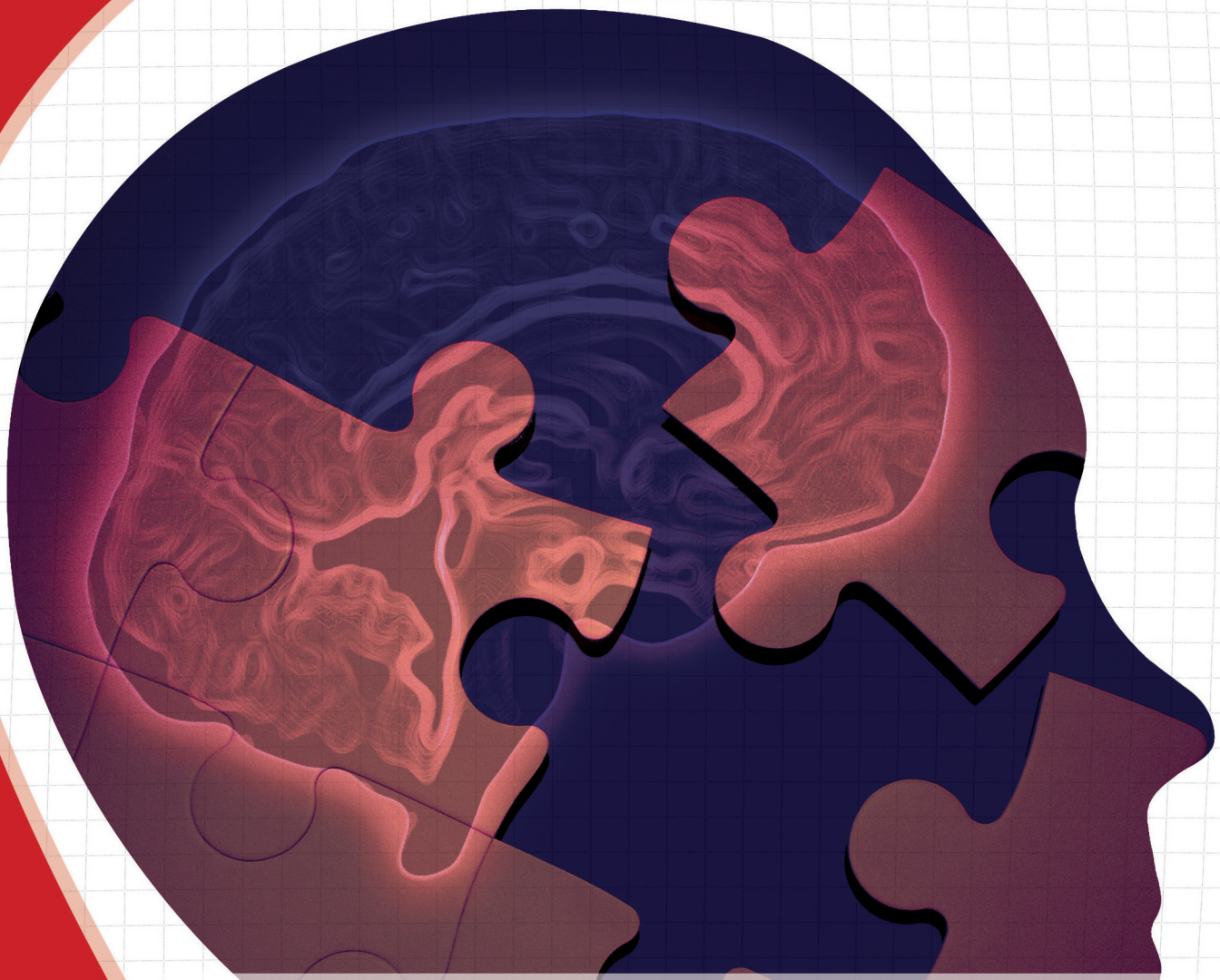
International Meeting for Autism Research

May 12 - 14, 2011

Manchester Grand Hyatt ■ San Diego, California



IMFAR 2001–2011
INTERNATIONAL MEETING FOR AUTISM RESEARCH
10TH ANNIVERSARY

www.autism-insar.org

PRESS BOOK

All IMFAR abstracts and interviews EMBARGOED until May 11, 2011, 12:00 noon PDT

IMFAR 2011 Press Book
Abstracts of Highlighted Papers, Keynote Addresses

Highlighted Study Abstracts — Page

***Note:** Confirmed Press Conference attendees are presented in **bold**

Additional Highlighted Studies

Keynote Presentations

INSAR | International Society for Autism Research

Summary:

Researchers conducted the first study of long-distance connections in the autistic brain in the first years of life when the behavioral symptoms begin. The first warning signs of autism involve a lack of normal social, communication, and language behavior. These behaviors depend on complex, long-distance connections in the brain, especially between areas known as the frontal and temporal lobes. In the youngest autistic infants and toddlers, we discovered abnormally accelerated development of long-distance connections between frontal and temporal lobes and between the left and right sides of the frontal lobes. Our second discovery was that by about 3 years of age in autism there was abnormal slowing of further change and so, eventually pathway development in the typical child began to surpass that in the autistic child. It appears that autism begins as a disorder of both excess neuron numbers and aberrant overabundant connectivity, not disconnectivity. We theorize that in infants and toddlers with autism, connections are too rapidly made in a sort of blind, biologically-driven fashion without the normal benefit and guidance of experience and learning that comes with time and the gradual selection and construction of connections. This results in dysfunctional connections that eventually slow further development of both connections and behavior. This may help explain why early identification and treatment may be so beneficial for infants and toddlers with autism: Intensive early treatment may forestall the too rapid development of connections and enable experience and learning to better influence the adaptive selection of connections.

Abstract:

Abnormally Accelerated Development of Higher-Order Long-Distance Cerebral Tracts In ASD Infants and Toddlers.

S. Solso*[1], W. Thompson[2], K. Campbell[3], C. Ahrens-Barbeau[4], R. Stoner[5], C. Carter[4], M. Weinfeld[6], S. Spendlove[4], J. Young[4], M. Mayo[4], J. Kuperman[3], D. Hagler[3], R. J. Theilmann[3], L. T. Eyler[3], K. Pierce[3], E. Courchesne[3] and A. Dale[3], (1)*University of California San Diego, UCSD Autism Center of Excellence*, (2)*University of California San Diego*, (3)*University of California, San Diego*, (4)*University of California, San Diego, UCSD Autism Center of Excellence*, (5)*Neurosciences and UCSD Autism Center of Excellence*, (6)*University of California, San Diego, UCSD Autism Center of Excellence*

Background: Autism is a heritable disorder of early brain overgrowth that has been hypothesized, but not demonstrated, to involve abnormal structural development of local and long-distance connectivity and, thus, aberrant functioning (Courchesne & Pierce, 2005). Understanding putative early connectivity defects in autism could aid in the development of animal models, point to significant genetic pathways, and possibly be used as an early biomarker

for autism to aid in early diagnosis and treatment. Unfortunately, currently there are no studies of cerebral tracts in the autistic brain at the age of first clinical signs.

Objectives: To identify abnormally as well as normally developing major long-distance cerebral tracts in ASD infants and toddlers.

Methods: We collected 51-angle DTI datasets from N=39 ASD and N=23 typically developing male infants and toddlers (13 months to 43 months) and analyzed FA values in 25 different tracts using a new DTI probabilistic atlas. Subjects were recruited as young as 12-months via the 1-Year Well Baby Check-up approach (Pierce et al., in manuscript) and diagnoses confirmed at later ages.

Results: Logistic regression models show that for multiple cerebral tracts infants and toddlers with greater FA values were more likely to have an ASD diagnosis. Significant tracts included the superior longitudinal fasiculus, forceps minor and uncinate as well as the corpus callosum. Furthermore within these tracts the ability of large FA values to predict ASD was strongest at the youngest ages.

Conclusions: Results are consistent with evidence of early brain overgrowth and suggests that it involves major cerebral white matter tracts as well as cortical gray matter. They are also consistent with MRI evidence of abnormal expansion of specific prefrontal and temporal subregions in ASD infants and toddlers. We theorize that these early developmental defects in connectivity in ASD result from genetic abnormalities in prenatal processes that regulate neuron numbers, migration and neurite outgrowth. We are currently exploring the degree to which DTI profiles could be used alone, or in combination with other imaging indices, as early predictive biomarkers of risk for autism.

INSAR | International Society for Autism Research

Summary:

The goal of this pilot study was to assess the tolerability and effectiveness of N-acetylcysteine (NAC), a glutamatergic modulator and an antioxidant known to replete the antioxidant glutathione, in the treatment of behavioral deficits in children with autism. In the 12-week, double-blind, randomized, placebo-controlled study of NAC in 33 children with autism, NAC resulted in significant improvements in overall aberrant behaviors and irritability. The results suggest that NAC is a safe and potentially effective in treating irritability and disruptive behaviors in children with autism, and larger studies are recommended.

Abstract:

A Randomized Controlled Double-Blind Trial of N-Acetylcysteine In Children with Autism. A. Y. Hardan*[1], L. K. Fung[2], R. A. Libove[1], T. V. Obukhanych[1], S. Nair[2], T. W. Frazier[3], L. Herzenberg[1] and R. Tirouvanziam[1], (1)*Stanford University School of Medicine*, (2)*Stanford University*, (3)*Cleveland Clinic*

Background: An imbalance in the excitatory/inhibitory systems with abnormalities in the glutamatergic pathways has been implicated in the pathophysiology of autism. Further, chronic oxidative imbalance, as reflected notably by a deficit by the antioxidant glutathione (GSH), was recently linked to autism. The goal of this pilot study is to assess the tolerability and effectiveness of N-acetylcysteine (NAC), a glutamatergic modulator and an antioxidant known to replete GSH, in the treatment of behavioral deficits in children with autism.

Methods: This is a 12-week, double-blind, randomized, placebo-controlled study of NAC in 33 children with autism. Subjects randomized to NAC were initiated at 900 mg daily for 4 weeks, then 900 mg twice daily for 4 weeks and 900 mg three times daily for 4 weeks. Primary behavioral measure (Aberrant Behavioral Checklist; ABC; total and irritability subscale) and safety measures were performed at baseline, 4, 8, and 12 weeks. Additional, measures were included to assess the social and repetitive behaviors domains as measured by the Social Responsiveness Scale and the Repetitive Behavior Scale Revised-Revised, respectively.

Results: NAC was overall well-tolerated with limited side effects. Compared to placebo, NAC resulted in significant improvements in overall aberrant behaviors and irritability. No statistical differences were found in the other secondary measures, except for stereotypic/repetitive

behaviors. However, this finding became insignificant when accounting for changes in irritability.

Conclusions: Data from this pilot investigation suggest that NAC is a safe and potentially effective in treating irritability and disruptive behaviors in children with autism. Large randomized controlled investigations are warranted.

INSAR | International Society for Autism Research

Summary:

The care of children with autism spectrum disorders (ASD) is often demanding and expensive. Because of the limited availability and high cost of specialized child care, parents may reduce paid employment to care for their children themselves, resulting in substantial earning loss for the family. It has been suggested (but not yet substantiated) that the largest component of lifetime costs of ASD is this type of indirect costs. Most research has examined healthcare costs to insurance companies. A more comprehensive view of the costs of ASD must go beyond the system-level costs to include the economic impact on the family of the child. These data are critically needed to inform ongoing policy discussions regarding the best ways to support families and finance care for children with ASD.

This study estimated the average loss of parental earnings associated with childhood autism in the United States using a nationally representative sample. We compared labor force participation and annual earnings of parents of children with ASD to those of parents of children with functional limitations and parents of healthy children. We find that mothers' of children with ASD are 5% less likely to be employed than the mothers of children with functional limitations and 12% less likely to be employed than the mothers of healthy children. In addition, mothers' of children with ASD earn 26% (6300$) less than the mothers of children with functional limitations and 39% ($11,540) less than the mothers of healthy children. We don't find significant differences in employment rates and annual earnings among fathers. Our findings translate into a 20% (11,900$) reduction in annual family earnings of children with ASD compared with children with functional limitations and a 27% ($17,640) reduction compared with healthy children.

These results suggest significant economic burden for families of children with ASD. Given that these families face substantial health care expenses, the potential economic impact of having lower income in addition to these expenditures is substantial. This suggests the need for additional evaluation of available supports for families and specific barriers to optimizing family income. It is essential to design both universal healthcare and workplace policies that recognize the full impact of autism, as well as targeted policies and resources to alleviate costs for the families with greatest needs.

Abstract:

The Effect of Childhood Autism on Parental Employment. Z. Cidav*[1], S. C. Marcus[2] and D. S. Mandell[1], (1)*University of Pennsylvania School of Medicine*, (2)*University of Pennsylvania*

Background: The care of children with autism imposes direct care costs on families, as well as indirect costs resulting from loss of earnings due to increased caregiving responsibilities. Previous research on the cost of autism has been restricted primarily to studying medical costs incurred by the healthcare service system. A more comprehensive view of costs must include the financial impact on families and go beyond the costs of medical care. By examining parental employment consequences of childhood autism, this study will provide new insight on indirect costs to families. Having a child with autism imposes additional time and financial constraints for family members. Added time constraints would imply reduced employment, whereas additional financial constraints may lead to increased employment. The net effect on parental employment is an empirical question.

Objectives: to 1) estimate the effect of caring for a child with autism on parents' labor force participation and hours of market work; 2) examine how this estimated effect varies as a function of child's individual, family characteristics and community factors.

Methods: We will use the Medical Expenditure Panel Survey (MEPS) from the years 2002-2007. The MEPS is an annual survey that collects detailed information on healthcare use, costs, health insurance, health status, socio-economic, demographic and employment characteristics for nationally representative samples of U.S. households. We will identify children with autism using Medical Condition files that provide information on household-reported medical conditions. Using the parent identifier, we will match children with their parents. We will conduct the analysis separately for mothers and fathers. The main independent variable will be an indicator of whether the child has autism. State-of-the-art econometric techniques will be used to estimate the effect of childhood autism on mothers' and fathers' likelihoods of employment and hours of work.

Results: Analyses are ongoing. There were 47942 children living with their mothers, 147 of whom were diagnosed with autism. 62% of mothers of children with autism were employed, compared with 71% of mothers of other children. Average weekly work hours of mothers of children with autism were 34 (sd=12), compared with 35 (sd=11) for mothers of other children. There were 34937 children whose fathers were present in the household. Of these, 113 were diagnosed with autism. 91% of fathers of children with autism were employed, compared with 95% of other fathers. The average weekly work hours of fathers of children with autism were 46 (sd=11), compared with 44 (sd=10) for fathers of other children.

Conclusions: Our preliminary results suggest a negative effect of childhood autism on parental employment. To date, much of the discussion regarding the financial impact of autism has focused on system-level direct care costs. This results in a one-sided argument that favors insurance companies regarding the impact of different strategies for financing services for individuals with autism. This study will provide the most comprehensive estimate of a major source of family costs. This information is essential in designing healthcare and workplace policies that recognize the full impact of autism and appropriately target resources to alleviate its effects.

INSAR | International Society for Autism Research

Summary:

Inclusion in general education classrooms has become increasingly common practice for children with special needs. Inclusion has met with resistance from some teachers, especially when the students being included have been diagnosed with autism. This issue is often exacerbated in schools located in large, urban districts, which contend with additional barriers related to a lack of resources. What happens in these districts is particularly important, since they serve a disproportionately large number of children with autism in the United States. This study was designed to assess the attitudes and perceptions of general education teachers in one large school district toward the inclusion of children with autism in their classrooms. The study examined teachers' beliefs about the appropriateness of these children's placement in their classrooms, and what factors might account for these beliefs.

A survey was developed and administered to nine teachers as part of a pilot study. Each teacher had between one and four students with autism included in her classroom. Teachers answered survey items about the individual students, as well as about the classroom and school supports for inclusion. All teachers reported positive attitudes about including children with autism in their classrooms; however, some teachers were unsure whether this setting would lead to better educational outcomes for these students. Most students in the sample spent at least half of the day in the general education classrooms, and 63% of their teachers believed that this was appropriate. Teachers felt that their own skills in managing a child with autism were strong, but that the students did not always come into the classroom prepared to meet the demands of the general education setting. This attitude may reflect an understanding of inclusion as determined by child readiness, rather than teacher willingness to adapt the classroom environment to best suit the needs of the child. Resource needs mentioned by the teachers included increased support from professional staff (i.e. special education teachers, trained paraprofessionals), strategies for promoting socialization between students with autism and their peers, and training on topics such as the implementation of IEP goals and differentiated instruction. Overall, teachers reported that they were not resistant to having children with autism included in their classrooms, but felt they needed additional resources to make this process successful.

Abstract:

General Education Teachers' Perceptions of Inclusion for Children with Autism. P. Rosen*[1], E. Rotheram-Fuller[1] and D. S. Mandell[2], (1)*Temple University*, (2)*University of Pennsylvania School of Medicine*

Background: In recent years, inclusion has become increasingly common practice for children

with special needs (Kasari, Freeman, Bauminger, & Alkin, 1999). Despite this growing trend, there has been some resistance from general education teachers, especially when students being included have been diagnosed with autism (McGregor & Campbell, 2001). This issue often is exacerbated in schools located in large, urban districts, which often contend with additional barriers to inclusion related to a lack of resources. Yet these districts serve a disproportionately large number of children with autism. More information is needed to better understand the beliefs and attitudes of general education teachers in these urban classrooms, as well as to assess their resource needs.

Objectives: To assess general education teachers' perceptions and attitudes toward the inclusion of children with autism in their classrooms, their beliefs regarding the child's educational placement, and specific child, classroom, and school-related factors impacting these attitudes.

Methods: A survey including both quantitative and semi-structured components was developed and administered to elementary school teachers in a large, urban district as part of a pilot study. Teachers answered survey items about individual students presently being included, as well as their perceptions of the success of inclusion in their schools. Eight teachers were administered the survey and offered consultation services. Teachers had an average of 10.25 years (range 1-30) of experience, while teaching experience specifically with students with autism ranged from 0 to 15 years (M=4.75). On average, teachers had 25.5 students in their classrooms, with between 2 to 4 students with autism included.

Results: Preliminary survey results indicate some general trends in beliefs about students' educational placement. Teachers rated the placement of only 44% students as being "completely appropriate," with placement for 33% of students was considered as "somewhat appropriate," and placement for 22% students deemed "somewhat inappropriate." When asked specifically if they would suggest a change of placement, teachers reported that they would recommend 33% of students for more restrictive settings, although overall, teachers thought that the majority of students (66%) should remain in their present placements. Teachers felt their own skills in managing a child with autism were strong, but that the students did not always come in to the classroom prepared for the demands of the general education setting. Resource needs mentioned by teachers included strategies for promoting socialization between children with autism and their peers, training regarding the implementation of IEP goals, as well as continued support from professional staff (i.e. special education teachers). Overall, all teachers reported positive attitudes about including children with autism in their classrooms.

Conclusions: Although these findings represent a small sample of teachers, the information collected provides an in-depth look at the needs of these teachers within the classroom. Results also indicate the need to explore child 'readiness,' prior to entering the general classroom setting. Overall, teachers were not resistant to having children with autism included in their classroom, but felt they need additional resource to make this process successful.

INSAR | International Society for Autism Research

Irva Hertz-Picciotto, Ph.D. will present on three studies that are all related and based on work from the CHARGE (CHildhood Autism Risks from Genetics and Environment) Study, a population-based study of children from three groups: with an autism spectrum disorder (ASD), with developmental delay but not autism, or with typical development.

Summary:

Based on data from nearly 1000 children from the CHARGE Study (539 with ASD, 421 with typical development), an analysis was conducted to determine whether maternal reports of influenza or fever during the pregnancy were predictive of later development of autism or ASD in the child. No association was found for maternally reported influenza during pregnancy, nor during any specific trimester. However, mothers of affected children were twice as likely to report having had a fever during the pregnancy, as compared with mothers of typically developing children. The risks were particularly elevated when the fever was reported to occur in the 1st or 2nd trimester. This work is consistent with earlier studies showing higher risk in association with maternal viral infections during pregnancy, but several lines of evidence suggest that it is not the virus itself, but more likely, the maternal inflammatory response, that influences neurodevelopment.

Abstract:

Prenatal Influenza or Fever and Risk of Autism/Autism Spectrum Disorders. O. Zerbo*[1], I. Hertz-Picciotto[2], A. M. Iosif[3], R. L. Hansen[4] and C. K. Walker[4], (1) *University of California at Davis*, (2)*University of California, Davis*, (3) *University of California at Davis*, (4)*University of California at Davis*

Background: Maternal infections during pregnancy have been suggested to be associated with autism. However, to what extent prenatal influenza plays a role has not been well-investigated in epidemiological studies.

Objectives: To determine if maternal influenza infection or fever during pregnancy is associated with increased risk of autism/autism spectrum disorders.

Methods: The analysis is part of a large population-based case control study known as the Childhood Autism Risk from Genetics and Environment (CHARGE) Study. 462 children with autism/autism spectrum disorders, 136 with developmental disorders but not autism, and 265 typically developed children born in California age between 2 and 5 years at the time of

recruitment were included. Diagnostic category for all participants was determined by standardized clinical assessments. The two main exposures, maternal influenza and fever during pregnancy, were both assessed by telephone interviews. We conducted two types of analyses. One set of analysis was performed applying sampling weights and another without. The weights were determined based on the probabilities of participating in the study taking into account both the three case group sampling strata and a set of socio-demographic variables. Multivariate logistic regression models were fitted to the data to obtain odds ratios (ORs) with their 95% confidence intervals (CI) as measures of association and precision between the main exposures and autism.

Results: We did not find a strong association between maternal influenza during pregnancy and autism (OR 1.52, 95% CI 0.81 – 2.85) or developmental delay (2.32, 95% CI 0.72 - 7.42) after applying the sampling weights in the analysis. The unweighted analysis showed similar results.

More mothers of children with autism reported having fever during pregnancy than those of children with typical development in the analysis where the sampling weights were applied (OR = 1.86 95% CI 1.14 - 3.02). Second trimester showed the strongest association (OR=2.13 95% CI 1.00 - 4.52). However, in the analysis where we did not apply the sampling weights, the OR of the association between fever and autism did not reach statistical significance (1.25, 95% CI 0.81 – 1.92).

Conclusions: In our analyses, maternal influenza showed no association with autism or developmental delay, but fever during pregnancy was associated with autism in our weighted analysis, which corrects for selection bias to some degree. We consider these results to be preliminary and more analyses will be performed.

INSAR | International Society for Autism Research

Summary:

Data on cesarean birth, complications of pregnancy, and complications of labor & delivery were obtained for CHARGE Study participants through structured telephone interviews with the mother and from medical records. This paper focuses on mode of delivery: elective cesarean, non-elective cesarean, or vaginal birth among over 500 cases of ASD and over 300 typically developing controls. Elective cesareans occur prior to labor and rupture of membranes; cases and controls showed no significant differences, in comparison with vaginal deliveries. Non-elective cesareans (Non-ECD) occur after onset of labor or rupture of membranes. Initial analyses suggested an elevated risk for autism spectrum disorder when birth occurred by non-ECD, but after adjustment for maternal age, health insurance, pre-eclampsia and diabetes, the risk was not significant. Non-ECD commonly resulted from intra-amniotic infection, prolonged labor, placental insufficiency, and abnormal (e.g., breech) presentation. It is possible that one or more of these factors may increase risk for ASD in the child. At this stage, cesarean delivery does not appear to independently increase the risk for ASD.

Abstract:

Cesarean Birth and Autism Spectrum Disorder. C. K. Walker*, P. Krakiowiak, A. S. Baker, R. L. Hansen, S. Ozonoff and I. Hertz-Picciotto, *UC Davis*

Background: Some studies have suggested a higher risk for autism spectrum disorder (ASD) after cesarean birth. Such an association could stem from physical consequences of the operation itself or from the indications which led to the decision to perform the cesarean delivery.

Objectives: We hypothesize that children with autism spectrum disorder are more likely to have been the product of aberrant labor courses that result in non-elective cesarean delivery.

Methods: The CHARGE (Childhood Autism Risk from Genetics and the Environment) Study is an ongoing case-control study of the etiology of autism. Data from maternal self-report and medical records documenting the course of labor and delivery were available for the mothers of 477 children with a diagnosis of autism spectrum disorder (ASD) and 272 population-based frequency-matched controls. We collected demographic data and information about the pregnancy, delivery, and child's early life in the Environmental Exposure Questionnaire, a telephone-administered interview. Covariates related to medical conditions of pregnancy as well as the labor and delivery process were abstracted in a systematic fashion. We performed the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observation Schedule on study

cases to confirm the diagnosis of autism. Logistic regression was used to examine the relationships between delivery mode and autism status. Because the risk of intraamniotic infection (IAI), use of antimicrobials, and cesarean rates and indications vary according to gestational age, we generated a Cox proportional hazards regression model with time-dependent covariates as a mechanism to evaluate the combined effects of IAI risk and antimicrobial use on mode of delivery.

Results: After adjustment for preeclampsia and / or diabetes and IAI risk, non-elective cesarean delivery following labor and / or ruptured membranes was more common among mothers whose children developed ASD compared with those who delivered vaginally (OR 1.71, 95% CI 1.04, 2.81). There was no association between elective cesarean delivery and ASD. A Cox proportional regression analysis examining the effect of IAI risk and antimicrobial use on the outcome of non-elective cesarean delivery and controlling for labor duration identified that women with both IAI risk and antimicrobial usage were twice as likely to have had a non-elective cesarean delivery compared to women who did not have IAI risk and did not take antimicrobials (OR 2.14, 95% CI 1.12, 4.07).

Conclusions: Our analysis suggests that it is not birth by cesarean itself that is associated with ASD. Rather, it appears that factors associated with difficult labor courses, including prolonged labor and membrane rupture, as well as occult and overt infection within the amniotic cavity may drive the relationship between non-elective cesarean delivery and ASD.

INSAR | International Society for Autism Research

Summary:

Based on medical records and self-reported interview information from about 1000 children (517 ASD cases, 315 children with typical development, and 172 with developmental delay but not ASD), maternal metabolic conditions were evaluated. These included maternal Type 2 or gestational diabetes, chronic hypertension, and pre-pregnancy obesity. Each of these conditions was found to be more common in mothers of ASD children, and also in mothers of children with developmental delay, as compared with those of the typically developing children. After adjusting for socioeconomic and demographic factors, mothers of ASD children were about 60% more likely to have one of these conditions, and mothers of developmentally delayed children, 150% more likely. In separate analyses of ASD and non-ASD children, those with diabetic mothers had significantly poorer scores on expressive language, as compared with the corresponding children who had non-diabetic mothers. Given the rapid rise in obesity and diabetes over the last few decades, these findings may have substantial import for public health.

Abstract:

The Role of Maternal Diabetes and Related Conditions In Autism and Other Developmental Delays. P. Krakowiak*, A. A. Bremer, A. S. Baker, C. K. Walker, R. L. Hansen and I. Hertz-Picciotto, *University of California, Davis*

Background: Recent trends indicate a rising prevalence of diabetes as well as obesity and hypertension, conditions indicative of elevated insulin resistance. These trends parallel the increasing rates of autism. Although the etiology of this disorder is unknown, studies suggest that its pathogenesis begins *in utero*.

Objectives: This study examined whether prenatal exposure to maternal gestational or type 2 diabetes, hypertension, and/or obesity was associated with (1) an increased risk of having a child with autism or autism spectrum disorders (AU/ASD) or other developmental delays (DD) and (2) greater impairments in cognitive development.

Methods: Data came from 1001 children (508 AU/ASD, 178 DD, and 315 typical controls [TD]) enrolled in The CHARGE (CHildhood Autism Risks from Genetics and the Environment) Study, an ongoing population-based case-control study. Maternal conditions were ascertained from medical records or telephone interview with parent. Maternal diabetes and hypertension were considered to be present if these conditions were recorded in the prenatal medical record or self-reported in a telephone interview. Obesity was defined as body mass index (BMI) ≥30.0, calculated using height and pre-pregnancy weight recorded in the prenatal medical record or via

interview. Models were adjusted for mother's education, delivery payer, calendar time, and frequency-matching variables child's age and sex, and Regional Center catchment area.

Results: Women with diabetes, hypertension, and/or obesity had a nearly two-fold increased risk of having a child with AU/ASD or DD compared to women without these conditions (odds ratio [OR] 1.84, 95% confidence interval [CI] 1.30-2.62; OR 2.13, 95% CI: 1.37-3.30, respectively). Among children with ASD, Mullen Scales of Early Learning (MSEL) expressive language scores were significantly lower for children of mothers with diabetes compared to those whose mothers did not have diabetes (Least Squares [LS] mean 22.29, standard error [SE] 1.15 vs. LS mean 26.06, SE 0.54; $P = 0.0025$); no significant differences in MSEL scores were observed with other maternal conditions in the ASD group. Among children with no ASD (DD + TD), children of mothers with hypertension, compared to children of mothers without hypertension, had significantly lower MSEL fine motor (LS mean 32.52, SE 2.96 vs. LS mean 42.79, SE 0.82; $P = 0.0008$), receptive language (LS mean 33.89, SE 2.79 vs. LS mean 41.59, SE 0.74; $P = 0.0072$), and expressive language (LS mean 35.48, SE 2.50 vs. LS mean 41.55, SE 0.74; $P = 0.0190$). Similarly, compared to children of mothers with no conditions of interest, children of mothers with one or more conditions had significantly lower fine motor (LS mean 39.09, SE 1.52 vs. LS mean 43.47, SE 0.92; $P = 0.0128$), receptive language (LS mean 37.67, SE 1.37 vs. LS mean 42.50, SE 0.83; $P = 0.0020$), and expressive language scores (LS mean 37.61, SE 1.31 vs. 42.56, SE 0.84; $P = 0.0011$).

Conclusions: Our findings suggest that diabetes and other conditions indicative of elevated insulin resistance, such as hypertension and obesity, may play a role in the pathogenesis of developmental disorders.

INSAR | International Society for Autism Research

Abstract:

Autism Behavioral Pheotype and Health Across the Life Span. M. M. Seltzer*, *Waisman Center, University of Wisconsin-Madison*

Background: Little is known about adults with autism spectrum disorders during the midlife and aging stages of the life course, as few in these age groups were correctly diagnosed with autism. Yet the baby boom generation of individuals who warrant an autism diagnosis is now well into midlife and some are approaching old age, with a concomitant increase in the need for health care and services.

Objectives: The goal of the present study is to describe the behavioral and health profile of autism in later life, drawing upon the available data from a 10-year longitudinal study of autism during adolescence and adulthood.

Methods: The present sample included 406 individuals with autism spectrum disorders who were age 10-52 when the study began and are currently 10 years older. Data have been collected six times over the 10 year period, making it possible to examine age-related changes in health, medications, functional abilities, behavioral problems and autism symptoms, and adult outcomes. The present analysis includes three methodological approaches: (1) cross-sectional comparisons with adults who do not have disabilities, drawn from a nationally-representative sample, and adults with Down syndrome, (2) semi-longitudinal trajectories estimated by Friedman's "supersmoother" (a non-parametric regression approach implemented in *R*, and (3) examination of mortality in adults during the 10-year study, including causes of death.

Results: In comparison with age peers who do not have disabilities, adults with ASD were significantly more likely to be in poor health and less likely to be in excellent health. Semi-longitudinal regressions revealed a pattern of slow age-related decline in health with more rapid decline after age 45, an increase in prescription medications (again more sharply after age 45), a steady decline in behavior problems during adulthood, and stability in functional abilities. Eleven adults died during the 10-year study period, with four deaths caused by heart attacks and three as a result of accidents. Adults with ASD who do not have an intellectual disability (ID) had better adult outcomes (residential independence, vocational independence, and social contact with friends) than adults with ASD and ID, or than adults with Down syndrome.

Conclusions: These findings suggest that adults with ASD have a long-term reliance on the public service system and the family, with limited profiles of independence in midlife. The baby boom generation with ASD (who may or may not be diagnosed with ASD) is approaching old

age and many will need long-term care services. The need for planning for the future in terms of adult sibling involvement and other services is evident in the data. The heterogeneity of ASD is evident in the later years of the life course, just as it characterizes children with ASD. Finally, the data offer implications for health surveillance and accident prevention in adults with ASD.

Summary:

Several studies have pointed out the importance of genetic background and environmental exposures during pregnancy in the inception of mental disorders of developmental origin including autism. Also, current evidence suggests a crucial role of immunologic dysfunction in Autism Spectrum Disorders (ASD). While being exposed to different infections during pregnancy has been linked to a number of psychiatric diseases such as schizophrenia and autism, several studies suggest that the role of viral or bacterial infections in autism is indirect and probably through triggering an inflammatory state in the mother during pregnancy.

In our study, we analyzed samples of amniotic fluid collected during pregnancy since 1982 in Copenhagen, Denmark from Danish mothers of children diagnosed later in life with ASD and their controls. We measured number of inflammatory markers (namely pro-inflammatory cytokines) along with examining the mothers' hospital records for diagnoses of infections. Although we found no difference in hospital admissions due to infections in mothers of ASD cases compared to controls during pregnancy, some of the inflammatory markers examined were in higher levels in mothers of ASD children (specifically a cytokine called TNF-α). Interestingly, this finding was seen more among girls compared to boys. Overall, findings from our study not only support the idea that immune dysfunction plays an important role in autism, but also confirm that this is happening actually before birth.

Abstract:

Cytokine Levels In Amniotic Fluid: a Marker of Maternal Immune Activation In Autism?

M. W. Abdallah*[1], N. Larsen[2], J. Grove[3], B. Nørgaard-Pedersen[2], E. L. Mortensen[4] and D. M. Hougaard[2], (1)*Institute of Public Health, Aarhus University*, (2)*Statens Serum Institut*, (3)*Faculty of Health Sciences, Aarhus University*, (4)*Institute of Public Health and Center for Healthy Aging, University of Copenhagen*

Background: Converging evidence sheds the light on the important role of immunologic dysfunction in Autism Spectrum Disorders (ASD), and many studies have repeatedly reported abnormal cytokines profiles in ASD patients. To our knowledge, no investigations have been carried out using amniotic fluid samples combined with clinical data regarding maternal immune activation (MIA) during pregnancy.

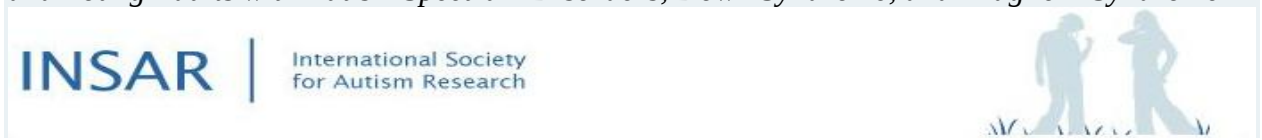
Objectives: To assess differences between children with ASD and controls in their amniotic fluid levels of seven MIA associated inflammatory cytokines (Interleukins 1ß, 6, 8 and 18,

Interleukin 6 receptor alpha, Tumor Necrosis Factor alpha and Triggering receptor expressed on myeloid cells 1) and the potential role of MIA in the development of ASD.

Methods: We adopted a case-control study design including all singleton offspring born in Denmark from January 1, 1982 through December 31, 2000 with a reported diagnosis of ASD (ICD-8 codes 299, ICD-10 codes F84) in the Danish Psychiatric Central Register and with a corresponding amniotic fluid sample in a historic birth cohort (HBC) kept and maintained at Statens Serum Institute (SSI) in Copenhagen . Controls were randomly selected from the HBC and frequency matched to cases by sex and year of birth. Perinatal data were retrieved from the Medical Birth Register and The Danish National Hospital Register (DNHR). Amniotic fluid samples from 414 singleton cases and 820 singleton controls were analyzed for seven cytokines using Luminex xMAP technology. Case-control differences in biomarker levels were assessed as continuous measures (Tobit censored regression model) or dichotomized at below the 10^{th} percentile or above the 90^{th} percentile cutpoints derived from control biomarker distributions (logistic regression). MIA was assessed through utilizing the DNHR for different intrauterine maternal infection/inflammation diagnoses.

Results: There was a significantly increased risk for ASD overall with elevated TNFα [elevated 90th percentile OR=1.63 (95% CI 1.13 - 2.36)]. This pattern was mainly seen for TNFα in girls [2.85(1.28-6.35)]. TNFα was still significantly different in cases compared to controls when controlling for any intrauterine maternal infections diagnoses. We found no significant association between ASD and maternal intrauterine infections/inflammation retrieved from the DNHR in our study population.

Conclusions: Children later diagnosed with ASD are more likely to have levels of TNFα falling in the upper centile of the distribution of this biomarker in children without ASD. This pattern of TNFα may reflect either a response to an adverse environmental stimulus, specifically MIA, which is possibly contributing to the development of ASD or an inherent dysregulation of this immune biomarker later diagnosed with ASD.



Summary:

Despite decades of research on family adaptation in the context of having a child with a developmental disability, the psychological well-being of fathers remains poorly understood. There is considerable evidence that certain disabilities take a greater toll on the psychological well-being of mothers than other disabilities. The nature of autism spectrum disorders (ASD) has been shown to be particularly challenging for mothers both early on and during later parenting years. Little is known about whether the nature of ASD is also uniquely challenging for fathers. The objectives of the current study were to: 1. Compare the psychological well-being of fathers of adolescents and young adults with an ASD to that of fathers of adolescents and young adults with Down syndrome (DS) and fragile X syndrome (FXS); and 2. Identify the factors (child, mother, and father variables) that contribute to these group differences. Findings indicated that fathers, similar to mothers, are affected by child-related stress and the nature of their child's disability. Moreover, this stress is not limited to the early parenting years but also occurs during the son or daughter's adolescence and adulthood. Fathers of grown children with an ASD had a higher level of depressive symptoms and lower level of pessimism than fathers of grown children with DS, with fathers of grown children with FXS falling in the middle of these groups. Group differences in father's depressive symptoms were, at least in part, related to differences in father's age, child's behavior problems, risk of having additional children with a disability, and mother's depressive symptoms. In contrast, fathers of grown children with an ASD continued to have a higher level of pessimism than fathers of grown children with DS after accounting for these factors.

Abstract:

Psychological Well-Being In Fathers of Adolescents and Young Adults with Autism Spectrum Disorders, Down Syndrome, and Fragile X Syndrome.

S. L. Hartley*[1], M. M. Seltzer[2], L. Abbeduto[1] and L. Head[3], (1)*Waisman Center*, (2)*Waisman Center, University of Wisconsin-Madison*, (3) Gundersen Lutheran Medical

Background: Despite decades of research on family adaptation in the context of having a child with a developmental disability, the psychological well-being of fathers remains poorly understood. There is considerable evidence that the challenges that mothers face and their psychological well-being varies by the child's diagnosis. The nature of autism spectrum disorders (ASD) has been shown to be particularly challenging both early on and during later parenting years; mothers of children and adults with an ASD report higher levels of stress (Herring et al., 2006) and increased depressive symptoms (Abbeduto et al., 2004; Dumas et al.,

1991) as compared to mothers of children and adults with other disabilities. Little is known about whether the nature of ASD is also uniquely challenging for fathers.

Objectives: We compared the psychological well-being of fathers of adolescents and young adults with an ASD, Down syndrome (DS), and fragile X syndrome (FXS). We also identified factors that account for diagnostic-related variation in paternal psychological well-being.

Methods: One-way analyses of covariance were used to compare self-reported ratings of depressive symptoms, pessimism, and coping in fathers of adolescents and young adults with an ASD (n = 135), DS (n = 59), and FXS (n = 46), and (n = 135). Hierarchical linear regressions were used to examine the extent to which four factors (paternal age, child behavior problems, presence of additional children with a disability, and maternal depressive symptoms) contributed to diagnostic-related differences in paternal psychological well-being.

Results: Whereas 30.4% of fathers of adolescents and young adults with an ASD reported depressive symptoms warranting clinical attention, 15.9% of fathers of adolescents and young adults with FXS, and only 6.8% of fathers of adolescents and young adults with DS had a clinically significant level of depressive symptoms. Fathers of adolescents and young adults with DS reported a lower level of pessimism than fathers of adolescents and young adults with an ASD or FXS. There were no diagnostic differences in paternal coping. The 'ASD disadvantage' in terms of heightened depressive symptoms as compared to both the DS and FXS groups was, at least in part, related to the child's heightened number of behavior problems, increased risk of having additional children with a disability, and increased maternal depressive symptoms.

Conclusions: Results confirm that fathers, like mothers, are affected by child-related stress and the nature of their son or daughter's disability. The influence of child-related stress on paternal well-being is not confined to the early parenting years, but is evident in the son or daughter's adolescence and young adulthood. Results can start to inform practitioners and health providers about the experiences of fathers, and suggest that fathers of adolescents and young adults with an ASD are particularly in need of services.

Summary:

Physical aggression, name calling, intimidating gestures, spreading of rumours, and exclusion from the group by powerful others are all examples of behaviours that comprise peer victimization. Results from a handful of existing studies clearly indicate that children and adolescents with an Autism Spectrum Disorder (ASD) are at much greater risk of peer victimization than their typically developing classmates (Carter, 2009; Little, 2002). The aim of this study was to investigate various social and cognitive factors that may contribute to peer victimization in adolescent boys with and without an ASD.

We found that high-functioning adolescent boys (aged 12-18) with ASD experience more bullying than their typically developing peers. We also found that adolescents with ASD had more difficulty with the social use of language, understanding of their own and other's emotions, regulating their own behaviour, and reflecting on their own behaviour and thinking processes. How well adolescents were able to manage their own stress and control their own emotions predicted how often they were victimized by their peers. Adolescents with ASD should be taught strategies for stress-reduction and emotion regulation in order to help them negotiate the stressful adolescent peer environment more effectively.

Abstract:

Predictors of Peer Victimization In Adolescents with and without An Autism Spectrum Disorder. E. A. Kelley*[1], P. Kloosterman[1], J. Parker[2], W. Craig[1] and C. Javier[3], (1)*Queen's University*, (2)*Trent University*, (3)*Laurier University*

Background: Physical aggression, name calling, intimidating gestures, spreading of rumours, and exclusion from the group by powerful others are all examples of behaviours that comprise peer victimization. Surprisingly, little research has explored the prevalence of peer victimization in adolescents with an Autism Spectrum Disorder (ASD). Results from a handful of existing studies clearly indicate that children and adolescents with an ASD are at much greater risk of peer victimization than their typically developing classmates (Carter, 2009; Little, 2002).

Objectives: The aim of this study was to investigate how deficits in various social and cognitive factors may relate to peer victimization in adolescents with and without an ASD.

Methods: Participants were 68 adolescent boys ranging in age from 11 to 18 years of age (M = 14.60; SD = 1.89) and their parents. Thirty-one adolescents had a primary diagnosis of an ASD

and 37 were typically-developing (TD). ASD diagnoses were confirmed using the ADOS-G. All adolescents were administered the *Wechsler Abbreviated Scale of Intelligence* (Wechsler, 1999) and the pragmatic judgment subtest of the *Comprehensive Assessment of Spoken Language* (Carrow-Woolfolk, 1999). As well, adolescents completed the self-report *Emotional Quotient Inventory: Youth Version* (Bar-on & Parker, 2000) as a measure of emotional intelligence (EI) along with a questionnaire regarding their experiences of peer victimization (World Health Organization, 2003). Parents completed the *Behavior Rating Inventory of Executive Function* (BRIEF; Gioia, Isquith, Guy, &Kenworthy, 2000) to provide a measure of executive functioning for their child.

Results: The two groups of adolescents did not differ in age, however the ASD adolescents had significantly lower (yet in the average range) IQ scores than the TD adolescents [$t(66) = 2.18$, $p < .05$]. As a result, IQ was considered a covariate in all analyses. With age as an additional covariate, the ASD adolescents were found to have significantly poorer pragmatic judgment [$F(1,67) = 13.68$, $p < .05$] and total EI [$F(1,67) = 7.90$, $p < .05$] in comparison to the TD adolescents. In contrast to their typical peers, significant cognitive impairments in executive functioning for the ASD adolescents were found across both the behaviour regulation [$F(1,64) = 45.63$, $p < .05$]and metacognition [$F(1,62) = 36.33$, $p < .05$] subtests of the BRIEF. A series of multiple regressions were conducted to determine whether these social and cognitive deficits might predict peer victimization. Results revealed that the stress management domain of EI ($p = .004$) and the emotional control domain of the BRIEF ($p = .045$) were significant predictors of peer victimization for both ASD and TD adolescents. Pragmatic judgment failed to emerge as a significant predictor of peer victimization.

Conclusions: ASD adolescents displayed deficits in many areas of social and cognitive functioning in comparison to TD adolescents. Difficulty modulating emotional responses appropriately and a lack of ability to cope with stress appear to place adolescents with and without an ASD at risk for peer victimization.

Keynote Presentations

INSAR | International Society for Autism Research

Understanding Autism From a Cross-Syndrome Developmental Perspective
Speaker: A. Karmiloff-Smith *Birkbeck Centre for Brain & Cognitive Development, University of London*

Background: Autism and the neurodevelopmental disability, Williams syndrome, have often been characterized at opposite ends of a neural and cognitive continuum in terms of their social and cognitive profiles, whereas in-depth analyses reveal many commonalities that emerge across their developmental trajectories. In this address, I will show how tracing domain-specific phenotypic outcomes back to their domain-relevant processes in the infant start states can help to identify the ways in which tiny initial impairments can cascade over developmental time to result in large developmental differences in the end state.

The Developmental Neurobiology of Autism: The First Steps and the Road Ahead
Speaker: E. Courchesne *University of California, San Diego*

Background: Studies that identify early neurobiological defects in autism will open new avenues for iPS cell, animal model, postmortem and genetic research on autism. Knowledge gained from such developmental research will be essential to developing early biomarkers of risk for autism. Such knowledge will also be essential to developing behavioral and biotherapeutic treatments that ameliorate consequences of brain maldevelopment and enable optimal clinical outcome for each affected individual.

Using Induced Pluripotent Stem Cells to Study Autism
Speaker: R. E. Dolmetsch *Stanford University*

Background: Autism Spectrum Disorders (ASDs) are a complex group of neurodevelopmental diseases many of which have a genetic basis. While we are starting to identify some of the mutations that confer susceptibility to ASDs, we known little about how these mutations alter the development and function of the human brain. The ability to generate induced pluripotent stem (iPS) cells from the skin of patients with ASDs, combined with our ability to differentiation of these cells into cortical neurons, allows us to establish cellular models of ASDs in the lab. We have generated iPS cells from the skin of patients with syndromic forms of autism and have differentiated these cells into neurons. We have identified cellular phenotypes in neurons from some of these patients that provide novel insights into the underlying cellular basis of autism. I will describe our results and discuss some of the challenges of using iPS cells to study ASDs. This strategy is allowing us to study the development of patient-derived neurons for the first time and is helping us identify therapeutic targets for the development of new pharmaceuticals to treat ASDs and other neurodevelopmental disorders.