THE SCIENCE OF AUTISM: TRANSFORMATIVE ADVANCES PAVING THE WAY TO A NEW FUTURE

SPEAKER: DR. NANCY MINSHEW, UNIVERSITY OF PITTSBURGH

Autism Society
Northwestern Pennsylvania
October 26, 2013
New Terminology: ASD

- **DSM-IV**: category was *Pervasive Developmental Disorder* (PDD) and diagnoses were Autistic Disorder, Asperger Disorder, and PDDNOS (Atypical Autism)

- **DSM-5**: category and diagnosis is *Autism Spectrum Disorder* (ASD); specifiers for intellectual disability, language level, & identified causes rather than subdiagnoses
Why Do We Have To Give Up DSM-IV?

Autistic Disorder: DSM-IV

3 Core Symptoms
Associated symptoms: sensory, motor
Co-morbid Conditions: intellectual disability, ADHD, seizures, mood problems, long list of behavior issues

Not reliably differentiated from Asperger’s or PDDNOS which confuses parents & clinicians.
No longer clinically or biologically valid.
DSM-5: A Monumental Effort

Started 2005

World-wide work of many

A $20 Million investment by APA

18 work groups

International, cross cultural, all genders
Future DSM-5 Developments

DSM-5 will go electronic:
- adding links to key supporting documents/evidence/descriptions and
- electronic communications between patients and clinicians
Urban Myth 1. “An Epidemic”

A real epidemic, or
A re-appreciation of the spectrum and
initiation of epidemiologic studies
Epidemiologic Studies of Autism: Rare Before 1980

• Very few studies prior to 1980
• By 2000, 2 non-US studies published
• And CDC establishes 14 Autism and Developmental Disabilities Monitoring (ADDM) sites and 7 Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) to study prevalence in U.S.
### Autism & ASD Prevalence: 2000 to 2006

<table>
<thead>
<tr>
<th>Prevalence 3 Fold Increase</th>
<th>Baird¹</th>
<th>Chakrabarti &amp; Fombonne²</th>
<th>Brick Township NJ³</th>
<th>CDC⁴</th>
<th>CDC⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>30.8/10,000</td>
<td>16.8/10,000</td>
<td>40.5/10,000</td>
<td>34/10,000</td>
<td></td>
</tr>
<tr>
<td>Other ASDs</td>
<td>27.1/10,000</td>
<td>45.8/10,000</td>
<td>26.9/10,000</td>
<td></td>
<td>90/10,000</td>
</tr>
<tr>
<td>Total for ASDs⁵</td>
<td>57.9/10,000</td>
<td>62.6/10,000</td>
<td>67.4/10,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total for ASDs</td>
<td>1/170</td>
<td>1/160</td>
<td>1/150</td>
<td></td>
<td>1/110</td>
</tr>
</tbody>
</table>

⁵This number was 20/10,000 in 1980 ⁶Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators; CDC
### Identified Prevalence of Autism Spectrum Disorders

**ADDM Network 2000-2008**

Combining Data from All Sites

<table>
<thead>
<tr>
<th>Surveillance Year</th>
<th>Birth Year</th>
<th>Number of ADDM Sites Reporting</th>
<th>Prevalence per 1,000 Children (Range)</th>
<th>This is about 1 in X children...</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>1992</td>
<td>6</td>
<td>6.7 (4.5-9.9)</td>
<td>1 in 150</td>
</tr>
<tr>
<td>2002</td>
<td>1994</td>
<td>14</td>
<td>6.6 (3.3-10.6)</td>
<td>1 in 150</td>
</tr>
<tr>
<td>2004</td>
<td>1996</td>
<td>8</td>
<td>8.0 (4.6-9.8)</td>
<td>1 in 125</td>
</tr>
<tr>
<td>2006</td>
<td>1998</td>
<td>11</td>
<td>9.0 (4.2-12.1)</td>
<td>1 in 110</td>
</tr>
<tr>
<td>2008</td>
<td>2000</td>
<td>14</td>
<td>11.3 (4.8-21.2)</td>
<td>1 in 88</td>
</tr>
</tbody>
</table>
# ASD Prevalence 2007 to 2012

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Survey of Children’s Health¹</td>
<td>2007</td>
<td>1/86</td>
</tr>
<tr>
<td>CDC 14-site ADDM network²</td>
<td>2008</td>
<td>1/88</td>
</tr>
<tr>
<td>National Survey of Children’s Health³</td>
<td>2011-2012</td>
<td>1/50</td>
</tr>
</tbody>
</table>


NHS Phone Surveys of ASD Prevalence: 1/86 in 2007 to 1/50 in 2012


  – Parent report of ASD diagnosis in 6-17 year olds
    2007: 1 in 86 or 1.16%
    2011-2012: 1 in 50 or 2%

Increase due to new diagnosis of children in this group, particularly adolescents, with previously unrecognized & milder ASD

- Direct screening of all 7-12 year olds in a South Korean community in collaboration with Yale U

1 in 35 or 2.64% with ASD;

66% of these ASD cases were in mainstream school population, undiagnosed and untreated
Public Experience of ASD Reflects Generational Knowledge & Practices

• Baby boomers (born 1945*-1964) 80 million. Little to nothing known about autism. No one recognized it or heard of it. [*1st report 1943]
• Gen X (born 1965-1985) 69 million. Little known until late 80’s and few cases identified.
• Gen Y (born 1985-2010) 100 million. Autism became widely known. Recognition growing rapidly and, with it, prevalence estimates.

  • Courtesy of Debbie and Mark Fornefeld
Dramatic increase in autism prevalence parallels explosion of research into its biology and causes.
What is the cause of the growing prevalence estimates?

• Consequence of new diagnostic criteria that include milder cases? **Yes, yes, and yes.**
• Growing awareness among parents and professionals leading to increased screening? **Yes.**
• Over-diagnosis? **Mostly under.**
• Actual increase in occurrence? **Doubtful.**
Another argument for an epidemic?

If autism is not an epidemic, why are there no adults with autism?

- 38 adults diagnosed with developmental language disorder as children re-evaluated
- All had ADI (parents) and ADOS (participant): 8 met criteria for autism on both instruments and 4 met criteria for autism spectrum disorder
- Some children who nowadays would be diagnosed unambiguously with autism were diagnosed as developmental language disorder in the past.
“Prevalence of autism and its correlates in state hospital” Mandell et al., 2012

• 10% of 141 inpatients at one psychiatric hospital met SRS criteria for ASD
• Not previously diagnosed with ASD
• Had a variety of psychiatric diagnoses
Prevalence and correlates of autism in a state psychiatric hospital.


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Abstract
This study estimated the ASD prevalence in a psychiatric hospital and evaluated the Social Responsiveness Scale (SRS) combined with other information for differential diagnosis. Chart review, SRS and clinical interviews were collected for 141 patients at one hospital. Diagnosis was determined at case conference. Receiver operating characteristic (ROC) curves were used to evaluate the SRS as a screening instrument. Chi-squared Automatic Interaction Detector (CHAID) analysis estimated the role of other variables, in combination with the SRS, in separating cases and non-cases. Ten percent of the sample had ASD. More than other patients, their onset was prior to 12 years of age, they had gait problems and intellectual disability, and were less likely to have a history of criminal involvement or substance abuse. Sensitivity (0.86) and specificity (0.60) of the SRS were maximized at a score of 84. Adding age of onset < 12 years and cigarette use among those with SRS <80 increased sensitivity to 1.00 without lowering specificity. Adding a history substance abuse among those with SRS >80 increased specificity to 0.90 but dropped sensitivity to 0.79. Undiagnosed ASD may be common in psychiatric hospitals. The SRS, combined with other information, may discriminate well between ASD and other disorders.
New: Some Adults Lose ASD Diagnosis

• A small percentage of those diagnosed with autism as children lose their diagnosis and function within the normal limits as adults
• How many of today’s very successful adults might have met criteria for ASD as children?
• How many of those with ASD will become highly successful as adults, especially in STEM? How do we maximize that number?
WHAT’S KNOWN ON THIS SUBJECT: Studies examining the prevalence and associated features of autistic traits (ATs) in children with ADHD with exclusionary autism spectrum disorders suggest that children with ATs exhibit more severe social and interpersonal dysfunction reminiscent of the deficits in children with autism spectrum disorders.

WHAT THIS STUDY ADDS: Our results suggest that ATs are overrepresented in ADHD children when compared with control subjects. They also suggest that the presence of ATs is associated with more severe psychopathology as well as more impaired interpersonal, school, family, and cognitive functioning.

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KEY WORDS
ADHD, ADHD, attention deficit disorder, attention-deficit/hyperactivity disorder, AT, autistic traits, autism traits, comorbidity, social disability
OBJECTIVE: To assess the implications of autistic traits (ATs) in youth with attention-deficit/hyperactivity disorder (ADHD) without a diagnosis of autism.

METHODS: Participants were youth with ($n=242$) and without ($n=227$) ADHD and controls without ADHD in whom a diagnosis of autism was exclusionary. Assessment included measures of psychiatric, psychosocial, educational, and cognitive functioning. ATs were operationalized by using the withdrawn + social + thought problems T scores from the Child Behavior Checklist.

RESULTS: A positive AT profile was significantly overrepresented among ADHD children versus controls ($18\%$ vs $0.87\%$; $P < .001$). ADHD children with the AT profile were significantly more impaired than control subjects in psychopathology, interpersonal, school, family, and cognitive domains.

CONCLUSIONS: A substantial minority of ADHD children manifests ATs, and those exhibiting ATs have greater severity of illness and dysfunction. *Pediatrics* 2013;132:e612–e622
Increasing Prevalence of Milder Cases and Now Traits: Time For A New Plan

• Time to formally recognize social, communication, and problem solving skills in the same way as reading, writing and arithmetic.
• And establish skill goals for each grade with training/educational lessons and contingencies for remediation plans.
New Evidence: Autism Onset Precedes Environmental Exposures
Autism Signs Detected By 3-5mos in Infants At Increased Genetic Risk For ASD

• Longitudinal studies of infants who have an older sibling with autism to define earliest signs
• At 3-5 months: postural instability, reduced fine motor coordination
• By 9 months: unusual response to sensory stimuli, odd motor movements, and unusual visual preoccupation with objects
• 12-24 months: all traditional “core” and “co-morbid” manifestations emerge together
White Matter Microstructure and Atypical Visual Orienting in 7-Month-Olds at Risk for Autism

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Jason J. Wolff, Ph.D.
J. Steven Reznick, Ph.D.
Noah J. Sasson, Ph.D.
Hongbin Gu, Ph.D.
Kelly N. Botteron, M.D.
Stephen R. Dager, M.D.
Annette M. Estes, Ph.D.
Alan C. Evans, Ph.D.
Guido Gerig, Ph.D.
Heather C. Hazlett, Ph.D.
Robert T. Schultz, Ph.D.

Martin Styner, Ph.D.
Lonnie Zwaigenbaum, M.D.
Joseph Piven, M.D.

for the IBIS Network

Objective: The authors sought to determine whether specific patterns of oculomotor functioning and visual orienting characterize 7-month-old infants who later meet criteria for an autism spectrum disorder (ASD) and to identify the neural correlates of these behaviors.

Method: Data were collected from 97 infants, of whom 16 were high-familial-risk infants later classified as having an ASD, 40 were high-familial-risk infants who did not later meet ASD criteria (high-risk negative), and 41 were low-risk infants. All infants underwent an eye-tracking task at a mean age of 7 months and a clinical assessment at a mean age of 25 months. Diffusion-weighted imaging data were acquired for 84 of the infants at 7 months. Primary outcome measures included average saccadic reaction time in a visually guided saccade procedure and radial diffusivity (an index of white matter organization) in fiber tracts that included corticospinal pathways and the splenium and genu of the corpus callosum.

Results: Visual orienting latencies were longer in 7-month-old infants who expressed ASD symptoms at 25 months compared with both high-risk negative infants and low-risk infants. Visual orienting latencies were uniquely associated with the microstructural organization of the splenium of the corpus callosum in low-risk infants, but this association was not apparent in infants later classified as having an ASD.

Conclusions: Flexibly and efficiently orienting to salient information in the environment is critical for subsequent cognitive and social-cognitive development. Atypical visual orienting may represent an early prodromal feature of an ASD, and abnormal functional specialization of posterior cortical circuits directly informs a novel model of ASD pathogenesis.

Environmental Factors Are Intra-uterine Associations; Associations Are Not Causation; Science and Time Will Tell

- Toxicologic studies report *associations* with exposures during pregnancy and early postnatal period (Volk et al, 2013)
- Latest study concludes that environmental effects in ASD are before birth & hypothesize link to industrial societies (Scott et al, 2013)
- Recent associations reported: advanced parent age at conception, maternal diabetes, smog and pesticides during pregnancy, maternal febrile illness, and *protective effect* of maternal folate supplementation
Traffic-Related Air Pollution, Particulate Matter, and Autism

Heather E. Volk, PhD, MPH; Fred Lurmann; Bryan Penfold; Irvan Hertz-Picciotto, PhD; Rob McConnell, MD

JAMA Psychiatry. 2013;70(1):71-77
Environmental Contributions to Autism: Explaining the Rise in Incidence of Autistic Spectrum Disorders

James G. Scott¹,²,³, Michael Duhig²,³, Jess Hamlyn⁴, Rosana Norman⁵,⁶

Abstract
The incidence of autism spectrum disorders, a heterogenous group of neurodevelopmental disorders is increasing. In response, there has been a concerted effort by researchers to identify environmental risk factors that explain the epidemiological changes seen with autism. Advanced parental age, maternal migrant status, maternal gestational stress, pregnancy and birth complications, maternal obesity and gestational diabetes, maternal vitamin D deficiency, use of antidepressants during gestation and exposure to organochlorine pesticides during pregnancy are all associated with an increased risk of autism. Folic acid use prior to pregnancy may reduce the risk of autism. Exposure to antenatal ultrasonography, maternal gestational cigarette and alcohol use do not appear to influence the risk of autism in offspring. There is little evidence that exposure to environmental toxins such as thimerosal, polybrominated diphenyl ethers and di-(2-ethylhexyl) phthalate in early childhood increases the risk of autism. Apart from birth complications, the current evidence suggests that the majority of environmental factors increasing the risk of autism occur in the antenatal period. Consistent with the rise in incidence in autism, some of these environmental factors are now more common in developed nations. Further research is required to determine how these environmental exposures translate to an increased risk of autism. Understanding how these exposures alter neurodevelopment in autistic children may inform both the aetiopathogenesis and the strategies for prevention of autism.
Autism after infection, febrile episodes, and antibiotic use during pregnancy: an exploratory study.

Ásladóttir HÓ, Henriksen TB, Schendel DE, Parner ET.

Abstract

OBJECTIVES: Results of animal studies suggest that maternal immune activation during pregnancy causes deficiencies in fetal neurodevelopment. Infectious disease is the most common path to maternal immune activation during pregnancy. The goal of this study was to determine the occurrence of common infections, febrile episodes, and use of antibiotics reported by the mother during pregnancy and the risk for autism spectrum disorder (ASD) and infantile autism in the offspring.

METHODS: We used a population-based cohort consisting of 96,736 children aged 8 to 14 years and born from 1997 to 2003 in Denmark. Information on infection, febrile episodes, and use of antibiotics was self-reported through telephone interviews during pregnancy and early postpartum. Diagnoses of ASD and infantile autism were retrieved from the Danish Psychiatric Central Register; 976 children (1%) from the cohort were diagnosed with ASD.

RESULTS: Overall, we found little evidence that various types of mild common infectious diseases or febrile episodes during pregnancy were associated with ASD/infantile autism. However, our data suggest that maternal influenza infection was associated with a twofold increased risk of infantile autism, prolonged episodes of fever caused a threefold increased risk of infantile autism, and use of various antibiotics during pregnancy were potential risk factors for ASD/infantile autism.

CONCLUSIONS: Our results do not suggest that mild infections, febrile episodes, or use of antibiotics during pregnancy are strong risk factors for ASD/infantile autism. The results may be due to multiple testing; the few positive findings are potential chance findings.
Hypothesized Mechanism of Environmental Influences: Epigenetic Effects

• Epigenetic effects refer to influences on DNA expression rather than alterations in the genetic code itself
• Alterations in methylation state of DNA is one such hypothesized mechanism
• A hot research topic and results are moving target
Comparison of Genomic and Epigenomic Expression in Monozygotic Twins Discordant for Rett Syndrome


Abstract

Monozygotic (identical) twins have been widely used in genetic studies to determine the relative contributions of heredity and the environment in human diseases. Discordance in disease manifestation between affected monozygotic twins has been attributed to either environmental factors or different patterns of X chromosome inactivation (XCI). However, recent studies have identified genetic and epigenetic differences between monozygotic twins, thereby challenging the accepted experimental model for distinguishing the effects of nature and nurture. Here, we report the genomic and epigenomic sequences in skin fibroblasts of a discordant monozygotic twin pair with Rett syndrome, an X-linked neurodevelopmental disorder characterized by autistic features, epileptic seizures, gait ataxia and stereotypical hand movements. The twins shared the same de novo mutation in exon 4 of the MECP2 gene (G269AfsX288), which was paternal in origin and occurred during spermatogenesis. The XCI patterns in the twins did not differ in lymphocytes, skin fibroblasts, and hair cells (which originate from ectoderm as does neuronal tissue). No reproducible differences were detected between the twins in single nucleotide polymorphisms (SNPs), insertion-deletion polymorphisms (indels), or copy number variations. Differences in DNA methylation between the twins were detected in fibroblasts in the upstream regions of genes involved in brain function and skeletal tissues such as Mohawk Homeobox (MKX), Brain-type Creatine Kinase (CKB), and FYN Tyrosine Kinase Protooncogene (FYN). The level of methylation in these upstream regions was inversely correlated with the level of gene expression. Thus, differences in DNA methylation patterns likely underlie the discordance in Rett phenotypes between the twins.
Genetics: Methyl groups on DNA modify Rett symptoms

Jessica Wright
20 August 2013

Methyl map: A set of twins with Rett syndrome have different methyl marks at 252 spots in the genome that may change nearby gene regulation.
The Other Face of Environmental Influences in ASD

• Improvements in function and brain documented at all ages now in response to interventions based on human interactions within typical environmental contexts

• Opportunities for cures of severe cases are emerging and of effective treatment across the life span
In encouraging news for parents of autistic children, researchers say early behavior therapy can help normalize brain patterns responsible for the symptoms of the condition. Children diagnosed with autism spectrum disorders who participated in the Early Start Denver Model program, which involves intensive social and linguistic engagement with toddlers, showed changes in the way their brains process human faces and objects. Autistic youngsters generally show more brain activity when they view images of an inanimate object like a toy than when they see a picture of a woman’s face. But after two years of ESDM therapy, the autistic children showed the opposite response, and these patterns came close to mimicking those found among normally developing children. It’s a hopeful sign that it’s possible to halt some of the brain changes linked to autism and possibly even reverse them. But the key to the program’s success involves early and intensive intervention with properly trained counselors who actively engage the toddlers in several hours of therapy a week.
Early Behavioral Intervention Is Associated With Normalized Brain Activity in Young Children With Autism

Geraldine Dawson, Ph.D., Emily J.H. Jones, Ph.D., Kristen Merkle, B.S., Kaitlin Venema, B.S., Rachel Lowy, B.S., Susan Faja, Ph.D., Dana Kamara, B.S., Michael Murias, Ph.D., Jessica Greenson, Ph.D., Jamie Winter, Ph.D., Milani Smith, Ph.D., Sally J. Rogers, Ph.D., Sara J. Webb, Ph.D.

Objective: A previously published randomized clinical trial indicated that a developmental behavioral intervention, the Early Start Denver Model (ESDM), resulted in gains in IQ, language, and adaptive behavior of children with autism spectrum disorder. This report describes a secondary outcome measurement from this trial, EEG activity. Method: Forty-eight 18- to 30-month-old children with autism spectrum disorder were randomized to receive the ESDM or referral to community intervention for 2 years. After the intervention (age 48 to 77 months), EEG activity (event-related potentials and spectral power) was measured during the presentation of faces versus objects. Age-matched typical children were also assessed. Results: The ESDM group exhibited greater improvements in autism symptoms, IQ, language, and adaptive and social behaviors than the community intervention group. The ESDM group and typical children showed a shorter Nc latency and increased cortical activation (decreased α power and increased θ power) when viewing faces, whereas the community intervention group showed the opposite pattern (shorter latency event-related potential [ERP] and greater cortical activation when viewing objects). Greater cortical activation while viewing faces was associated with improved social behavior. Conclusions: This was the first trial to demonstrate that early behavioral intervention is associated with normalized patterns of brain activity, which is associated with improvements in social behavior, in young children with autism spectrum disorder. J. Am. Acad. Child Adolesc. Psychiatry; 2012; 51(11): 1150–1159. Clinical trial registration information—Early Characteristics of Autism; http://
Early Start Denver Model: EIBI At 18 months

• If the dramatic cascade of deficits begins at 12 months, studies need to determine if starting this intervention at 12 months will prevent or significantly ameliorate status at 2-3 years.

• What about intervention at 5 months for postural instability which impedes object exploration and language initiation? Study in progress here.
Evidence suggests that children and adults diagnosed with autism spectrum disorders (ASD) exhibit difficulties with postural control. Retrospective video studies of infants later diagnosed with ASD indicate that infants who eventually receive an ASD diagnosis exhibit delays in postural development. This study investigates early posture development prospectively and longitudinally in 22 infants at heightened biological risk for ASD (HR) and 18 infants with no such risk (Low Risk; LR). Four HR infants received an autism diagnosis (AD infants) at 36 months. Infants were videotaped at home at 6, 9, 12, and 14 months during everyday activities and play. All infant postures were coded and classified as to whether or not they were infant-initiated. Relative to LR infants, HR infants were slower to develop skill in sitting and standing postures. AD infants exhibited substantial delays in the emergence of more advanced postures and initiated fewer posture changes. Because posture advances create opportunities for infants to interact with objects and people in new and progressively more sophisticated ways, postural delays may have cascading effects on opportunities for infant exploration and learning. These effects may be greater for infants with ASD, for whom posture delays are more significant.
Early Interventions For Preschoolers

• Several preschool, classroom-based interventions in good education programs lead to improvement across interventions;
• Treatment response is not limited to Ph.D.s or to academic centers
• Treatment response is not limited to one method
Comparative Efficacy of LEAP, TEACCH and Non-Model-Specific Special Education Programs for Preschoolers with Autism Spectrum Disorders.

Boyd BA, Hume K, McBee MT, Alessandri M, Gutierrez A, Johnson L, Sperry L, Odom SL.

Division of Occupational Science and Occupational Therapy, University of North Carolina at Chapel Hill, 2050 Bondurant Hall, Chapel Hill, NC, 27599, USA, brian_boyd@med.unc.edu.

Abstract

LEAP and TEACCH represent two comprehensive treatment models (CTMs) that have been widely used across several decades to educate young children with autism spectrum disorders. The purpose of this quasi-experimental study was to compare high fidelity LEAP (n = 22) and TEACCH (n = 25) classrooms to each other and a control condition (n = 28), in which teachers in high quality special education programs used non-model-specific practices. A total of 198 children were included in data analysis. Across conditions, children's performances improved over time. This study raises issues of the replication of effects for CTMs, and whether having access to a high quality special education program is as beneficial as access to a specific CTM.

PMID: 23812661 [PubMed - as supplied by publisher]
Mean Age of ASD Diagnosis in U.S.

- 4-5 years of age
- Diagnosis of milder cases often delayed until teens or adulthood
- See John Robison for an example “Look Me In The Eye”, “Being Different” and “Raising Cubby”
With a simple checklist, college students quickly and accurately rated home videos such as this one for autism-related behaviors.

Dennis Wall Wins IMFAR Award for Research on Quick Diagnostic Test

Date: May 09, 2013

Promising diagnostic test for autism asks parents to answer 7 questions and upload short home video; more families needed to participate
Peer Training Outperforms Traditional Autism Interventions

Training classmates produces greater gains in social inclusion than even one-on-one training between therapist and child

Making the connection: randomized controlled trial of social skills at school for children with autism spectrum disorders.

Kasari C, Rotheram-Fuller E, Locke J, Gulsrud A.

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Abstract

BACKGROUND: This study compared two interventions for improving the social skills of high functioning children with autism spectrum disorders in general education classrooms. One intervention involved a peer-mediated approach (PEER) and the other involved a child-assisted approach (CHILD).

METHOD: The two interventions were crossed in a 2 × 2 factorial design yielding control, PEER, CHILD, and both PEER and CHILD conditions. Sixty children participated from 56 classrooms in 30 schools. Interventions involved 12 sessions over 6 weeks, with a 3-month follow-up. Outcome measures included self, peer and teacher reports of social skills and independent weekly observations of children on their school playground over the course of the intervention.

RESULTS: Significant improvements were found in social network salience, number of friendship nominations, teacher report of social skills in the classroom, and decreased isolation on the playground for children who received PEER interventions. Changes obtained at the end of the treatment persisted to the 3-month follow-up.

CONCLUSIONS: These data suggest that significant improvements can be made in peer social connections for children with autism spectrum disorders in general education classrooms with a brief intervention, and that these gains persist over time.
Social Peers Rescue Autism-Relevant Sociability Deficits in Adolescent Mice*

Mu Yang, Kayla Perry, Michael D. Weber, Adam M. Katz, and Jacqueline N. Crawley

Behavioral therapies are currently the most effective interventions for treating the diagnostic symptoms of autism. We employed a mouse model of autism to evaluate components of behavioral interventions that improve sociability in mice. BTBR T+tf/J (BTBR) is an inbred mouse strain that exhibits prominent behavioral phenotypes with face validity to all three diagnostic symptom categories of autism, including robust and well-replicated deficits in social approach and reciprocal social interactions. To investigate the role of peer interactions in the development of sociability, BTBR juvenile mice were reared in the same home cage with juvenile mice of a highly social inbred strain, C57BL/6J (B6). Subject mice were tested as young adults for sociability and repetitive behaviors. B6 controls reared with B6 showed their strain-typical high sociability. BTBR controls reared with BTBR showed their strain-typical lack of sociability. In contrast, BTBR reared with B6 as juveniles showed significant sociability as young adults. A 20-day intervention was as effective as a 40-day intervention for improving social approach behavior. High levels of repetitive self-grooming in BTBR were not rescued by peer-rearing with B6, indicating specificity of the intervention to the social domain. These results from a robust mouse model of autism support the interpretation that social enrichment with juvenile peers is a beneficial intervention for improving adult outcome in the social domain. This novel paradigm may prove useful for discovering factors that are essential for effective behavioral treatments, and biological mechanisms underlying effective behavioral interventions.
Brain Plasticity is Lifelong: Neurocognitive Treatment Improves Function & Changes Brain At All Ages
New Treatment for Adults With ASD Targets Core Symptoms & Adaptive Function

• Many early treatments failed to generalize outside the original setting.
• Focus is now on changing thinking and feeling rather than changing behavior; this is the basis of improving adaptive or daily life function.
• Learning while experiencing by using secondary learning supported by cognition. This is how Temple Grandin improved and continues to grow
Supported employment improves cognitive performance in adults with Autism

D. García-Villamisar¹ & C. Hughes²

Background
The purpose of this study was to examine the effects of a supported employment programme on measures of executive functions for 44 adults with autism, assessed at the beginning and the end of the programme period. The average length of time of the community employment was 30 months.

Methods
Based on their predominant work activity over the study period, participants were classified into two groups: supported employment and unemployed. At the start of the programme, the groups did not differ on any of the cognitive measures.

Results
Repeated measures analysis of variance (ANOVA) demonstrated that by the end of the programme, the supported employment group showed higher scores for executive functions on variables of CANTAB (Spatial Span Task – span length recalled; Spatial Working Memory Task – strategy; Planning task ‘Stockings of Cambridge’ – problems solved in minimum moves; Planning task ‘Stockings of Cambridge’ – mean planning time) and other tasks such as Trail Making Test – part B, time; Matching Familiar Figures (first answer and errors). In contrast, the unemployed group showed no change over time in their cognitive performance.

Conclusion
Results of this study suggested that vocational rehabilitation programmes have a beneficial impact upon cognitive performance in people with autism.
The Biggest “E” Effect in ASD is Behavioral and Cognitive Interventions

• Lots of evidence that human environmental influences of parents and school programs are strong and positive
• Studies are demonstrating brain changes as a result of these interventions
• Think about “E” effects in a new way
Urban Myth 3: We don’t know much about what causes autism.

Truth: We know a lot about the etiology and pathophysiology of autism. We also know a lot about the cognitive basis of autism behavior.

It is just not widely known.

SFARI website has excellent reviews of scientific studies. https://sfari.org/
As does Autism Science Foundation. http://autismsciencefoundation.org/
ASD Finally Recognized As Affecting Multiple Brain Systems Simultaneously

• Longitudinal studies of infants at increased genetic risk for ASD define earliest symptoms
• At 3-5 months: postural instability, reduced fine and gross motor coordination
• By 9 months: unusual response to sensory stimuli, odd motor movements, and unusual visual preoccupation with objects
• 12-24 months: all traditional “core” and “co-morbid” manifestations emerge together

Rogers et al. 2009
Traditional Manifestations Emerge Together in 2nd Year

• “Associated symptoms” like motor and sensory & “co-morbid disorders” such as hyperactivity, mood lability, intellectual disability, poor motor development emerge together with “core” symptoms in 2nd year.

• “These findings do not support the notion that autism is primarily a social-communicative disorder and instead suggest that autism disrupts multiple aspects of development rather simultaneously.” More about this later.

Rogers et al, 2009
Multiple Brain Systems View Connects the Clinical to A Large Body of Known Biology

• ASD selectively affects higher order abilities across many domains

• Extensive imaging studies show that this pattern reflects under development of cortical systems.

• Cortical systems development is highly regulated by genes and involves well defined but elaborate, highly complex mechanisms.
Pathophysiology & Etiology of ASD: Big Advances, Driven By Technology

“Decades of research have clearly implicated genes that regulate how brain cells and networks develop and interconnect.”

Relationship to the clinical syndrome often not articulated or understood.
Exciting times for genetics of Autism Spectrum Disorders

[Graph showing the increase in the total number of autism genes identified from 1995 to 2010.]
Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting.

Betancur C.
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Abstract
There is increasing evidence that autism spectrum disorders (ASDs) can arise from rare highly penetrant mutations and genomic imbalances. The rare nature of these variants, and the often differing orbits of clinical and research geneticists, can make it difficult to fully appreciate the extent to which we have made progress in understanding the genetic etiology of autism. In fact, there is a persistent view in the autism research community that there are only a modest number of autism loci known. We carried out an exhaustive review of the clinical genetics and research genetics literature in an attempt to collate all genes and recurrent genomic imbalances that have been implicated in the etiology of ASD. We provide data on 103 disease genes and 44 genomic loci reported in subjects with ASD or autistic behavior. These genes and loci have all been causally implicated in intellectual disability, indicating that these two neurodevelopmental disorders share common genetic bases. A genetic overlap between ASD and epilepsy is also apparent in many cases. Taken together, these findings clearly show that autism is not a single clinical entity but a behavioral manifestation of tens or perhaps hundreds of genetic and genomic disorders. Increased recognition of the etiological heterogeneity of ASD will greatly expand the number of target genes for neurobiological investigations and thereby provide additional avenues for the development of pathway-based pharmacotherapy. Finally, the data provide strong support for high-resolution DNA microarrays as well as whole-exome and whole-genome sequencing as critical approaches for identifying the genetic causes of ASDs.
Recent developments in the genetics of autism spectrum disorders.

Murdoch JD, State MW.
Department of Genetics, Yale University School of Medicine, New Haven, CT 06510, United States.

Abstract
The last several years have marked a turning point in the genetics of autism spectrum disorder (ASD) due to rapidly advancing genomic technologies. As the pool of bona fide risk genes and regions accumulates, several key themes have emerged: these include the important role of rare and de novo mutation, the biological overlap among so-called syndromic and 'idiopathic' ASD, the elusive nature of the common variant contribution to risk, and the observation that the tremendous locus heterogeneity underlying ASD appears to converge on a relatively small number of key biological processes. Perhaps most striking has been the revelation that ASD mutations show tremendous phenotypic variability ranging from social disability to schizophrenia, intellectual disability, language impairment, epilepsy and typical development.
SFARI Gene

SFARI Gene is an evolving database for the autism research community that is centered on genes implicated in autism susceptibility. The SFARI Gene web portal seamlessly integrates different kinds of genetic data that are being generated by research studies, and in so doing encourages the generation of new hypotheses.

On 5 December, SFARI Gene was relaunched as SFARI Gene 2.0. This version offers several new features, including intuitive, tab-based investigation for cross-referencing all information on any given gene in the database. Researchers interested in the potential role of a particular gene in autism spectrum disorders (ASD) can access SFARI Gene 2.0 for information in five ways:

**Human Gene Module** lists more than 284 genes implicated in autism, with annotations and links to the published papers.

**Gene Scoring Module**, new to SFARI Gene 2.0, offers a critical evaluation of the strength of the evidence for each gene’s association with ASD. Six expert geneticists working on ASD collaborated on this effort, which will be continually updated.

**Copy Number Variant Module**, also new to SFARI Gene 2.0, provides exhaustive detail on all copy number variants reported in individuals with ASD.

**Protein Interaction Module** curates all of the protein-protein and protein-nucleic acid interactions reported in the literature for the genes in the Human Gene Module.

**Animal Model Module** lists more than 288 lines of mice that carry mutations in the genes that populate the Human Gene Module. The animal model list is accompanied by extensive information about each line of mice, including information on the phenotypes of greatest relevance to ASD. New to this module is a list of ‘non-genetic’ models, which reflect the potential role of environmental risk factors in ASD.
Network Topologies and Convergent Aetiologies Arising from Deletions and Duplications Observed in Individuals with Autism

Hyun Ji Noh¹, Chris P. Ponting¹, Hannah C. Boulding¹, Stephen Meader¹, Catalina Betancur²,³,⁴, Joseph D. Buxbaum⁵, Dalila Pinto⁶, Christian R. Marshall⁷, Anath C. Lionel⁷, Stephen W. Scherer⁷, Caleb Webber¹*

Abstract

Autism Spectrum Disorders (ASD) are highly heritable and characterised by impairments in social interaction and communication, and restricted and repetitive behaviours. Considering four sets of de novo copy number variants (CNVs) identified in 181 individuals with autism and exploiting mouse functional genomics and known protein-protein interactions, we identified a large and significantly interconnected interaction network. This network contains 187 genes affected by CNVs drawn from 45% of the patients we considered and 22 genes previously implicated in ASD, of which 192 form a single interconnected cluster. On average, those patients with copy number changed genes from this network possess changes in 3 network genes, suggesting that epistasis mediated through the network is extensive. Correspondingly, genes that are highly connected within the network, and thus whose copy number change is predicted by the network to be more phenotypically consequential, are significantly enriched among patients that possess only a single ASD-associated network copy number changed gene (p = 0.002). Strikingly, deleted or disrupted genes from the network are significantly enriched in GO-annotated positive regulators (2.3-fold enrichment, corrected p = 2×10⁻⁵), whereas duplicated genes are significantly enriched in GO-annotated negative regulators (2.2-fold enrichment, corrected p = 0.005). The direction of copy change is highly informative in the context of the network, providing the means through which perturbations arising from distinct deletions or duplications can yield a common outcome. These findings reveal an extensive ASD-associated molecular network, whose topology indicates ASD-relevant mutational deleteriousness and that mechanistically details how convergent aetiologies can result extensively from CNVs affecting pathways causally implicated in ASD.
Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations.


Abstract

It is well established that autism spectrum disorders (ASD) have a strong genetic component; however, for at least 70% of cases, the underlying genetic cause is unknown. Under the hypothesis that de novo mutations underlie a substantial fraction of the risk for developing ASD in families with no previous history of ASD or related phenotypes--so-called sporadic or simplex families--we sequenced all coding regions of the genome (the exome) for parent-child trios exhibiting sporadic ASD, including 189 new trios and 20 that were previously reported. Additionally, we also sequenced the exomes of 50 unaffected siblings corresponding to these new (n = 31) and previously reported trios (n = 19), for a total of 677 individual exomes from 209 families. Here we show that de novo point mutations are overwhelmingly paternal in origin (4:1 bias) and positively correlated with paternal age, consistent with the modest increased risk for children of older fathers to develop ASD. Moreover, 39% (49 of 126) of the most severe or disruptive de novo mutations map to a highly interconnected β-catenin/chromatin remodelling protein network ranked significantly for autism candidate genes. In proband exomes, recurrent protein-altering mutations were observed in two genes: CHD8 and NTNG1. Mutation screening of six candidate genes in 1,703 ASD probands identified additional de novo, protein-altering mutations in GRIN2B, LAMC3 and SCN1A. Combined with copy number variant (CNV) data, these results indicate extreme locus heterogeneity but also provide a target for future discovery, diagnostics and therapeutics.
Customized high resolution CGH-array for clinical diagnosis reveals additional genomic imbalances in previous well-defined pathological samples.


High-resolution array comparative genomic hybridization (aCGH) is a powerful molecular cytogenetic tool that is being adopted for diagnostic evaluation of genomic imbalances and study disease mechanisms and pathogenesis. We report on the design and use, of a custom whole-genome oligonucleotide-based array (called KaryoArray®v3.0; Agilent-based 8 × 60 K) for diagnostic setting, which was able to detect new and unexpected rearrangements in 11/63 (~17.5%) of previous known pathological cases associated with known genetic disorders, and in the second step it identified at least one causal genomic imbalance responsible of the phenotype in ~20% of patients with psychomotor development delay and/or intellectual disability. To validate the array, first; we blindly tested 120 samples; 63 genomic imbalances that had previously been detected by karyotyping, FISH and/or MLPA, and 57 sex-matched control samples from healthy individuals; secondly a prospective study of 540 patients with intellectual disabilities, autism spectrum disorder and multiple congenital anomalies were evaluated to confirm the utility of the tool. These data indicate that implementation of array technologies as the first-tier test may reveal that additional genomic imbalances could co-exist in patients with trisomies and classical del/dup syndromes, suggesting that aCGH may also be indicated in these individuals, at least when phenotype does not match completely with genotype. © 2013 Wiley Periodicals, Inc.
Behavioral Profiles of Mouse Models for Autism Spectrum Disorders

Elodie Ey, Claire S. Leblond, and Thomas Bourgeron

Autism spectrum disorders (ASD) are characterized by impairments in reciprocal social communication, and stereotyped verbal and nonverbal behaviors. In approximately 10–25% of the affected individuals, a genetic mutation associated with the condition can be identified. Recently, mutations altering synapse formation, cellular/synaptic growth rate and regulation of excitatory and inhibitory currents were identified in patients with intellectual disability, typical autism, Asperger syndrome or neurological syndromes associated with autistic traits. Following these genetic findings, mouse models carrying mutations similar to those identified in patients have been generated. These models offer the opportunity to investigate in vivo the physiological and behavioral consequences of the mutations. Here, we review the existing data on the phenotypes of mice carrying mutations in genes associated with ASD including neuroligin, neurexin and Shank mutant mice as well as the Fmr1, Mecp2, Ube3a, Nf1, Pten and Tsc1/Tsc2 mutant mice. The diversity and complexity of the phenotype of these mouse models reflect the broad range of phenotypes observed in patients with ASD. Remarkably, results from therapeutic approaches (e.g., modulation of gene expression, administration of pharmacological and nonpharmacological substances, enriched environment) are encouraging since some behavioral alterations could be reversed even when treatment was performed on adult mice. These ongoing studies should therefore increase our understanding of the biological alterations associated with ASD as well as the development of knowledge-based treatments.
Modifying Behavioral Phenotypes in Fmr1KO Mice: Genetic Background Differences Reveal Autistic-Like Responses


Fragile X syndrome (FXS) is the most common inherited form of intellectual disability in humans. In addition to cognitive impairment, patients may exhibit hyperactivity, attention deficits, social difficulties and anxiety, and autistic-like behaviors. The degree to which patients display these behaviors varies considerably and is influenced by family history, suggesting that genetic modifiers play a role in the expression of behaviors in FXS. Several studies have examined behavior in a mouse model of FXS in which the Fmr1 gene has been ablated. Most of those studies were done in Fmr1 knockout mice on a pure C57BL/6 or FVB strain background. To gain a better understanding of the effects of genetic background on behaviors resulting from the loss of Fmr1 gene expression, we generated F1 hybrid lines from female Fmr1 heterozygous mice on a pure C57BL/6J background bred with male Fmr1 wild-type (WT) mice of various background strains (A/J, DBA/2J, FVB/NJ, 129S1/SvImJ and CD-1). Male Fmr1 knockout and WT littermates from each line were examined in an extensive behavioral test battery. Results clearly indicate that multiple behavioral responses are dependent on genetic background, including autistic-like traits that are present on limited genetic backgrounds. This approach has allowed us to identify improved models for different behavioral symptoms present in FXS including autistic-like traits.
Autism spectrum disorder (ASD) depends on a clinical interview with no biomarkers to aid diagnosis. The current investigation interrogated single-nucleotide polymorphisms (SNPs) of individuals with ASD from the Autism Genetic Resource Exchange (AGRE) database. SNPs were mapped to Kyoto Encyclopedia of Genes and Genomes (KEGG)-derived pathways to identify affected cellular processes and develop a diagnostic test. This test was then applied to two independent samples from the Simons Foundation Autism Research Initiative (SFARI) and Wellcome Trust 1958 normal birth cohort (WTBC) for validation. Using AGRE SNP data from a Central European (CEU) cohort, we created a genetic diagnostic classifier consisting of 237 SNPs in 146 genes that correctly predicted ASD diagnosis in 85.6% of CEU cases. This classifier also predicted 84.3% of cases in an ethnically related Tuscan cohort; however, prediction was less accurate (56.4%) in a genetically dissimilar Han Chinese cohort (HAN). Eight SNPs in three genes (KCNMB4, GNAO1, GRM5) had the largest effect in the classifier with some acting as vulnerability SNPs, whereas others were protective. Prediction accuracy diminished as the number of SNPs analyzed in the model was decreased. Our diagnostic classifier correctly predicted ASD diagnosis with an accuracy of 71.7% in CEU individuals from the SFARI (ASD) and WTBC (controls) validation data sets. In conclusion, we have developed an accurate diagnostic test for a genetically homogeneous group to aid in early detection of ASD. While SNPs differ across ethnic groups, our pathway approach identified cellular processes common to ASD across ethnicities. Our results have wide implications for detection, intervention and prevention of ASD.
Conclusions

• Understand much about the genetic architecture of autism; will understand much more very soon.
• More genes and more potential drug targets
• Momentum for discovery is huge and due to
  – Pooling data
  – Funding
• 5 years from now gene discovery in ASD will become passé: translation will be the key for ASD in the near future!

Bernie Devlin 2012
Gene Identification Leads to Developmental Neurobiologic Mechanisms

• Follow the trail
• Knowing molecular mechanisms is the key to radical, biologically based improvements in treatment.
Major Neurobiologic Events in Brain Development

- Organogenesis
- Neuronal proliferation*
- Neuronal migration*
- Neuronal organization**
- Glial proliferation
- Myelination

** indicate mechanisms found in ASD so far

**Dendrite Morphology/Function**
- SHANK3/SHANK2
- Reelin
- DLGAP2

**Synaptic CAMs**
- Neurexins/Neuroligins
- Cadherings
- CNTN4
- CNTNAP2
- SYNGAP1

Axonal Outgrowth/Pathfinding
- Slit/LRRs
- Reelin
- Tau Kinases
- Cadherings
- SYNGAP1
Linking Gene Alterations to Brain Development to Brain Systems

- Abnormal neuronal migration
- Abnormalities in patterning (regionalization or connectivity)
- Faulty wiring/axon pathfinding
- Aberrant synaptogenesis or synaptic function
- Dendritic abnormalities
- Dysfunctional neural transmission

Genetic modifier loci
(CNTNAP2, MET, rs4307059, etc...)

Stochastic or Environmental processes

Developmental disconnection of critical brain circuits:
- Fronto-striatal
- Fronto-temporal
- Fronto-parietal

ASD

(dup) 15q11-13
TSC1
FMR1
(del) 22q
(del) 16p
CACNA1C
Gene Identification Also Leads to Identification of Cell Signaling Pathways
Cellular Signaling Pathways Lead to New Biologic Treatments Critical to Treatment of Severe Cases

- Clinically, there are **two worlds of autism**. One world is that of the less severe cases for whom various neurocognitive rehabilitation strategies are changing outcome. The second world is that of the severe cases where treatments are not working.
Can Biological Treatments Change The Brain?
In severe cases? At what age?

The first ones exist. Others are entering trials.

Biological interventions impact signaling pathways in brain cells to stop over-growth or start connecting.
Mammalian target of rapamycin (mTOR) inhibition: potential for antiseizure, antiepileptogenic, and epileptostatic therapy.

Ryther RC, Wong M.

New epilepsy treatments are needed that not only inhibit seizures symptomatically (antiseizure) but also prevent the development of epilepsy (antiepileptogenic). The mammalian target of rapamycin (mTOR) pathway may mediate mechanisms of epileptogenesis and serve as a rational therapeutic target. mTOR inhibitors have antiepileptogenic and antiseizure effects in animal models of the genetic disease, tuberous sclerosis complex. The mTOR pathway is also implicated in epileptogenesis in animal models of acquired epilepsy and infantile spasms, although the effects of mTOR inhibitors are variable depending on the specific conditions and model. Furthermore, beneficial effects on seizures are lost when treatment is withdrawn, suggesting that mTOR inhibitors are "epileptostatic" in only stalling epilepsy progression during treatment. Clinical studies of rapamycin in human epilepsy are limited, but suggest that mTOR inhibitors at least have antiseizure effects in tuberous sclerosis patients. Further studies are needed to assess the full potential of mTOR inhibitors for epilepsy treatment.
Systemic Delivery of MeCP2 Rescues Behavioral and Cellular Deficits in Female Mouse Models of Rett Syndrome

Saurabh K. Garg,1,2,* Daniel T. Lioy,1,2* Hélène Cheval,3* James C. McGann,1,2 John M. Bissonnette,4,5 Matthew J. Murtha,7 Kevin D. Foust,6 Brian K. Kaspar,7 Adrian Bird,3 and Gail Mandel1,2

De novo mutations in the X-linked gene encoding the transcription factor methyl-CpG binding protein 2 (MECP2) are the most frequent cause of the neurological disorder Rett syndrome (RTT). Hemizygous males usually die of neonatal encephalopathy. Heterozygous females survive into adulthood but exhibit severe symptoms including microcephaly, loss of purposeful hand motions and speech, and motor abnormalities, which appear after a period of apparently normal development. Most studies have focused on male mouse models because of the shorter latency to and severity in symptoms, yet how well these mice mimic the disease in affected females is not clear. Very few therapeutic treatments have been proposed for females, the more gender-appropriate model. Here, we show that self-complementary AAV9, bearing MeCP2 cDNA under control of a fragment of its own promoter (scAAV9/MeCP2), is capable of significantly stabilizing or reversing symptoms when administered systemically into female RTT mice. To our knowledge, this is the first potential gene therapy for females afflicted with RTT.
Autistic-like social behaviour in Shank2-mutant mice improved by restoring NMDA receptor function.


Department of Biological Sciences, KAIST, Daejeon 305-701, Korea.

Abstract

Autism spectrum disorder (ASD) is a group of conditions characterized by impaired social interaction and communication, and restricted and repetitive behaviours. ASD is a highly heritable disorder involving various genetic determinants. Shank2 (also known as ProSAP1) is a multi-domain scaffolding protein and signalling adaptor enriched at excitatory neuronal synapses, and mutations in the human SHANK2 gene have recently been associated with ASD and intellectual disability. Although ASD-associated genes are being increasingly identified and studied using various approaches, including mouse genetics, further efforts are required to delineate important causal mechanisms with the potential for therapeutic application. Here we show that Shank2-mutant (Shank2(-/-)) mice carrying a mutation identical to the ASD-associated microdeletion in the human SHANK2 gene exhibit ASD-like behaviours including reduced social interaction, reduced social communication by ultrasonic vocalizations, and repetitive jumping. These mice show a marked decrease in NMDA (N-methyl-D-aspartate) glutamate receptor (NMDAR) function. Direct stimulation of NMDARs with D-cycloserine, a partial agonist of NMDARs, normalizes NMDAR function and improves social interaction in Shank2(-/-) mice. Furthermore, treatment of Shank2(-/-) mice with a positive allosteric modulator of metabotropic glutamate receptor 5 (mGluR5), which enhances NMDAR function via mGluR5 activation, also normalizes NMDAR function and markedly enhances social interaction. These results suggest that reduced NMDAR function may contribute to the development of ASD-like phenotypes in Shank2(-/-) mice, and mGluR modulation of NMDARs offers a potential strategy to treat ASD.
Autism spectrum disorder (ASD) depends on a clinical interview with no biomarkers to aid diagnosis. The current investigation interrogated single-nucleotide polymorphisms (SNPs) of individuals with ASD from the Autism Genetic Resource Exchange (AGRE) database. SNPs were mapped to Kyoto Encyclopedia of Genes and Genomes (KEGG)-derived pathways to identify affected cellular processes and develop a diagnostic test. This test was then applied to two independent samples from the Simons Foundation Autism Research Initiative (SFARI) and Wellcome Trust 1958 normal birth cohort (WTBC) for validation. Using AGRE SNP data from a Central European (CEU) cohort, we created a genetic diagnostic classifier consisting of 237 SNPs in 146 genes that correctly predicted ASD diagnosis in 85.6% of CEU cases. This classifier also predicted 84.3% of cases in an ethnically related Tuscan cohort; however, prediction was less accurate (56.4%) in a genetically dissimilar Han Chinese cohort (HAN). Eight SNPs in three genes (KCNMB4, GNAO1, GRM5) had the largest effect in the classifier with some acting as vulnerability SNPs, whereas others were protective. Prediction accuracy diminished as the number of SNPs analyzed in the model was decreased. Our diagnostic classifier correctly predicted ASD diagnosis with an accuracy of 71.7% in CEU individuals from the SFARI (ASD) and WTBC (controls) validation data sets. In conclusion, we have developed an accurate diagnostic test for a genetically homogeneous group to aid in early detection of ASD. While SNPs differ across ethnic groups, our pathway approach identified cellular processes common to ASD across ethnicities. Our results have wide implications for detection, intervention and prevention of ASD.
Can we measure these brain changes so that we can link symptom variability to brain structure and function and then can we develop targeted treatments and monitor their impact on the brain. **Getting there fast.**
Genetics of autism spectrum disorders

Daniel H. Geschwind\textsuperscript{1,2,3}

Characterized by a combination of abnormalities in language, social cognition and mental flexibility, autism is not a single disorder but a neurodevelopmental syndrome commonly referred to as autism spectrum disorder (ASD). Several dozen ASD susceptibility genes have been identified in the past decade, collectively accounting for 10–20% of ASD cases. These findings, although demonstrating that ASD is etiologically heterogeneous, provide important clues about its pathophysiology. Diverse genetic and genomic approaches provide evidence converging on disruption of key biological pathways, many of which are also implicated in other allied neurodevelopmental disorders. Knowing the genes involved in ASD provides us with a crucial tool to probe both the specificity of ASD and the shared neurobiological and cognitive features across what are considered clinically distinct disorders, with the goal of linking gene to brain circuits to cognitive function.
Figure 2. Occipital–frontal (OFC) Z-score measurements (N=195) with mean estimated growth trajectory for 28 children with autism spectrum disorder (hierarchical linear model two-piece linear model centered at 12 months).
Scientists have discovered that the brain is even more beautifully organized than they had imagined.

Neurons in the brain zip messages to one another along long white fibers called axons. Previously scientists traced axon pathways in dissected animal brains, but now they can see the structure of this amazing information superhighway in a living human organ. Using new software with a technique called “diffusion tensor MRI” that tracks water molecules as they move along the axons, Van Wedeen of Massachusetts General Hospital and colleagues found that the fibers are arranged in a surprisingly regular 3-D grid.

“Biology gives you a brain. Life turns it into a mind.” Jeffrey Eugenides

By Laura Helmuth
Neurons in the brain zip messages to one another along long white fibers called axons. Previously scientists traced axon pathways in dissected animal brains, but now they can see the structure of this amazing information superhighway in a living human organ. Using new software with a technique called "diffusion tensor MRI" that tracks water molecules as they move along the axons, Van Wedeen of Massachusetts General Hospital and colleagues found that the fibers are arranged in a surprisingly regular 3-D grid. For instance, the red axons in the image converge on the purple pathway at a 90-degree angle. Axons are interwoven like "the warp and weft of a fabric," the researchers say, with the pattern bent along the brain's convolutions. "It's really pretty, all the little loops and folds," Wedeen says.
The technique Wedeen and colleagues use is called "diffusion spectrum MRI," a variation on an existing technique. By monitoring how water moves along axons and at what angle these brain fibers cross one another, the researchers found a surprisingly geometric pattern. The three-dimensional grid is visible in this detail from a rhesus monkey brain.
Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants With Autism


Objective: Evidence from prospective studies of high-risk infants suggests that early symptoms of autism usually emerge late in the first or early in the second year of life after a period of relatively typical development. The authors prospectively examined white matter fiber tract organization from 6 to 24 months in high-risk infants who developed autism spectrum disorders (ASDs) by 24 months.

Method: The participants were 92 high-risk infant siblings from an ongoing imaging study of autism. All participants had diffusion tensor imaging at 6 months and behavioral assessments at 24 months; a majority contributed additional imaging data at 12 and/or 24 months. At 24 months, 28 infants met criteria for ASDs and 64 infants did not. Microstructural properties of white matter fiber tracts reported to be associated with ASDs or related behaviors were characterized by fractional anisotropy and radial and axial diffusivity.

Results: The fractional anisotropy trajectories for 12 of 15 fiber tracts differed significantly between the infants who developed ASDs and those who did not. Development for most fiber tracts in the infants with ASDs was characterized by higher fractional anisotropy values at 6 months followed by slower change over time relative to infants without ASDs. Thus, by 24 months of age, those with ASDs had lower values.

Conclusions: These results suggest that aberrant development of white matter pathways may precede the manifestation of autistic symptoms in the first year of life. Longitudinal data are critical to characterizing the dynamic age-related brain and behavior changes underlying this neurodevelopmental disorder.
Changes in prefrontal axons may disrupt the network in autism.

Zikopoulos B, Barbas H.

Abstract
Neural communication is disrupted in autism by unknown mechanisms. Here, we examined whether in autism there are changes in axons, which are the conduit for neural communication. We investigated single axons and their ultrastructure in the white matter of postmortem human brain tissue below the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and lateral prefrontal cortex (LPFC), which are associated with attention, social interactions, and emotions, and have been consistently implicated in the pathology of autism. Area-specific changes below ACC (area 32) included a decrease in the largest axons that communicate over long distances. In addition, below ACC there was overexpression of the growth-associated protein 43 kDa accompanied by excessive number of thin axons that link neighboring areas. In OFC (area 11), axons had decreased myelin thickness. Axon features below LPFC (area 46) appeared to be unaffected, but the altered white matter composition below ACC and OFC changed the relationships among all prefrontal areas examined, and could indirectly affect LPFC function. These findings provide a mechanism for disconnection of long-distance pathways, excessive connections between neighboring areas, and inefficiency in pathways for emotions, and may help explain why individuals with autism do not adequately shift attention, engage in repetitive behavior, and avoid social interactions. These changes below specific prefrontal areas appear to be linked through a cascade of developmental events affecting axon growth and guidance, and suggest targeting the associated signaling pathways for therapeutic interventions in autism.
Functional Imaging Has Greatly Improved Understanding of Behavior
Is He Being Bad? Social and LanguageBrain Networks
during Social Judgment in Children with Autism

Elizabeth J. Carter¹,²*, Diane L. Williams³, Nancy J. Minshew⁴, Jill F. Lehman⁵

Abstract

Individuals with autism often violate social rules and have lower accuracy in identifying and explaining inappropriate social behavior. Twelve children with autism (AD) and thirteen children with typical development (TD) participated in this fMRI study of the neurofunctional basis of social judgment. Participants indicated in which of two pictures a boy was being bad (Social condition) or which of two pictures was outdoors (Physical condition). In the within-group Social–Physical comparison, TD children used components of mentalizing and language networks [bilateral inferior frontal gyrus (IFG), bilateral medial prefrontal cortex (mPFC), and bilateral posterior superior temporal sulcus (pSTS)], whereas AD children used a network that was primarily right IFG and bilateral pSTS, suggesting reduced use of social and language networks during this social judgment task. A direct group comparison on the Social–Physical contrast showed that the TD group had greater mPFC, bilateral IFG, and left superior temporal pole activity than the AD group. No regions were more active in the AD group than in the group with TD in this comparison. Both groups successfully performed the task, which required minimal language. The groups also performed similarly on eyetracking measures, indicating that the activation results probably reflect the use of a more basic strategy by the autism group rather than performance disparities. Even though language was unnecessary, the children with TD recruited language areas during the social task, suggesting automatic encoding of their knowledge into language; however, this was not the case for the children with autism. These findings support behavioral research indicating that, whereas children with autism may recognize socially inappropriate behavior, they have difficulty using spoken language to explain why it is inappropriate. The fMRI results indicate that AD children may not automatically use language to encode their social understanding, making expression and generalization of this knowledge more difficult.
Underconnectivity between voice-selective cortex and reward circuitry in children with autism

Daniel A. Abrams¹, Charles J. Lynch³, Katherine M. Cheng³, Jennifer Phillips³, Kaustubh Supekar³, Srikanth Ryali³, Lucina Q. Uddin³, and Vinod Menon⁴⁵

Individuals with autism spectrum disorders (ASDs) often show insensitivity to the human voice, a deficit that is thought to play a key role in communication deficits in this population. The social motivation theory of ASD predicts that impaired function of reward and emotional systems impedes children with ASD from actively engaging with speech. Here we explore this theory by investigating distributed brain systems underlying human voice perception in children with ASD. Using resting-state functional MRI data acquired from 20 children with ASD and 19 age- and intelligence quotient-matched typically developing children, we examined intrinsic functional connectivity of voice-selective bilateral posterior superior temporal sulcus (pSTS). Children with ASD showed a striking pattern of underconnectivity between left-hemisphere pSTS and distributed nodes of the dopaminergic reward pathway, including bilateral ventral tegmental areas and nucleus accumbens, left-hemisphere insula, orbitofrontal cortex, and ventromedial prefrontal cortex. Children with ASD also showed underconnectivity between right-hemisphere pSTS, a region known for processing speech prosody, and the orbitofrontal cortex and amygdala, brain regions critical for emotion-related associative learning. The degree of underconnectivity between voice-selective cortex and reward pathways predicted symptom severity for communication deficits in children with ASD. Our results suggest that weak connectivity of voice-selective cortex and brain structures involved in reward and emotion may impair the ability of children with ASD to experience speech as a pleasurable stimulus, thereby impacting language and social skill development in this population. Our study provides support for the social motivation theory of ASD.
Most psychiatric disorders are moderately to highly heritable. The degree to which genetic variation is unique to individual disorders or shared across disorders is unclear. To examine shared genetic etiology, we use genome-wide genotype data from the Psychiatric Genomics Consortium (PGC) for cases and controls in schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD). We apply univariate and bivariate methods for the estimation of genetic variation within and covariation between disorders. SNPs explained 17-29% of the variance in liability. The genetic correlation calculated using common SNPs was high between schizophrenia and bipolar disorder (0.68 ± 0.04 s.e.), moderate between schizophrenia and major depressive disorder (0.43 ± 0.06 s.e.), bipolar disorder and major depressive disorder (0.47 ± 0.06 s.e.), and ADHD and major depressive disorder (0.32 ± 0.07 s.e.), low between schizophrenia and ASD (0.16 ± 0.06 s.e.) and non-significant for other pairs of disorders as well as between psychiatric disorders and the negative control of Crohn’s disease. This empirical evidence of shared genetic etiology for psychiatric disorders can inform nosology and encourages the investigation of common pathophysiology for related disorders.
No neural evidence of statistical learning during exposure to artificial languages in children with autism spectrum disorders.

Scott-Van Zeeland AA, McNealy K, Wang AT, Sigman M, Bookheimer SY, Dapretto M.

Abstract

BACKGROUND: Language delay is a hallmark feature of autism spectrum disorders (ASD). The identification of word boundaries in continuous speech is a critical first step in language acquisition that can be accomplished via statistical learning and reliance on speech cues. Importantly, early word segmentation skills have been shown to predict later language development in typically developing (TD) children.

METHODS: Here we investigated the neural correlates of online word segmentation in children with and without ASD with a well-established behavioral paradigm previously validated for functional magnetic resonance imaging. Eighteen high-functioning boys with ASD and 18 age- and IQ-matched TD boys underwent functional magnetic resonance imaging while listening to two artificial languages (containing statistical or statistical + prosodic cues to word boundaries) and a random speech stream.

RESULTS: Consistent with prior findings, in TD control subjects, activity in fronto-temporal-parietal networks decreased as the number of cues to word boundaries increased. The ASD children, however, did not show this facilitatory effect. Furthermore, statistical contrasts modeling changes in activity over time identified significant learning-related signal increases for both artificial languages in basal ganglia and left temporo-parietal cortex only in TD children. Finally, the level of communicative impairment in ASD children was inversely correlated with signal increases in these same regions during exposure to the artificial languages.

CONCLUSIONS: This is the first study to demonstrate significant abnormalities in the neural architecture subserving language-related learning in ASD children and to link the communicative impairments observed in this population to decreased sensitivity to the statistical and speech cues available in the language input.
Big Challenges

• Define mechanistic bases of heterogeneity at neural systems and molecular levels
• Translate mechanisms into effective treatments
• Develop technology for wide dissemination of new treatments that focus on thinking not behavior to improve generalization
• Anticipate that neurocognitive and biologic treatments for ASD will also be applicable to disorders with overlapping symptoms