There are three primary criteria for establishing the validity of an animal model as a true representation of the process under study: face, construct and predictive validity. Face validity refers to the outward similarity in appearance between the model and the disorder. Does the mouse model “look like” features of the human disorder? Construct validity refers to the internal mechanism that underlies the disorder. Does the mouse model contain the same genetic modification found in the human disorder? Predictive validity refers to the ability of the model to identify therapeutic treatments for the disorder. Does the treatment (genetic interaction, pharmacological, etc) restore or rescue measurable outcomes? Ideally, an animal model should possess both construct and predictive validity in order to be used to understand the mechanisms and the etiology of the disorder and to identify promising treatments. [For more information: view the course materials and attend Session VI: Animal Models, led by Joseph Buxbaum]
Recommended Background Reading


Get Engaged

Continue the conversation and connect with peers currently working or interested in autism.

- Join SFARI’s private autism research discussion group on Facebook: http://on.fb.me/1yWVOoO
- Become an INSAR member: http://www.autism-insar.org/membership
- Contact the INSAR Student & Trainee Committee: studentcommittee@autism-insar.org