


MIND*lab*, Interacting Minds, Autism@Aarhus, DNC Seminar:

**Autism@Aarhus 2014 Symposium: 4th Anniversary Meeting**
**Wednsday 27 August 2014**
13.30-17:00
DNC Auditorium, Building 10G
Aarhus University Hospital, Nørrebrogade 44, 8000 Aarhus C.

Please come to the fourth Autism@Aarhus Anniversary meeting. You will hear what is happening now in autism research within, as well as outside, Aarhus University.

ALL INTERESTED ARE WELCOME. We look forward to seeing you!

PROGRAMME:

13.30-13.40
**Uta Frith & Line Gebauer**
*Welcome & Introduction*

13.40-14.10 + 5 mins Q&A

1. **Sven Bölte** (Karolinska Institutet)
   *High-risk for autism infant sibling research: Sweden, Europe, and the world*

14.15-14.35 + 5 mins Q&A

2. **Jakob Christensen & Diana Schendel** (Aarhus University)
   *Epilepsy and Autism in Siblings*

14.40-15.00 + 5 mins Q&A

3. **Jørgen Scheel-Krüger, Freja Bertelsen, Maria Møller Skovborg, Anne M. Landau, Pia Weikop, Arne Møller** (Aarhus University)
   *High risk factors for autism during pregnancy and their modulation of critical neurotransmitters in the central nervous system: the putative significance of a novel preclinical model*

15.05-15.25
*Break with Refreshments*

15.30-15.50 + 5 mins Q&A

4. **Therese Koops Grønborg** (Aarhus University)
   *Familial aggregation of autism spectrum disorders*

15.55-16.15 + 5 mins Q&A

5. **Joshua Skewes** (Aarhus University)
   *Reduced influence of prior perceptual knowledge in autism*

16.20-16.40 + 5 mins Q&A

6. **Riccardo Fusaroli & Ethan Weed** (Aarhus University)
   *Linguistic adaptation between parents and children in ASD: a longitudinal approach*

16.45-16.55
**Uta Frith**
*Concluding Remarks*

**High-Risk for Autism Infant Sibling Research: Sweden, Europe and the World**
*Sven Bölte*

Today, many cases of autism can be reliably diagnosed by at age two years. Until some 10 years ago, it was fairly uncommon for children to get diagnosed with autism before the age of three or four years. Even in today's clinical practice, in many cases, especially milder variants of ASD, late ASD diagnoses frequently occur. Early autism research is an evolving field of science. Key objectives are fine mapping of neurodevelopmental trajectories and identifying biomarkers in order to improve risk assessment, diagnosis and treatment. In recent years, a growing interest in infant development and early detection of ASD has emerged, mostly driven by the insight that early identification is a prerequisite for early intervention, which itself may improve long-term outcomes for individuals with ASD. Common early signs are primarily delays and deficits in response to name and joint attention and limited or perseverative early play. Nevertheless, many of these signs are neither specific for nor universal to ASD, with low positive predictive values, and a risk for overreferral particularly in case of one stage screening.
Longitudinal studies of high-risk sibling populations provide the potential to generate unique knowledge about the development of autism during infancy and toddlerhood prior to symptom onset, and neurodevelopmental trajectories in general. In this key note, I will give an overview on the state-of-the-art in early autism identification in general and studies of high-risk populations in particular, including recent research and development at the Center of Neurodevelopmemtal Disorders at Karolinska Institutet in cooperation with the Uppsala Child and Babylab (e.g. using eye tracking, NIRS, standardized scales etc), the ESSEA COST Network (Enhancing the Scientific Study of Early Autism; European Cooperation in Science and Technology; www.cost-essea.com), and "Eurosibs", part of EU-AIMS (www.eu-aims.eu), the largest European autism science network ever, as well as the Baby Sib Research Consortium (BSRC) in North America.

**Epilepsy and Autism in siblings**
*Jakob Christensen & Diana Schendel*

**BACKGROUND:**
Epilepsy and autism spectrum disorder (ASD) often occur together in the same individual and increased frequencies in siblings of epilepsy and ASD have been reported. However, it is not known whether ASD in one sibling increases the risk of epilepsy a younger sibling and vice versa.
**METHODS:**
This was a population-based cohort study in Denmark of all children born in Denmark between January 1, 1980, and December 31, 2004. Children were identified and followed up to December 31. 2010. We calculated the adjusted hazard ratio for epilepsy and ASD among younger siblings of older siblings with and without these disorders. We also estimated the risk of these disorders in half-siblings.
**RESULTS:**

We followed 1,547,720 children during 26,850,507.31 person-years of follow-up. We identified 13,363 children with autism spectrum disorder (incidence rate, 49.77 cases per 100,000 person-years) and 24,787 children of with epilepsy (incidence rate, 92.31cases per 100,000 person-years).
The overall relative risk (hazard ratio) for **epilepsy** was 1.63 (95% CI: 1.28 - 2.06) in children with an older sibling with ASDs and 4.31 (95% CI: 2.58 - 7.20) in children with an older sibling with both epilepsy and ASDs compared with children not having an older sibling with epilepsy and ASDs.
The overall relative risk (hazard ratio) for **ASD** was 1.45 (95% CI: 1.24 - 1.68) in children with an older sibling with epilepsy and 4.26 (95% CI: 2.60 - 6.97) in children with an older sibling with both epilepsy and ASDs compared with children not having an older sibling with epilepsy and ASDs.
**CONCLUSIONS:**
We found an increased risk of epilepsy and ASD in younger siblings of children affected with these disorders. The results offer important information to healthcare providers, researcher as well as parents of children with autism and epilepsy, and suggest common familial factors for both disorders.

**High risk factors for autism during pregnancy and their modulation of critical neurotransmitters in the central nervous system: the putative significance of a novel preclinical model.**
*Jørgen Scheel-Krüger, Freja Bertelsen, Maria Møller Skovborg, Anne M. Landau, Pia Weikop, Arne Møller*

As already discussed by *Sven Bölte* in this symposium, early detection and intervention are important for the young 2-4 year old infant with a possible diagnosis of autism or ASD symptoms, which may improve their future long-term outcomes and daily living. It has also become obvious that ASD is not only one disease or syndrome, but involves several etiological factors. Among the identified causes of autism, genetics represent one important factor together with the prenatal environment for the fetus in the uterus. The exposure of pregnant women, particularly in the early trimester, to rubella, radioactivity, thalidomide, misoprostol and various antiepileptic drugs could lead to the development of ASD. In addition to an early diagnosis and intervention with supporting psychotherapy, it would be of much interest to identify early significant biomarkers.
In recent years, there has been considerable interest for the development of new preclinical animal models of ASD, which include genetic models and drug induced models. It appears that several features in these models, including measurements of social interaction, sensory sensitivity and cognition, may have at least some translational significance for the human syndrome of ASD.
In recent years, our team at CFIN has become interested in the valproate (VPA) rodent model of autism. The antiepileptic drug VPA is teratogenic in most animal species tested and produces neuropathological changes when administered either pre- or postnatally to rodents. VPA is a first-line effective substance for the treatment of a number of neurological and psychiatric disorders such as epilepsy, migraine, pain, and bipolar disorders that in general, require continuous treatment in all stages of life, including during pregnancy. Despite the fact

that the teratogenic potential of VPA has been known for more than 30 years, and despite guidelines that discourage its use during pregnancy, VPA still appears to be a common treatment in women of childbearing age, in particular in developing countries. A newly published Danish population-based study of 655615 children identified 5437 children as having ASD of which 508 children were exposed to VPA and representing the strongest evidence to date that fetal VPA exposure is associated with ASD (absolute risk 4.42%; adjusted hazard ratio 2.9 (Jacob Christensen et al. 2014).
Our team has developed a new VPA rat model, which aims to mimic the human clinical condition by using a long-term administration of VPA at low doses that were estimated to be non-toxic and assumed to be relevant to the human clinic. The pups were exposed to VPA during maternal pregnancy from prenatal day E12.5-E22 until delivery.
A summary of our current findings will be presented and will include 1) behavioural results of early social attraction to maternal nesting, juvenile play behaviour, ultrasonic vocalization and calls, learning and memory testing, 2) neuroanatomy with results of changes in cortical cell numbers and cortical thickness, and 3) brain serotonin levels, autoradiography studies of GABA, serotonin and oxytocin receptor levels. The relevance and ability to translate these findings to human ASD will be discussed.

**Familial aggregation of Autism Spectrum Disorder**

*Therese Koops Grønborg*
Autism spectrum disorder (ASD) has consistently been shown to aggregate in families. There are mainly two different approaches to study familial aggregation; sibling recurrence risk ratio and heritability.
Sibling recurrence risk is defined as the risk of disease manifestation given that one's sibling has the disease, and sibling recurrence risk ratio is defined as the sibling recurrence risk relative to the disease risk in the general population. Previous studies have found ASD sibling recurrence risk estimates much higher than the general ASD risk. These studies have, however, been limited by small study samples and ascertainment bias.
Heritability is defined as the proportion of phenotypic variation attributed to genetic factors as opposed to environmental factors. Heritability of autism has mainly been estimated using study samples consisting of twin pairs with estimates around 80%. These studies also support a strong genetic component in the etiologic pathway to ASD. A recent Swedish study estimated heritability using not just twin pairs but also other sibling pairs and found a much lower heritability of 50%.
The prevalence of autism spectrum disorder has increased during the past two decades and possible explanations for this rise have been many. To add to this discussion, time trends in both the sibling recurrence risk ratio and heritability are of great interest.
This talk will focus on sibling recurrence risk ratio and heritability for autism spectrum disorder in a population-based cohort of Danish children, as well as possible time trends in the two measures.

**Reduced influence of prior perceptual knowledge in autism**
Joshua Skewes

Scientists have shown that autistic people are better at perceiving fine detail, but that they also have difficulties interpreting the context in which that detail is presented. For instance, autistic people are better at discriminating pitch in sound, but may have trouble using pitch to interpret emotions in speech. These phenomena have been notoriously difficult to explain. Scientists have focused on differences in 'bottom-up' sensory processing – or differences in how much detail people are able to get out of their sensory experiences; and on differences in 'top-down' cognitive integration of sensory information – or differences in how much people attend to structure and patterns and context in sensory information. Neither has been able to account for the wide range of phenomena which scientists and clinicians have observed. Recently, a third model has offered a way to synthesize top-down and bottom-up approaches, and provide a fuller integration of existing findings. According to this theory, the function of the perceptual system – and the brain more generally – is to integrate prior expectations about the world with new evidence from the senses. The question is whether autistic people are better at perceiving fine detail because they receive better sensory information (a bottom up process), or because they rely less on prior expectations and take sensory information more at face value (a top-down process). I present results from experiments on vision and hearing that show that autistic people do not necessarily receive more sensory information, but that they do tend to represent that information more independently of its structures and context.

**Linguistic adaptation between parents and children in ASD: a longitudinal perspective**
*R. Fusaroli; E. Weed*

How does language develop in children with ASD? Do interactional skills impact long term language development? We investigate these issues in a longitudinal corpus (6 visits over 2 years) of parent-child naturalistic interactions in 66 children, 33 with ASD and 33 TD, from age 2 to age 5. We focus on amount (word and utterance tokens) and complexity (word types, syntactic structure) of linguistic behavior. We show that parent and child adapt to each other, and this increases with age, though less for ASD children. We show that parents linguistic behavior seems to have an impact on the child's development. However, ASD children differences in interactional strategies may impact and simplify the parents' behavior, which in turn impacts the children's development.