Offord CENTRE FOR CHILD STUDIES

McMaster University

GENETICS OF AUTISM RESEARCH UPDATE

NOVEMBER 2014

INSIDE THIS ISSUE

What's Happening?

We have had an exciting past few years, working on our Genetics of Autism projects. We are continuing to recruit families with one or more children with an Autism Spectrum Disorder in order to collect detailed clinical information and complete genetic analysis using the latest, state-of-the-art technology. While the basis of our genetic research has not changed, we are excited to have joined the Province of Ontario Neurodevelopmental Disorders (POND) Network to investigate ASD alongside other disorders with similar clinical characteristics. As a result of this partnership, we have the opportunity to offer a variety of new studies open to your participation.

The success of the Genetics of ASD studies has been, and will always be, dependent on the dedication of the families and children involved. For this, we are extremely grateful for your continued support of the study and your enthusiasm for research! As we continue to work on new discoveries, the Genetics of ASD Projects continue to represent strong partnerships between the Sick Kids Hospital/University of Toronto and the Offord Centre for Child Studies/McMaster University and families.

As well, we have seen a change in our leadership here at the Offord Centre. I am delighted to introduce three new investigators, who over the years have made significant contributions to ASD research at McMaster. We are happy that Marc Woodbury-Smith, Stelios Georgiades and Terry Bennett have agreed to take the scientific leads at McMaster University for the varying ASD studies, including Genetics, POND Network and Pathways in ASD Studies.

Dr. Peter Szatmari, M.D. MSc, FRCPC

Autism Spectrum Disorder Medication Treatment Study <u>Participants Needed</u>

Medication Offers Promising New Option for Autism Treatment

Currently there are no medications approved to treat the core deficits of autism (social skills, repetitive behaviours). McMaster University/McMaster Children's Hospital is conducting a research study to investigate whether the drug Riluzole may be helpful with these symptoms. Riluzole is a drug that is already Health Canada & FDA approved for treating adults with neurological disorders.

Why is Riluzole being considered a treatment for ASD? The human brain is never quiet: every region constantly fires electrical signals. Some signals are loud and clear and others are muffled murmurs. In autism, the background murmurs are hard to tune out and the brain becomes noisy, making it difficult to receive clear signals. It's like trying to have a private conversation in a crowded room, some words get lost and the message is hard to understand. Riluzole is a drug that may help some people with ASD tune out brain background noise so that they can receive clear signals. In this way, Riluzole may improve compulsive, aggressive and repetitive behaviours. Unlike current drug treatments, Riluzole may also improve social skills and help kids with ASD talk to other children, make friends and enjoy activities with other people.

Who can participate? Children aged 6-17 diagnosed with Autism Spectrum Disorder (ASD, Autism, PDD-NOS, or Asperger's Syndrome) may be eligible. You do not have to reside within the hospital's catchment area in order to participate. Expenses related to participation (e.g. parking, cost of drug) will be paid for by the study. Participants will also receive compensation for their time as a token of appreciation.

How do I know if this trial would be a good fit for my child? Decisions about medication always require careful consideration. Dr. Bennett will meet with you at the beginning to provide information and discuss whether this study is right for you and your child.

How do I learn more? To learn more, or to participate, please contact **Dr. Teresa Bennett's** Research office at 905-521-2100 extension 74906.

Introducing Our New Investigators

Marc Woodbury Smith, MD, PhD

I am a psychiatrist specialising in the diagnosis and management of autism spectrum disorders and disorders of intellectual development. I have been working in specialist clinics for this population of children and adults for the last 15 years. Having previously worked in Cambridge in the UK and at the Yale Child Study Center in the U.S., I have now been located in Hamilton for the last six years. I am particularly interested in the clinical needs and wider social outcomes among higher functioning adolescents and adults, and my research currently focuses on investigating the genetic underpinning of ASD. In particular, I am interested in evaluating the genetics of novel ASD phenotypes, combining established and emerging methods of genetic analysis. In addition, I am the lead investigator for the Hamilton limb of a collaborative study investigating oxytocin as a treatment for the social vulnerabilities in ASD.

Stelios Georgiades, PhD

I am an Assistant Professor in the Department of Psychiatry and Behavioural Neurosciences and a Core Member of the Offord Centre for Child Studies at McMaster University. As a researcher I have expertise in child psychiatric epidemiology. My program of research aims to generate knowledge that will inform our efforts to overcome one of the main challenges in the study of neurodevelopmental disorders – the remarkable clinical and biological heterogeneity. Specifically, my research aims to identify meaningful subgroups in Autism Spectrum Disorders (ASD) something that can inform treatment selection and tailoring based on each child's strengths, challenges, and comorbidities. Moreover, empirical classification of children with ASD based on similarities and differences in clinical profiles can inform our quest for understanding the shared and unique biological underpinnings of the disorder.

Teresa (Terry) Bennett, MD, PhD

As a child psychiatrist, my job involves working with kids, families and their support teams to help decrease the suffering related to emotional and behavioural problems. Our shared goal is to help kids live up to their unique potential, enjoy their daily lives and connect with others in their own way. My special interest is in "developmental cascades" in childhood – that is, teasing apart patterns in child development to understand how progress or difficulties in one domain (e.g., social skills) can help or hold back progress in another part of a child's development (e.g. language, learning). This way we can target treatments that yield the most "spillover effects" for people with ASD and other mental health or developmental differences. One type of treatment is medication: I am the lead McMaster investigator on a medication trial called RILISE. We are testing whether a medication called Riluzole is helpful and safe in children with autism spectrum disorders (ASD).

Advances in Genetic Testing Technologies for Autism Spectrum Disorder Research

The last 10 years of research have produced an incredible amount of information about autism spectrum disorders (ASD), but much still remains to be understood. We know that genes play a role in contributing to ASD, but the genetic causes of ASD are complex and not yet well defined. Humans have approximately 30 000 genes which are the instructions that tell our bodies how to grow and function. Changes to genes can disrupt the typical pattern of development, which can contribute to a diagnosis of ASD. Our research is focused on trying to identify the underlying genetic changes in individuals with ASD through the use of genetic testing technologies.

Over the course of the study there have been tremendous advances in the types of genetic tests used in the research lab. Currently our testing protocol includes microarray analysis and whole genome sequencing (WGS). Both microarray analysis and WGS look at all of an individual's genetic information (genome), but differ in the types of genetic changes they can identify. Microarray analysis can identify missing (deletion) or extra (duplication) genes or parts of genes, where as WGS can identify spelling mistakes in genes. WGS is the most comprehensive, highest resolution genetic test available to date. With the use of WGS, we can theoretically identify all genetic changes in the genome, which we can then further investigate to see if they play a role in causing ASD.

These advancements in genetic testing have enabled us to identify hundreds of genetic changes that confer a genetic risk for ASD, most of which play a role in brain cell development and function. For individual families, identifying genetic risk factors that contribute to their child's diagnosis of ASD can help direct medical care for their child, can more accurately estimate their chances of having another child with ASD, and can connect families who share similar or the same genetic change through community/support groups. It is such an exciting time for research in ASD given the power of these new genetic testing technologies. With the help and valuable contributions of families enrolled in our research study, we hope to advance our understanding of the genetics of autism with the ultimate goal of early detection and intervention, and targeted therapeutic development in order to enhance the quality of life of individuals with ASD.

Ny Hoang, MS, CGC
Genetic Counsellor, Autism Research Unit
The Hospital for Sick Children

NEW STUDY: Medication Study for Adults with Autism Spectrum Disorder

St. Joseph's Healthcare Hamilton and McMaster University are currently conducting a research study (clinical trial) to investigate whether the drug Intranasal Oxytocin (FDA approved) helps to improve symptoms of Autism Spectrum Disorder, specifically social functioning and repetitive behaviours. If you are between 18 and 45 years of age and are interested in learning more about this study, please contact **Dr. Marc Woodbury-Smith's** Research Office at 905-521-2100 extension 74906, or via email ipatrici@mcmaster.ca. Quick Fact: Oxytocin is NOT Oxycontin and is in NO way related to it.

POND NETWORK
Province of Ontario Neurodevelopmental Disorders

The **Province of Ontario Neurodevelopmental Disorders (POND) Network** is leading the charge in developing new and novel ways to ask questions about Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Obsessive Compulsive Disorder, and Intellectual Disability. By removing each disorder from its "diagnostic silo", the POND Network researchers believe collecting the same information across neurodevelopmental disorders (behavioural, genetic, biological, brain imaging) will improve our understanding of the symptoms of each disorder. This can potentially lead to more research about the types of treatments and therapies currently used in Ontario, and the world, for these neurodevelopmental disorders. However, this information is only useful to the citizens of Ontario if it is clearly communicated. The POND Network is dedicated to producing **"Research in Clear Language"** for all stakeholders (patients, parents, clinicians, researchers, policy makers, advocacy groups).

Below are two newsworthy scientific articles in clear language which describe specific research results that some of the POND Network investigators have been involved with recently. For all summaries, please refer to our website: www.pond-network.ca

GENETIC RELATIONSHIP BETWEEN FIVE PSYCHIATRIC DISORDERS

What is the research about? Many psychiatric disorders are heritable (passed from parent to child before birth) but the genetic overlap across disorders is unclear. The goal of this study was to examine the shared genetic etiology for five disorders: Schizophrenia, Bipolar Disorder, Major Depressive Disorder, Autism Spectrum Disorder (ASD), and Attention Deficit/Hyperactivity Disorder (ADHD).

What did the researchers find? This study found that some of the disorders studied might be more genetically similar than once thought. This provides evidence suggesting that individuals may share common risk factors for different psychiatric disorders. The researchers found the following genetic relationships between disorders: **High:** Schizophrenia and Bipolar Disorder; **Moderate:** Schizophrenia and Major Depressive Disorder, Bipolar Disorder and Major Depressive Disorder, ADHD and Major Depressive Disorder; **Low:** Schizophrenia and ASD

Take home message: It appears that individuals with schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder and attention deficit/hyperactivity disorder share certain similar genetic variations. Some of these psychiatric disorders may be more similar and related than once thought. This provides new insight into potential risk factors and causes for the development of these disorders.

NOTE: This research is done by the Cross-Disorder Group of the Psychiatric Genomics Consortium. (Nature Genetics, 2013, Sep;45(9):984-94)

AN UPDATE ON MEDICATION MANAGEMENT OF BEHAVIOURAL DISORDERS IN AUTISM

What is the research about?

ASD has become increasingly common over the past several decades. The core symptoms (social communication deficits and restricted interests and repetitive behaviours) of ASD are often accompanied by irritability, inattention, anxiety and hyperactivity. Currently, no medications are approved for treatment of the core symptoms and only 2 drugs are approved by the United States FDA for treatment of irritability associated with ASD. This review of several studies serves as a summary and update regarding medication management for behavioural disorders in ASD.

What did the researchers find?

•Medications for the treatment of ADHD. The use of ADHD medications in children with ASD is on the rise. Guidelines for use in the ASD population have been put forward by the Autism Treatment Network. Regular monitoring of overall health is important.

•Anticonvulsants. There is little evidence to date to support the use of anticonvulsants as treatment for behavioural disorders in ASD.

•Adrenergic Agents. Limited evidence supporting the use of these medications in ASD exists, however, given the fact that they are generally well tolerated and have limited side effects, their use may be considered for ADHD symptoms.

•Novel Agents. Over a dozen studies are currently examining the use of oxytocin in ASD, with early work gaining significant excitement. Many other novel agents are under investigation as possible treatments for the core symptoms and associated behaviours of ASD.

Take home message

The past 3 years have not produced any further medications approved for the treatment of the symptoms associated with ASD. Large trials for new medications (e.g. Oxytocin) are under way, with the promising results expected in the near future. Changes to the DSM 5 allow children to receive a diagnosis for ADHD along with ASD, permitting easier treatment of certain symptoms of ASD. Thanks to data being published, clinicians are now able to make more informed choice regarding medication treatment, however much more research in this field is needed.

Powerhouse Collaboration: Your Genes Reach the "Cloud"

Autism Genome Research embraces the concept of "Open Access" Science

Recently, Autism Speaks announced that geneticist Stephen Scherer (Hospital for Sick Children and University of Toronto) as the new director of a new Autism Speaks-led project. The first major announcement came from Dr. Scherer in a presentation at a conference in San Diego where he outlined the groundbreaking project "MSSNG" (pronounced missing). Vowels were intentionally removed from the spelling to highlight the unknown answers about whole genome sequencing the program hopes to uncover.

MSSNG is a collaboration between Autism Speaks, Google and SickKids Hospital in Toronto. The overarching mission of the project is to provide whole genome sequences of 10,000 individuals with autism and their family members to the scientific research community, as well as to the family members and their doctors involved in the project. Google will use the platform Google Cloud to provide storage for the genomes the MSSNG program. Once the genomes are sequenced, approved scientists will be able to access the whole genome using Google Cloud. Google Cloud will also provide powerful analytic tools that will allow approved geneticists, scientists, researchers and biostatisticians to process the information to test novel hypotheses.

Our Canadian families will play a role! For the families who have given their consent, your de-indentified information (collected as part of the Genetics of Autism studies) will be amongst the first group placed in the cloud. All of your identifying information will remain secure and confidential with our research team.

For more information about the MSSNG program visit Autism Speaks website (www.autismspeaks.org).
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NEW STUDY: The POND Network: Brain Imaging Study

The Province of Ontario Neurodevelopmental Disorders (POND) Network is currently recruiting participants with Autism Spectrum Disorder (ASD) and Obsessive Compulsive Disorder (OCD) for a brain imaging study being conducted at St. Joseph's Healthcare Hamilton. The research study is examining brain development in children with ASD or OCD. Participants will be asked to come to St. Joseph's Healthcare Hamilton to an MRI appointment, during which they will take pictures of the participants' brains as they watch a movie and play computer games. At the end of the session, the participant will have the option to ask for a picture of his or her brain! If your child has been diagnosed with ASD or OCD, is between the ages 6-18, and does NOT wear braces or have any metal implants in their body (i.e. Brain aneurysm clip, cochlear implants, etc.) then please contact **Dr. Geoff Hall's** Research Office at 905-525-9140 extension 24784 to learn more.

POND NETWORK
Province of Ontario Neurodevelopmental Disorders

5 MUST READ TIPS for Improving Your Child's Sleep

Parents have often reported how challenging it can be to put their child with ASD to bed. Preliminary findings from the Pathways in ASD study, a national longitudinal research program with more than 400 children enrolled, show that at least 60% of families are reporting their child having difficulties going to sleep and remaining asleep at night. That is no surprise to many families affected by ASD. Here are some helpful, "MUST READ TIPS" from Autism Speaks about improving your child's sleep.

1. Provide a comfortable sleep setting

Wherever your child goes to sleep at night, the place should be safe, quite, and the same each night (whether shared with a sibling or alone). Controlling for temperature, light, and sound is important for children who may have specific sensitivities to these and other obtrusive distractions.

2. Establish a regular bedtime routine

A bedtime routine should last between 15 and 30 minutes depending on the age of the child (a younger child will need a shorter routine). The bedtime habit should be short, predictable, and expected, and should encourage the child to relax and get ready for sleep. Identifying events that are calming or events that stimulating will help establish a routine. Some key tips recommended by Autism Speaks and researchers are:

a) the routine should take place in the child's bedroom where it is quiet

b) the routine should be done in the same order each night

c) move stimulating events to an earlier time in the evening (i.e. brushing teeth, bathing, etc.)

d) creating a visual schedule or "to-do list" (pictures, words) that help remind the child of the routine

3. Tips to keeping a regular schedule

Establishing a regular schedule is extremely important to a child's sleep habits and routines. Choosing a bedtime and wake up time that is the same 7 days a week is optimal. If your child has their "second wind" the hour before bedtime, consider moving up the bedtime routines by 30 minutes to 1 hour to cope with their natural schedule. As children age, they like to stay up a little later. Try and keep their schedule no more than 1 hour later for bedtime and 1 hour later for waking up on weekends. If your child is an earlier riser even if they go to bed late, it is important to keep the wake up time the same (or at least not more than 1 hour later). A more regular wake up time is recommended. If your child is younger and has a day time nap, keep the nap on a regular schedule, and in a comfortable sleep setting. Your child should eat breakfast at the same time every morning 7 days a week. At the end of the day, heavy meals or large snacks are not recommended. A light snack (cheese and crackers or fruit) may help your child fall asleep more easily. And finally, sunshine in the morning, and moonlight or street lights at night might disrupt the regular schedule. Eliminating any intrusive stimuli will help keep a regular schedule.

4. Teach your child to fall asleep alone

Children and adults often wake up several times a night, but quickly fall back asleep. If your child is used to sleeping alone, this will happen naturally. Otherwise, each time your child wakes up, they will have difficulty falling back asleep without someone around. Teaching them to fall asleep on their own is possible and can be done gradually over a few weeks' time. Here are some examples that will help teach a child to fall asleep on their own:

•If you lay with your child at night, try sitting up in the bed, then move gradually away to a chair, then gradually move the chair away from the bed until you are out of sight. Reduce the amount of attention you pay to your child as you do this.

•If your child is upset you are not in the room, wait a few minutes then check on the child very briefly providing little physical and verbal contact (e.g. a quick hug or saying 'It's time for bed, you are OK. Good night".)

•If you need to go back into the room, wait longer each time and make the visit more brief.

Bedtime Pass: A bedtime pass is a useful tool for older children. For example, if your child wakes at night, you may offer them a pass in the form of 1 visit from a parent, 1 drink of water, 1 nighttime hug, or 1 nighttime kiss. If they do not use the bedtime pass that night, they can be rewarded with a sticker, and after so many stickers that child can receive a special gift.

5. Promote daytime behaviours that encourage sleep

Physical activity during the day will help your child sleep better at night. Scheduling regular exercise (either at school or at home) will help your child fall asleep easier and have a deeper sleep at night. Exercise should be scheduled for the day because it might disrupt the child's evening bedtime routine. Avoiding caffeinated foods and beverages is a healthy practice to avoid. Caffeine can remain in your body for 3 to 5 hours and sometimes up to 12 hours.

Families often can help each other in establishing regular sleeping habits and routines. It is not uncommon for the family to adapt to a single schedule once it has become ritualized and repeated. Brothers and sisters can help with establishing routines by engaging in calming and relaxing activities before bedtime. It is not uncommon for children to have staggered bed times. This allows one-on-one time between the child and parent.

Researchers often refer to these kinds of tips as "good sleep hygiene". Establishing routines and habits can be done gradually over a few weeks' time. It is important to make sure everyone in the family is part of the process. If you find that these tips have not helped your child's sleep habits, you should talk to your doctor and discuss other options.

This information is courtesy of Autism Speaks. On their website, they provide full toolkits about sleep and other family services information. If you would like more detailed information about improving sleep in children with autism, please visit www.autismspeaks.ca/tool-kits/ .

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## NEW STUDY: MEASURING YOUR CHILD'S BRAIN ELECTRICAL ACTIVITY

The Language, Memory and Brain Lab (LMBlab) at McMaster University is looking for children between the ages of 6-14 with a primary diagnosis of Autism Spectrum Disorder to participate in a study recording their brain activity using electroencephalography (EEG) while they listen to tones, words and speech. EEG allows us to examine neurophysiological markers of brain function. We are particularly interested in markers of cognitive function in children diagnosed with autism. For Information about this study, contact: 905-525-9140 x 20380, email: lmblab@mcmaster.ca

POND NETWORK
Province of Ontario Neurodevelopmental Disorders

A Family Tree Study of Autism Spectrum Disorders

When ASD "runs in the family"

(A Molecular Genetic Study of Autism and Related Phenotypes in Extended Pedigrees)

Local investigator: Dr. Marc Woodbury-Smith
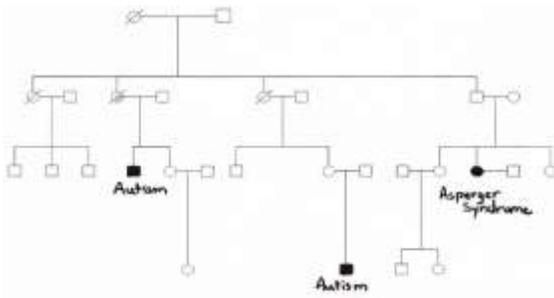
To date, researchers studying the genetic basis of autism have mainly been studying individual families composed of the child who has a diagnosis of ASD, their siblings and their parents. The Family Tree study is different because it is focused on family trees where there are there 3 separate but blood-related families that have at least one family member on the ASD spectrum. For example in the family tree to the left, there is a boy with Autism in the middle. His Mom has two cousins on the spectrum, one a female cousin with Asperger Syndrome and one a male cousin with Autism.

In the Family Tree study we gather blood samples from all the people in the family who have an Autism Spectrum Disorder diagnosis. Then we look for genetic differences that each person has. This helps us make a list of autism "suspect" genes--genes that may contribute to autism in some way. The difficulty is that all of us have many small genetic differences that make us unique, so the autism suspect list is still very long because of these other (non-ASD) genetic differences. We narrow down the list by looking at only those genetic differences that are shared by the three people who have the ASD diagnosis. In order to narrow down the list further, we hope to collect a blood sample from the unaffected people in the family tree as well (such as the child's aunts, uncles, grandparents). The reason for doing this is that these relatives will have some of the same genetic differences as those with ASD. If unaffected people have some of the genes on the "suspect" list, we then cross those genes off the list since these relatives don't have ASD. This method quickly trims down the "gene suspect" list and will more rapidly help us to understand the genetics of ASD.

A second contribution of family tree studies concerns the hunt for genes that may have only very small effects. Research so far suggests that there are likely 40-100 genes that contribute to an Autism Spectrum Disorder. Some genes may have a high impact and would definitely contribute to the cause of autism and others may have only a very small effect and would only very slightly increase someone's chances of developing an Autism Spectrum Disorder. Sometimes a person has a genetic difference contributing to ASD that was not inherited; it just arose spontaneously in that person as their cells were dividing. Other genes may be inherited. Some of the inherited genes may have a high impact and others may have very small effects. Our study hypothesizes a threshold model of autism in which a person may have a number of genetic differences (spontaneous or/and inherited) that would need to add up to have enough of an effect to "cross the ASD threshold". In that case, solving the Autism puzzle will involve trying to understand the genes that could have very small contributory effects (but don't in themselves result in autism). Genes like that might be expressed as more or less of typical personality traits would not, by themselves cause any real or lasting difficulty for a person carrying them. By studying a whole family tree we may gain important clues in the hunt for subtle contributory genes that we all carry, which only add small amounts of ASD susceptibility. We are trying to hunt for these "contributory" genes by gathering information about the personality styles of everyone in the family tree through questionnaires and a short interview.

Family tree studies have helped identify the genetic basis of other complex disorders such as diabetes & heart disease. We hope family trees approach will also lead to a better understanding of the causes of ASD. Much appreciation is owed to the many families who have participated so far! If you or someone you know may be interested in this study, please contact **Irene O'Connor at 905-521-2100 Ext. 74205, oconnoim@mcmaster.ca** Participating families would give a blood sample for DNA analysis, answer some questionnaires and complete some assessments of language and cognitive skills. Assessments can be completed at your home or at McMaster.