Autism: Integrating Genes, Brain and Behavior

Keynote Speakers: Daniel Geschwind (University of California, Los Angeles), Geraldine Dawson (Autism Speaks). Presented by Weill Cornell Medical College, Clinical & Translational Science Center (CTSC) and Hunter College of the City University of New York. Reported by Farooq Ahmed and Michael Eisenstein

Overview

It has become increasingly clear that the diverse developmental symptoms associated with autism spectrum disorders are a complex product of biological determinants and environmental factors. Accordingly, efforts to promptly identify autistic individuals and provide treatments that can improve their quality of life will require a concerted effort from experts working in diverse areas of basic and clinical research.

The 23rd Annual International Symposium of the Hunter College Center for Gene Structure and Function, held in New York on 15 January, 2010, brought together leaders in fields ranging from cell biology and neuroscience to developmental psychology and public health, with the common aim of describing ongoing progress – and yet-unmet challenges – in building a comprehensive picture of autism. Although the talks were divided into two distinct sections, one focused primarily at the cellular and molecular level and the other at the diagnostic and therapeutic level, all the presentations were nevertheless linked by the recognition that true breakthroughs in understanding and controlling the negative impact of this family of developmental disorders will ultimately require parallel progress in both areas.

Sponsorship

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Introduction

The core symptoms of autism have been recognized since at least 1943, when Johns Hopkins psychiatrist Leo Kanner published a seminal study that described eleven children with notable common deficits relating to communication and behavior. Although Kanner’s work still offers valuable insights for modern clinicians and researchers, the past 67 years have witnessed considerable expansion of the definition of autism to encompass a diverse array of ‘autism spectrum disorders’ (ASD) ranging in severity from relatively high-functioning Asperger syndrome to more debilitating conditions involving mental retardation or absence of language skills.

This broader understanding of the deficits associated with ASD has also been accompanied by progress in recognizing potential biological determinants for autism and the identification of associated
developmental disorders such as Fragile X syndrome (FXS). Nevertheless, it has proven a considerable challenge to assemble these various puzzle pieces of data into a coherent picture that can guide early diagnosis and effective treatment of ASD in young children, before these developmental impairments grow too severe.

Integration was the overarching theme of the 23rd Annual International Symposium of the Hunter College Center for the Study of Gene Structure and Function, which was held in New York on 15 January, 2010. This concept was directly emphasized through presentations of research efforts that closely pair biological and neuropsychological approaches, but was also reflected in the broad recognition that many core problems faced by individuals with ASD arise from failures in functional integration within the brain—and that treatment will require effective multivalent diagnostic and therapeutic strategies.

The biological bases of ASDs

The morning session began with a keynote from Daniel Geschwind, of the University of California at Los Angeles, whose presentation focused on the high heritability of autism and ongoing efforts to identify susceptibility genes. Although 10–15% of ASD cases are associated with other genetic disorders, scientists are still struggling to untangle the various subtle genetic risk factors that contribute to the autistic phenotype. However, Geschwind’s investigations of large families with ASD have revealed at least one promising candidate: CNTNAP2, a gene involved in cortical patterning and the development of neural circuits associated with language processing.

It is extremely difficult to investigate the structure and function of individual circuits within the crowded and complex cellular network of the brain, but Jeff Lichtman of Harvard University described next-generation fluorescent tools for neuronal imaging in mice that bring this goal within reach, and have enabled his group to visualize the highly dynamic process by which synapses form early in brain development only to be pruned away during maturation as the neural circuitry becomes ‘streamlined’. Hollis Cline and her colleagues at The Scripps Research Institute have also made progress on this front, investigating how excitation of retinal neurons correlates with the growth and stabilization of the dendritic branches that contribute to synaptic junctions. She showed how these connections are formed and strengthened in the visual system, and described a molecular mechanism for circuit formation as facilitated by CPEB, a protein that stimulates the production of factors involved in synapse development.

Among the numerous hereditary disorders associated with ASD, FXS is thought to be the most prominent, and although only ~1% of ASD individuals have FXS, as many as 60% of those with FXS manifest symptoms on the ASD spectrum. Jason Dictenberg from Hunter College explored how abnormalities in the expression of genes involved in synaptic signaling and plasticity might represent a common thread that binds these two disorders.

Christopher Walsh of Harvard University concluded the first session of talks with a presentation that, like Geschwind’s, covered progress in identifying genetic risk factors for ASD. Walsh has been working with large families with high levels of intermarriage in collaboration with the multinational Homozygosity Mapping Collaborative for Autism, and their work has spotlighted several candidate genes that – like those identified by Dictenberg, Cline and Geschwind – may contribute prominently to normal brain circuit formation.
Recognizing and treating the symptoms

Autism Speaks Chief Science Officer Geraldine Dawson’s keynote talk kicked off the second session with an overview of diagnostic tools that have been developed for the early identification of ASD in children as young as 6 months of age. Dawson also described her ongoing work with Sally Rogers at the University of California at Davis on the Early Start Denver Model, a ‘holistic’ intervention strategy for simultaneously targeting the diverse developmental issues confronting young autistic children.

Mirella Dapretto of the University of California at Los Angeles has been investigating the abnormal lack of preferential attention for human faces and voices among children affected with ASD, and presented findings suggesting that the issues may lie in the brain centers that enable individuals to interpret the actions of others and to recognize such social stimuli as ‘rewarding’. Intriguingly, these individual brain areas seem to function normally, but lack the strong long-range wiring required for integrated brain activity—echoing themes from the morning’s talks that were also evident in Helen Tager-Flusberg’s presentation about ASD-related language deficits. Her team at Boston University has identified connectivity issues and abnormal growth patterns in key areas of the brain in language-impaired ASD subjects, and she showed data suggesting that these could represent a useful endophenotype for early diagnosis.

Early diagnosis should ideally be followed by prompt therapeutic action, and both Rogers and Hunter College researcher Michael Siller described their efforts at developing effective intervention strategies. Rogers presented data from early trials of the Early Start Denver Model, which favors a ‘naturalistic teaching’ approach that lets children take the lead in exploratory and interactive play while providing positive adult guidance and reinforcement, and thereby helps bolster development of brain circuits typically weakened in ASD. Siller has been particularly focused on language development, and his team recently completed a randomized controlled trial to test an intervention that guides parents in the use of ‘responsive language’ as a means for reinforcing joint attention in autistic children and thereby strengthening their capacity for verbal self-expression.

Finally, Marshalyn Yeargin-Allsopp of the Centers for Disease Control and Prevention put the importance of today’s presentations into context, with recent CDC data that show soaring prevalence of ASD among various demographic cohorts across the United States. In the past few decades, the number of children with ASD has gone from around 4 cases per 10,000 children to as high as 1 in 110; the reasons for this rise are presently unclear, and she concludes that fully exploring and addressing this problem will require a concerted effort between scientists, clinicians, and government and non-government agencies.

Autism Genetics: From Gene to Brain to Cognition and Behavior

Speaker:  
Daniel Geschwind, UCLA School of Medicine

Highlights:  
- Autism is more common than many other childhood diseases.  
- Autism disease status is on a continuum with normal cognition and behavior.  
- The disease’s mode of inheritance is not known, but researchers point to a polygenic model.  
- Studies with autism patients who have delayed language ability have lead to the identification of CNTNAP2, which is expressed in brain regions that are highly evolved in primates.
• The concept of developmental disconnection may provide a neurobiological framework to understand autism.

The Autisms

Autism has been defined as a highly heritable, neurodevelopmental disorder characterized by deficits in three areas: communication and language, social interactions, and restrictive repetitive behavior—with an onset prior to three years of age.

The disorder affects males at a greater rate than females, at a 4:1 ratio. It affects at least 1 in 160 children, with some studies suggesting numbers as high as 1:110 children. These figures make autism more common than many other childhood diseases. Because autism does not affect overall life-expectancy, the disease also poses a significant public health risk as autistic children age and will need to be cared for as adults. Up to 25% of patients will also develop epilepsy and significant numbers have intellectual disabilities.

One of the major challenges is disentangling autism from intellectual disability and discovering how they are related. In addition, autistic behaviors are shared by some other genetic disorders, including fragile X syndrome and untreated phenylketonuria.

Ongoing research has shown, however, that like height, weight, and lipid and sugar levels, autism is not a unitary disorder. Instead, it exists on a continuum with normal cognition and physiological function, akin to metabolic syndrome or hypertension. [1] As a result, researchers often refer to the disease in the plural, as “the autisms” or call it autism spectrum disorder (ASD).

This shift in terminology underscores the fact that no single gene has been shown to definitely cause the disease. In fact, autism’s mode of inheritance has remained unknown, although it has a heritability of up to 90%. Researchers predict a polygenic model for the disease, with many genes and even common genetic variance playing a role [2]—with room left for contributing environmental factors. [3]

“Researchers predict a polygenic model for autism, with many genes and even common genetic variance playing a role”

Open Resource Aids Analysis

In response to the growing recognition of autism’s genetic heterogeneity and the role of common genetic polymorphisms, The Cure Autism Now foundation in collaboration with scientists including UCLA’s Daniel Geschwind started an open resource called Autism Genetic Resource Exchange (AGRE; www.agre.org). The website aids over 100 registered researchers from around the world by providing a one-stop-shop of data on autism patients.

AGRE contains pedigree information on nearly 1,200 families as well as genetic linkage scans and association studies; karyotyping and molecular cytogenetics; and clinical analysis and phenotype data, including medical histories; basic cognitive and language testing; and the results of physical and neurological examinations. This wealth of information has alleviated some of the challenges associated with connecting genotype to phenotype in autism.

Using AGRE and other data, Geschwind’s lab studies heritable, biologically-based intermediate phenotypes, called endophenotypes. They seek to identify small risk factors that might interact with each other and contribute to autism—although each risk factor accounts for no more than 10% of
autism cases. [4]

Language Delay and Genetic Variation

One such analysis conducted in Geschwind’s lab began with a linkage study. The research identified a locus on chromosome 7q that was co-inherited with language delay in families with autism. [5] Broadly defined, language delay measures the age of a child at their first spoken word, and is an often seen endophenotype in autistic children.

Genotyping and DNA sequencing conducted by Geschwind and colleagues uncovered a single nucleotide polymorphism in a gene called contactin associated protein-like 2 (CNTNAP2) that associated with language delay. [6] Several patients with intellectual disability or autism were subsequently shown to have chromosomal rearrangements that disrupted this gene, and Amish children with recessive symptomatic focal epilepsy had a mutation that completely abolished CNTNAP2 function. [7] These patients had evidence of severe cortical dysplasia on MRI. CNTNAP2 appears to be part of a molecular, language-related pathway downstream of FoxP2, a highly conserved protein that is crucial for language development.

Furthermore, variation in CNTNAP2 strongly associated with a condition called specific language impairment (SLI). [8] This highly heritable disease affects approximately 5% of children. They do not develop language skills normally despite having normal non-verbal intelligence, the opportunity to learn, and no other medical condition. Autistic children do poorly at one of the most heritable and quantifiable markers of SLI, non-word repetition.

CNTNAP2 in the Brain’s Language Centers

Gene expression profiling demonstrated that CNTNAP2 was expressed in highly evolved human brain regions such as the frontal lobe of the cortex. The gene is thought to have played a role in the evolution of this region as it is also expressed in this area in non-human primates—in mice and rat brains it is ubiquitous. CNTNAP2 expression in humans localizes to the anterior peri-sylvian cortex in the frontal and temporal lobes and the basal ganglia. [9]

Geschwind’s collaborator at UCLA, Susan Bookheimer, hypothesized that patients with CNTNAP2 variants would also have defects in implicit learning, given the role of the frontal striatal circuits in this process. The research prompted further studies into the gene’s role in neurobiological function and structure.

Due to a disconnection in the neural circuitry of the frontal lobe, CNTNAP2 risk allele carriers do not show the typical response to externally directed task attention. By using functional connectivity analysis, Ashley Scott, a graduate student in the UCLA Neurobehavioral Genetics Program in the labs of Mirella Dapretto and Susan Bookheimer, was able to show that CNTNAP2 risk carriers have stronger local and weaker long-range connectivity than normal individuals. [10] This connectivity disorder has been hypothesized to play a role in the pathogenesis of autism.

“By connecting a disruption in one gene to neurobiological and behavior deficits, Geschwind’s work has shown the convergence of genetics with cognitive neuroscience”

By connecting a disruption in one gene to neurobiological and behavior deficits, Geschwind’s work as well as that of other autism researchers has shown the convergence of genetics with cognitive
neuroscience. The work supports a paradigm for discovery in autism research: By focusing on just one gene, CNTNAP2, investigators have been able to create a broader understanding of autism spectrum disorders. This multi-stage analysis of genetic risk variants will be useful in providing the necessary evidence to begin understanding how genes relate to higher cognition and health and disease in autism patients.

**Connectomics in the Developing Nervous System**

**Speaker:**
Jeff Lichtman, Harvard University

**Highlights:**
- Behavior results from environmental influences that subtly alter neuronal structure and connections during development.
- The pattern of connections between nerve cells is crucial to normal brain function.
- Connectomics seeks to map out the complete wiring diagram of the nervous system in much the same way that geneticists have mapped the genome.
- Colored fluorescent proteins can be used to track neuronal progress and retraction.
- Neuronal wiring diagrams are like fingerprints—no two are alike.
- Connectomics research may allow researchers to compare the brain circuits of autistic patients to those in normal individuals and gain a further understanding of the causes of the disease.

**Wiring Diagrams of the Brain**

“The pattern of connections between nerve cells is of fundamental importance to normal brain function, and disruptions in this pattern may underlie certain nervous system disorders”

Despite having over 99.5% genetic similarity, humans and human behavior are far from preprogrammed or predetermined. Behavior results from environmental influences that subtly alter neuronal structure and connections during development. Infants, for example, have fundamentally different nervous systems than young adults, who have different nervous systems than older adults.

The pattern of connections between nerve cells is of fundamental importance to normal brain function. Research has shown that disruptions in the pattern of connections may underlie certain nervous system disorders, including the autism spectrum disorders and intellectual impairment.

The importance of neuronal connections to brain function has been a well understood concept in physiology since the turn of the last century. Although they were nemeses of each other, Camillo Golgi and Santiago Ramón y Cajal together received the Nobel Prize in Physiology or Medicine in 1906 for their studies of the structure of the nervous system. Golgi developed a stain that densely labeled a fraction of brain nerve cells and allowed scientists including Cajal to draw neuronal circuits in the cerebral cortex and other regions of the brain.

These early scientists created a type of wiring diagram of the brain. It traced the flow of electrical impulses from a neuronal axon, into the cell body, out of the dendrites, across a synaptic junction, and finally back into a neighboring neuron’s axon. The tracings and their subsequent analyses were pivotal to develop an understanding of the nervous system; they gave insights into how information might flow
through neuronal circuits. A number of issues remained murky, however. Golgi's technique only stained a few neurons. Also, at that time scientists did not know about inhibitory neurons; they believed that all nerve cell conduction was excitatory.

**Connectomics Maps Neuronal Connections**

While this view of the nervous system remained for decades, a number of technologies have been developed to help disambiguate neuronal wiring. At the forefront is work being conducted by Harvard University’s Jeff Lichtman. His lab studies how neuronal connections develop in early postnatal life by mapping out the complete wiring diagram of the nervous system in much the same way that geneticists have mapped out the genome.

Lichtman’s connectomics project, a branch of biotechnology, applies the techniques of computer-assisted image acquisition and analysis to the structural mapping of sets of neural circuits and to the nervous system as a whole. He compares the work to the fields of proteomics or genomics, which seek holistic knowledge of the way in which proteins and genes function in organisms. According to Lichtman, connectomics might be used in animal models of neurological diseases, such as the autism spectrum disorders. A comparison of neuronal connections in sick animals versus their healthy genetic siblings, for example, could lead to insights into disease development and progression.

Lichtman’s research has already shown the ways in which the nervous systems of baby mice are more complicated than adult animals. Studies of neuromuscular junctions, the sites at which nerves from the spinal cord innervate muscle fibers, demonstrated that in early postnatal life multiple neurons contact each junction. [1] Over the course of a few weeks, in the case of mice, and a few months, in humans, a trimming occurs and each neuromuscular junctions ends up innervated by only one neuron—there is no neuronal death, just retraction and synapse loss. As a result, motor units in the muscle fibers also become physically smaller. Once the animal has developed, this rearrangement is stable for the rest of its life. [2]

Further research has shown that the wiring changes—neuronal retraction and connection loss—identified by Lichtman’s group occur throughout the central nervous system, not just in the periphery, as developing animals grow and individuate.

Research on the development of neuromuscular junctions relied on the use of fluorescent proteins and confocal microscopy, which have become major tools of connectomics research. In contrast to Golgi’s monochromatic stain, Lichtman expressed differently colored fluorescent proteins in neurons and tracked their progress and retraction during neuromuscular junction development in mice in vivo and created time-lapse imagery.

**Fluorescent Neurons Aid Mapping**

After discovering neuronal retraction in neuromuscular junction development, Lichtman and others set out to identify the rules by which this reorganization occurs. They turned again to transgenic animals, called Brainbow mice, in which individual neurons express spectral variants of colored fluorescent proteins inside neurons. By randomly combining just three fluorescent proteins—red, green, and blue,
which correspond to humans’ trichromatic vision—each neuron in these animals expressed a different color. Scientists can disambiguate the wiring of the central nervous system by tracing a color, even over long distances. As an added benefit, the resultant images look more like impressionist paintings than physiological diagrams. [3]

Lichtman discovered that a dominant nerve cell, one that occupies more than 50% of a junction, might not “win-out” over its lesser neighbor. Once a neuron “won,” however, it would always win in whatever other junctions it was competing for and would emerge as a dominant neuron and take over the remaining synaptic input. Thus, the remaining axon was not randomly chosen; a “yellow” neuron that beat out a “blue” neuron at one site, was likely to beat the blue won out in every other site. [4] Furthermore, neurons maintained strong connections and exchanged information with only a small handful of other neurons. [5]

**Axonal Branches and Fingerprints: No Two are Alike**

Research in Lichtman’s lab also demonstrated the highly individual nature of axonal connections. His group mapped the connectome of the interscutularis muscle in mice. This tiny bundle of fibers allows mice to wiggle their ears, but its 15 axons required 100 gigabytes of data. After studying connections to the right and left ears in genetically identical animals, the researchers found that like fingerprints, no two patterns were the same. And, each pattern was unique in substantial ways: Axonal arbor shapes were different; axon branching patterns were different down to the smallest axon; and each had different numbers of branches and connections. [6]

The branching patterns themselves were suboptimal. They would often begin in one direction and loop back around to innervate a neighboring neuron—evidence, Lichtman says, that they were built “on-the-fly” rather than genetically preprogrammed. He believes that the patterning of synapse elimination “unfetters the mammalian nervous system from the tyranny of the genes.”

In the end, each animal or individual ends up with a nervous system that is very different from its neighbors. In a large part, these differences exist because of environmental influences. Information both by and about the world becomes ingrained in our brains—a development primarily seen in higher animals such as mammals and humans. Ultimately, connectomics research may allow researchers to compare the brain circuits of autistic patients to those in normal individuals and gain a further understanding of the causes of the disease.

*Note: Dr. Lichtman has not reviewed the content of this article for its accuracy.*

**Building Brain Circuits**

**Speaker:**
Hollis Cline, The Scripps Research Institute

**Highlights:**
- Brain circuits form through an iterative process.
- The organization of the visual cortex changes dramatically over time.
- Visual experience modifies axonal projections and the dendritic arbor.
- An mRNA binding protein coordinates neuronal development.
Mapping Sensory Systems

Since at least the early 16th century, when Leonardo DaVinci produced an anatomical sketch of the eye and head, scientists have been trying to map sensory systems and their connections to the central nervous system. A few centuries later, a visual system connectivity map was produced by assembling available published information. [1] This connectivity map displayed how information entered through retinal ganglion cells, transmitted information into the central nervous system, and then interacted with circuits in the brain's motor cortex.

While this map was a useful tool, later studies on the development of sensory systems demonstrated that brain circuits formed through an iterative process, in which feedback from developing synaptic connections governed subsequent events in circuit development and function.

Questions remained however, including how such a complex matrix of synaptic connectivity developed during the formation of the central nervous system. Also unknown was how sensory or visual experience shaped the development and plasticity of this connectivity. Such information could help scientists better understand the interplay of environment and neuronal organization, and how this interplay contributed to diseases like autism.

Organizing Inputs

Some of the central work in the effort to understand connections in the visual system was done by Simon LeVay, David Hubel, and Torsten Wiesel. The latter two won the Nobel Prize in Physiology or Medicine in 1981 for their discoveries. The scientists used anatomical techniques to identify portions of the brain responsible for visual processing from the left or right eye. They discovered that the visual cortex equally processed information from both eyes—there was no favoritism.

However, LeVay, Hubel, and Wiesel found that the visual cortex changed dramatically over time; [2] the organization of an adult animal's visual cortex was vastly different from a young animal's cortex. In cats, for example, the equal distribution of information from each eye developed gradually over the first few months. During this time, the animal received visual experience, which scientists hypothesized, created this organization of information.

When LeVay, Hubel, and Wiesel blocked visual input through one eye in young primates and kept the other eye open, they found that the open eye captured the greater amount of cortical space. The blocked eye lost this space in the brain. [3] The work showed how critical sensory experience was during the developmental period: the environment could permanently shape connections within the brain.

Later research on optic neurons sought to discover the mechanisms by which this cortical organization occurred. Were connections from individual neurons also altered by visual experience? Indeed, investigators were able to show that axons that conveyed information from a closed eye were physically smaller than those from an open eye. Every single nerve in the visual pathway could be affected by the environmental experience it received.

“Sensory experience is critical during the brain's developmental period; the environment permanently shapes connections within the brain”
Dynamic Dendrites (and Axons)

Hollis Cline of the Scripps Research Institute investigated how these changes occurred during brain development. Researchers in her lab conducted in vivo imaging experiments in frog tadpoles, which are conveniently transparent. They expressed fluorescent colored proteins in single cells in tadpoles as the animals developed and the nerves from the eyes formed connections to the optic tectum, which is the structure that leads to the formation of the vertebrate midbrain. Retinal axons, it turned out, were dynamic. Visual experience modified axonal projections, not just the overall physical size of the neurons.

By labeling neurons and synaptic connections, Cline was also able to study how the structure of the dendritic arbor developed. This part of the neuron receives information from the eye, processes it, and sends the information to the neuron’s axon, which eventually carries the signal to the spinal cord to control visually guided behaviors.

Even in short timeframes of less than an hour, Cline’s group witnessed a dramatic amount of dynamic rearrangement with alterations to nearly every branch within an arbor. Over longer intervals, eight hours or more, the arbor became much more elaborate—virtually every branch was added or retracted.

This research produced a comprehensive view of the mechanism of dendritic arbor development. The arbor began small, added new branches, and then stabilized only a minority of branches—the majority were retracted. The arbor continued this process iteratively until the animal was fully developed. Cline’s work dovetailed nicely with the Synaptotrophic Hypothesis, which states that synaptic connections between developing neurons control the exploratory behavior of developing neurons, the development of neuronal arbors, and consequently the establishment of neuronal circuits.

Cline then investigated how visual stimulation contributed to this dynamic growth process in the dendritic arbor. Researchers in her lab collected an image of a neuron in a tadpole, then put the animal in a dark chamber for a few hours, re-imaged the neuron, then provided the animal with a simulated motion stimulus for a few hours, and collected a final image. Visual stimulation, they found, spurred the neuron’s dendritic arbor development.

Electrophysiological recordings from these neurons demonstrated that not only was the dendritic arbor more elaborate, it also had modified synaptic connectivity with axons coming in from the retina. Pre-existing synapses became stronger and added more neurotransmitter receptors, and new synapses also formed. This research further confirmed the validity of the Synaptotrophic Hypothesis.

A Master Regulator of Neuronal Development

Several recent studies conducted by Cline’s lab applied molecular genetic, imaging, and electrophysiological methods to address the formation of entire functional brain circuits. Visual stimulation, they found, had a broad impact on circuit development: It increased gene expression, enhanced neuronal excitability, and modified the topographic map from one region of the brain to another. Her group began the search for an activity-dependent mechanism that could coordinate all of these diverse cellular and physiological events.

Cline recognized that many different classes of mRNA have a genetic tag at one end of the message

“Visual stimulation had a broad impact on neuronal circuit development: It increased gene expression, enhanced neuronal excitability, and modified the topographic map”
that allows them to be coordinately regulated at their translation. [5]. These molecules, a family of proteins called mRNA binding proteins, typically govern the translation of functionally-related sets of transcripts.

Cline’s lab focused on a highly conserved RNA-binding protein called CPEB or cytoplasmic polyadenylation element binding protein. Previous work demonstrated that CPEB was activated after synaptic stimulation. Cline created a dominant negative version of the protein and expressed it in tadpoles to see if CPEB was important in the development of the visual circuit. [6] The mutant proteins decreased the neuronal growth rate and greatly diminished dendritic branch length. The nerve cells were not growing, nor were they forming connections within the visual circuit.

Further research demonstrated the crucial nature of CPEB. The protein was required for at least dendritic arbor development; experience-dependent structural plasticity, which includes the capacity to learn and change in response to environmental changes; synapse development; and the integration of neurons into a functional circuit. CPEB also played a role in a disease related to autism, fragile X syndrome. One of the genetic cargos translated after CPEB activation is FMRP, the fragile X mental retardation protein.

**Imaging Synaptic Connectivity in Mouse Models of Autism**

**Speaker:**
**Jason Dictenberg, Hunter College, CUNY**

**Highlights:**
- Synapses are important for healthy brain function.
- Fragile X syndrome is cause by a trinucleotide genetic repeat on the X chromosome.
- Proteins involved in producing or maintaining synaptic connections are implicated in autism and fragile X syndrome.
- These altered synaptic proteins lead to altered neuronal plasticity and homeostasis.

**Synapses’ Connections to Disease**

In the early stages of development, nerve cells of the central nervous system come together and form billions of connections or synapses. While this process is dynamic and just a fraction of these connections persist into adulthood, the retention of important synapses for brain function involves the fine-tuned expression of genes at precise moments. Any cellular or physiological errors that disrupts the proper “wiring” of the brain can cause diseases such as autism and related disorders such as fragile X syndrome.

“Fragile X syndrome is the most common single gene cause of autism”

Fragile X syndrome, for example, is the leading cause of inherited intellectual disability and mental retardation in humans. It is also the most common single gene cause of autism with a prevalence of about 5%. A large fraction of fragile X patients have autism or are suspected to have the disease—up to 60%.

**RNA-Binding Protein Causes Fragile X**

Scientists are actively studying the connections between fragile X syndrome and autism. Their work has focused on genes involved in synapse formation and stability. Nearly two decades ago,
investigators identified a trinucleotide genetic repeat on the X chromosome that at high enough levels silenced the expression of an mRNA-binding protein. This gene, which they eventually called FMR1 for fragile X mental retardation-1, acts as a master regulator and governs the translation of a large number of RNA messages. Some of these messages direct the formation of proteins involved in synapse formation.

FMR1 is highly heritable. It passes from carrier parents with silent pre-mutations who have a few numbers of the CGG genetic repeat to their children in whom the repeat has expanded and who subsequently have the syndrome. Other disorders related to this repeat expansion include premature ovarian failure and fragile X-associated tremor/ataxia syndrome, a late onset neurodegenerative disorder.

FMR1 regulates the expression of a large number of proteins, some of which are thought to play a role in the development of autism spectrum disorders. A difference in expression of even a few of these genes could account for the large fraction of fragile X patients who are suspected of having autism. Proteins such as neuroligin, a trans-synaptic cell adhesion molecule that is important for synapse function and connectivity, may be altered in fragile X syndrome. Neuroligin is thought to be altered in autism as well and is expressed during early post-natal development at the synapse; it directly influences the connectivity of the brain.

**Studying Synapses in Fragile X Mice**

Using a mouse model for the disease, Hunter College’s Jason Dictenбер found that the characteristics of fragile X mice share many similarities with the human disorder: Altered learning, memory, and behavior; a greater susceptibility to seizures; and a preponderance of long, thin dendritic spines on Golgi stain. These spines, small protrusions from the dendrite that receive axonal input, are immature in fragile X patients. Work is currently being done on therapeutics to alter gene expression in dendritic spines to cause them to mature, and hence treat the disease.

Dictenбер sought to examine if the defects in dendritic spines altered homeostasis of neuronal excitability or plasticity in the fragile X mouse model. Furthermore, did changes in synaptic plasticity underlie changes in neuronal structure and function?

He first demonstrated that RNA transport was deficient in fragile X cells, and that this transport defect played a role in the syndrome. In the absence of FMRP, several mRNA targets were diminished in the dendrites of live hippocampal neurons in response to glutamatergic or excitatory signaling. [1]

**Altered Structural Proteins Lead to Defective Synapses**

Other groups’ research into FMRP’s mRNA targets identified a major post-synaptic scaffold protein called PSD-95. [2] Dictenбер found that altered expression of PSD-95 changed the ratio of excitatory and inhibitory synapses, which likely led to changes in synapse scaling—a form of homeostatic plasticity that controls the normal basal state of neurons. Thus, defects in scaling could contribute to altered neuronal plasticity.

In addition, previous research demonstrated that PSD-95 interacted with neuroligin. [3] Dictenбер investigated how altered PSD-95 expression in fragile x mice lead to an altered distribution of the trans-synaptic cell adhesion molecule.
His lab visualized gene expression at the synapses of cultured neurons, including well-known markers of synapses: Synapsin, MAP2, and actin. The researchers found that when they stimulated wild-type neurons, the cells increased their expression of PSD-95 at the synapse. Fragile X neurons, however, did not. Neuroligin expression was also decreased at the synapse in affected neurons, which subsequently produced a deficiency in the ability of neurons to form synapses. Specifically, the problem involved excitatory synapses, whose numbers are predictably reduced in fragile X syndrome.

Dictenberg also conducted live cell imaging of synaptogenesis in real-time using fluorescently tagged proteins to track protein movement. Dendritic branches, he observed, were very dynamic. The movement of proteins in the synapse correlated with structural changes during development.

In fragile X neurons, the protein dynamics were also altered in response to activity-dependent signaling. Synaptic mRNA targets of FMRP, including PSD-95 and neuroligin, were reduced in their stimulus-induced localization to dendrites in fragile X mice. The total numbers of excitatory synapses were also reduced, which affected neuronal structure. [4]

Dictenberg’s research demonstrates how a disruption in the genetic program that regulates the formation and maturation of synapses underlies fragile X syndrome. [5] The word also produces insights into the broader function of synaptic proteins, which are implicated in autism spectrum disorders.

World-Wide and Genome-Wide Searches for Autism Genes

Speaker: Christopher Walsh, Harvard University

Highlights:
- The causes for nearly 70% of genetic abnormalities that affect the brain remain unknown.
- Genetic research from across the world can help illuminate diseases locally.
- Studying intra-familial marriages has given clues to autism genetics.
- Errors in non-coding regions of suspected autism genes may explain why the disorder has a spectrum of phenotypes.

Developmental Disorders Affect the Brain

The total number of humans on the earth will soon hit seven billion people. An increasing global population may pose food availability, environmental, and land use issues. But for geneticists, each person represents a wellspring of information—particularly in the study of rare genetic mutations.

Harvard University’s Christopher Walsh leads a team of researchers and collaborators who use genetic information on patients from around that world to study human brain disorders. What they have learned about these conditions

“A disruption in the genetic program that regulates the formation and maturation of synapses underlies fragile X syndrome”

Walsh’s lab has identified several of the genes responsible for dramatic developmental disorders that affect the size and structure of the human brain.”
and their patterns of genetic inheritance have informed studies of autism spectrum disorders.

Some of the most dramatic developmental disorders affect the size and structure of the human brain—they make the brain too small, affect its folding pattern, or change its internal architecture. Walsh’s lab and others have identified several of the genes responsible for these abnormalities. However, the genetic causes for the vast majority (70%) of these disorders, which cause intellectual disabilities and seizures in patients, remain unknown.

**Global Research Acts Locally**

Part of the problem in studying brain malformations is the sheer diversity of the ways in which they can occur. The genetic heterogeneity of these conditions spans a list of Mendelian traits: Inherited mutations can be dominant, X-linked, or recessive. Most dominant mutations and several X-linked disorders emerge spontaneously. Rare recessive genetic mutations are ancient, with many tracing back hundreds of thousands of years. They mimic patterns of human migration and can be found across the globe, which complicates work for genetics and has spurred collaborations like the ones that Walsh is engaged in.

For example, his approach has led to the further description of a rare disorder called microcephaly with seizures (MCSZ). His group studied two children from the same family, each of whom had a mildly small head (microcephaly), developmental delay, and mild but treatable seizures. Although the patients were of mixed European-American descent and they were not the product of a consanguineous or intra-familial marriage, their condition resembled that of patients in the Middle East who were of Palestinian, Saudi, or Turkish descent—populations with high rates of consanguinity. [1]

Consanguineous marriages turn out to be very useful in the hands of geneticists. The marriages allow scientists to recognize recessive disorders, create pedigree mappings, and trace the origins of mutations. By studying families with MCSZ disorders, Walsh’s group and others discovered a silent mutation in chromosome 19 in an ancestor of Middle Eastern patients. In these individuals, this mutation was silently transmitted to the grandparents and to the parents, who each had single copies of the mutation. These alleles united in affected children, who were now homozygous for the mutant gene.

The common founder mutation that affected the Middle Eastern families was in a gene called PNKP. This gene encodes for a protein involved in DNA repair, and cells from affected individuals had strand break repair deficiencies. [2]

After examining this gene in the children of European-American descent, Walsh’s lab found that they had a milder, previously unreported error. While the mutation in the Middle Eastern families knocked-out the function of the PNKP protein, in the American family the mutation affected the mRNA splicing of the protein’s transcript. This change led to semi-functional PNKP proteins, and hence a milder form of the MCSZ disease.

**Studying Consanguineous Families for Clues to Autism**

Using similar methodology, Walsh studies the link between developmental brain disorders and autism. Between 50-70% of autistic children have intellectual disabilities that most likely come from inherited genetic disorders. Researchers believe that there are many reasons to think that autistic forms of intellectual disability follow similar genetic rules. Like these disorders, autism is itself highly heritable, nearly as heritable as eye-color.
One of the problems of identifying autism-related genes is the underlying genetic heterogeneity of the disorder. Most identified genetic causes account for no more than 10% of autism cases. Further complicating matters is the low penetrance of many of the suspected genes, which allows for any number of environmental factors to play mitigating roles.

In response to these challenges, five years ago Walsh and other researchers formed the Homozygosity Mapping Collaborative for Autism. Clinicians and geneticists in the U.S., Turkey, Kuwait, Saudi Arabia, and Pakistan study consanguineous families with autistic individuals. They have already mapped pedigrees for more than 200 families. [3]

These autistic patients, like the greater autistic population, have a variety of different disorders on the spectrum of the disease. The genes implicated in virtually every family had a distinct chromosomal linkage as well, reinforcing the genetic heterogeneity of autism.

Nevertheless, Walsh’s lab identified large copy number variants in a section of chromosome 22. Genetic errors in this part of the chromosome have been shown to cause intellectual disabilities. The five largest homozygous recessive deletions in this region implicated six genes, although none disable the associated proteins.

These candidate autism genes included proteins of unknown function, ion transporters and channels, molecules essential for axon growth, and a transcription activator. Four of the six affected genes were expressed in the hippocampus—the brain’s center for learning and memory. Other research has implicated hippocampal plasticity defects in autism.

Crucially, the genes identified by Walsh’s group were regulated by neuronal activity. [4] Synaptic firing governs both local protein translation at the synapse as well as a larger program of RNA transcription, which reinforces some neuronal connections and weakens others.

Microarray analysis allowed the scientists to focus on a copy number variant deletion near RNF8, which encodes for a transcriptional co-regulator. Further analysis demonstrated that the deletion near RNF8 removed a CREB binding site upstream of the protein. CREB is a transcription factor, without which the RNF8 protein cannot be transcribed from DNA. Thus, Walsh’s and others research demonstrated that some autism mutations may affect “switches” that control gene expression, rather than just the products of genes. These defects may cause genes to not be expressed at all, or at the wrong place or time.

Walsh’s data suggests that genetic autism mutations run a spectrum from disabling null mutations to milder mutations that may disrupt neuronal function only partially. The research illuminates the reason why autism is phenotypically a spectrum of disorders and not a singular one.

New Directions in Early Detection and Intervention in Autism

Speaker:
Geraldine Dawson, Autism Speaks
Highlights:
- More effective and reliable tools are needed to identify signs of autism spectrum disorders (ASD) as early in child development as possible.
- Infant siblings of children with autism show early changes in perceptual and electrophysiological activity, although the predictive value of these changes remains unclear.
- Early interventions that integrate principles of applied behavior analysis with developmental intervention approaches are being used with toddlers with autism below 30 months of age.
- Initial data suggest that the Early Start Denver Model offers an effective early intervention that can help mitigate a variety of mental, social and cognitive deficits.

Acting early

Keynote speaker Geraldine Dawson, Chief Science Officer of the research and advocacy organization Autism Speaks, led into the day’s second session of talks with an overview of the state of tools for early diagnosis of ASD.

Dawson cited a recent study describing the general failure of the healthcare system to fully address the needs of children with autism. [1] and the resulting burdens faced by the parents of these children, which include considerable financial expense and a significant time investment for additional childcare. The American Academy of Pediatrics has acknowledged the importance of accelerating the identification and treatment of ASD, and in 2007 issued a recommendation that pediatricians administer screening to all children at 18 and 24 months of age and provide referral services where necessary.

Fortunately, several early childhood screening options are now available, including questionnaire-based tools such as the First Year Inventory and Modified Checklist for Autism in Toddlers, which are designed for children aged 12 and 18 months, respectively. For still earlier screening for signs of autism, Canadian researchers Susan Bryson and Lonnie Zwaigenbaum have developed the Autism Observation Scale for Infants, which can be applied at 6 months of age.

“Efforts are underway to shift assessment to even earlier in child development”

Nevertheless, efforts are underway to shift assessment to even earlier in child development. Citing this morning’s discussions of the strong heritable component of ASD, Dawson pointed out that siblings of an autistic child are generally at greater risk for positive diagnosis than the general population, with odds jumping from around 1:110 to as high as 1:20. Accordingly, much work is now focused on prospective studies of these ‘high-risk infants’, with researchers attempting to recognize the earliest detectable signs of impairment. “This has allowed the field for the first time to watch the unfolding of autism as it develops,” she said.

Research from Dawson, Zwaigenbaum and others has shown that many infants who will ultimately develop ASD appear largely normal up until 6 months, at which point deficits in attention and selective engagement with human voices and faces begin to emerge. These problems with ‘social orienting’ generally continue to grow in severity until the age of 1 year, when the social and communicative characteristics of ASD tend to become readily apparent—although she also notes that for between a quarter and a third of affected children, initial onset of symptoms might be delayed until the first or second year of age.

Recognizing the signs

Dawson proceeded to describe recent studies that have applied innovative experimental methods to
characterize the bases for these ASD-associated deficits. Much of this work has focused on visual perception, such as a 2007 study from the University of California at San Diego, which found that high-risk infants showed reduced ability to distinguish lightness and darkness—potentially impacting their capacity to recognize and respond to human faces. [2]

Dawson’s group has led the field in the use of electrophysiological methods for characterizing event-related potentials (ERPs), fluctuations in brain activity in response to a particular stimulus. In a typically developing child, the sight of a human face triggers a very specific activity profile in a brain structure called the fusiform gyrus, and ERP studies from a former student in her lab have shown that the amplitude of this face-triggered component is greatly reduced in high-risk infants, and that it lacks the asymmetric, right-hemisphere-centered characteristics observed in their low-risk counterparts. [3]

The question remains open as to whether such data offer effective markers for predicting future onset of ASD, or whether they instead represent endophenotypes—subtler genetic indicators of potential predisposition. The goal, says Dawson, is to attempt to recognize 'risk processes': the confluence of biological and environmental factors that directly contribute to ASD development. “If a baby is not paying attention to social information, then they’re not receiving the normal kind of stimulation to the systems that underlie language and social behavior,” she says, “and so there’s a secondary impact that has to do with the interaction between the child and the environment.” She adds that these processes also have their own biological consequences, impacting gene expression and other cellular functions as discussed in the morning sessions.

Dawson proposes that lessons acquired from developmental psychology might guide the development of more beneficial alternatives, citing ongoing work in the science of learning that explores the concept of children as ‘intuitive statisticians’ [4] “We know that children naturally learn through active exploration of their world,” says Dawson. “In fact, they’re little hypothesis testers.” Based on this model, the goal of interventions would be to promote this exploration – and thus active learning and social development – in the context of highly stimulating and emotionally positive adult-child interactions.

This thinking has informed Dawson’s development, in collaboration with Sally Rogers at the University of California at Davis, of the ‘Early Start Denver Model’ (ESDM), a comprehensive intervention program and curriculum for young children with ASD. ESDM interventions bring together interdisciplinary teams of experts – physicians, intervention therapists, psychologists, speech pathologists and occupational therapists – to target as many autism-related deficits as possible, including social development, language, motor skills and cognitive abilities. “We’re building a baby from the ground up in all senses of the word,” said Dawson.

She and Rogers recently published data from a randomized controlled trial of ESDM, performed at the University of Washington with children between 18 and 30 months of age. [5] The experimental group received 20 hours of therapist intervention and 5 hours of parental intervention over the course of two years, and showed statistically significant improvements in IQ, receptive language and adaptive behavior relative to children from the control group, who did not receive the ESDM intervention but were still provided with access to top-quality local care.

Based on these promising early findings, Rogers is now performing an expanded ESDM study at three sites with 108 children, which will attempt both to replicate these first-round findings but also to identify factors that can enhance or inhibit the gains made by this intervention. Dawson concludes that ESDM

“Lessons from developmental psychology might guide development of more beneficial intervention alternatives”
and other interventions that partner therapists and experts with parents for effective early treatment of at-risk children may hold great promise for improving outcomes in the future.

Benefits of comprehensive intervention
It is well-established that the application of early intervention can effectively mitigate many of the deficits associated with ASD, and strategies based on Applied Behavior Analysis and Discrete Trial Training can have a significant impact on IQ and language development. On the other hand, the benefits of such interventions for adaptive behavior development are less clear cut.

Social Motivation, Attention and Learning in the Autistic Brain

**Speaker:**
Mirella Dapretto, University of California at Los Angeles

**Highlights:**
- Although children with ASD exhibit reduced preference for human faces and voices, evidence suggests that these responses can be boosted when their attention is actively focused.
- The lack of attention to these stimuli in ASD may in part result from a failure of the brain to perceive such socially-relevant input as ‘rewarding’.
- Reduced activity in mirror neuron centers, which help the brain to interpret the actions and mental states of others, may also contribute to these social attention deficits.
- These various brain regions appear to function properly at the local level in ASD, but lack the long-range connectivity and coordination necessary for normal social cognition.

“Individuals with ASD exhibit diminished activity in key brain regions involved in interpretation of emotional information”

Early in brain development, infants will preferentially focus their attention on human faces and voices—particularly that of their mother. However, this is not the case for children with ASD. As Dawson pointed out in her talk, face response is diminished in autistic children. These children also display a preference for neutral, computerized voices over a warm, tonally-rich human voice. Accordingly, several studies have revealed that individuals with ASD exhibit diminished activity in the fusiform ‘face area’ and the amygdala, key brain regions involved in the interpretation of emotional information.

Mirella Dapretto’s group has been exploring these phenomena in the context of understanding how neurological defects associated with autism disrupt brain activities associated with ‘theory of mind’ functions. “These are those skills we have that allow us to interpret other people’s intentions and actions, and to interpret their emotional state,” she said.

Some evidence suggests that these areas can be selectively activated under some conditions; for instance, familiar faces trigger normative fusiform activity in individuals with autism relative to the faces of complete strangers. [1] This suggests that this activity is at least partly dependent upon attention, and Dapretto’s team has performed studies that investigate the extent to which increased attention can improve the capacity of ASD-affected children to perceive subtle social cues.

In one series of experiments, she presented children with cartoon scenarios of social interaction in which a character makes the same remark in either a ‘positive’ and sincere or a ‘negative’ and ironic manner, and then asked them to characterize the nature of the remark. When told to simply ‘pay
attention’, unaffected children showed healthy levels of activity in the ventromedial prefrontal cortex, a theory of mind area, while children with ASD did not. However, when these children were instructed to specifically pay attention to characters’ tone of voice or facial expressions, the affected children exhibited normal activity levels in this area. [2]

The rewards of attention

With this evidence that brain function is essentially intact in these areas, Dapretto shifted her focus to explore the lack of a bias for facial and vocal stimuli in ASD. “According to the social motivation hypothesis, this lack of an attentional preference for these stimuli may reflect that they’re not ‘rewarding’,” she said.

Her team has tested this model with a series of experiments in which children performed simple learning tasks with positive or negative feedback given ‘socially’ (with a picture of a smiling or frowning woman) or ‘monetarily’ (with pictures of gold coins or the same coins marked with red X’s). Unaffected children showed stronger activity in the reward circuitry, including the ventral striatum, in response to both types of reinforcement relative to children with ASD, but the differences were especially significant for social rewards.

Various neuroimaging studies have suggested that activity in the so-called ‘mirror neuron’ system, which enables the brain to map and interpret the actions and intentions of others, may play an important role in social and emotional interactions. Accordingly, a growing body of data suggests that this system is typically impaired in ASD. Dapretto and colleagues previously performed an fMRI study in which autistic children were asked to mimic facial expressions conveying various emotions; although the children performed well at the physical task, they showed markedly reduced activity in mirror neuron centers of the brain. [3] The extent of these activity deficits was closely correlated with the severity of ASD symptoms related to social interaction.

Her group is also examining the role of a reduced attentional bias for speech and ASD-associated language deficits through experiments that make use of an artificially constructed language. Infants as young as 6 months old have already acquired the capacity to recognize word boundaries in a continuous stream of speech, and this ability has been correlated with subsequent language development (e.g., child’s vocabulary size). Dapretto’s team exposed children to streams of speech consisting of trisyllabic words with or without prosodic cues (e.g., stressed syllables), as well as a random syllable stream. Like normal adults, typically developing children selectively exhibited increasing activity in language centers—indicative of implicit learning—in response to repeated sequences of structured ‘words’. In children with ASD, only minimal increases in activity were observed in these regions—and intriguingly, the extent of activation observed in a given child could be directly correlated with their level of language impairment.

In accordance with other ASD models presented today, Dapretto concludes that social and emotional impairments might result largely from a lack of long-range integration between otherwise-functioning brain regions and be exacerbated by issues of reduced attentional bias, and her group is continuing to explore the potential impact of such deficits on linguistic development as well.

Connecting the dots

According to Dapretto, there may be a link between mirror neuron activity and attentional bias, and ongoing experiments from her group are investigating this question. Preliminary data from her group
offer evidence that autistic children lack coordinated activity between the reward centers and mirror neuron centers, a correlation that is strongly apparent in unaffected children. “Children who have highest activity in the ventral striatum when they were getting the smiling faces as positive feedback were also the children who showed greater activity in those mirroring regions that we think are important for interpreting another’s facial expression and how that person might feel,” she said.

More than words

Communication is based on much more than the transmission and reception of strings of sounds, and a great deal of meaning in social interactions is conveyed through a combination of facial expression and voice characteristics.

Language in ASD: From Behavioral Phenotypes to Neurobiology and Genetics

Speaker: Helen Tager-Flusberg, Boston University

Highlights:
- Language-impaired autistic individuals exhibit deficits in vocabulary, syntax and semantics similar to those observed in subjects with specific language impairment.
- Relative to typically-developing or autistic individuals with intact language skills, language-impaired autistic subjects exhibit atypical growth and development of brain language centers.
- Differences in structural language ability are also correlated with the extent of physical connectivity between Broca’s and Wernicke’s areas.
- The language deficits associated with ASD appear to represent an endophenotype that can be measured in first-order relatives of autistic children.
- Preliminary data suggest that language processing abnormalities can initially be detected – and perhaps targeted – at 7 to 9 months of age.

Different levels of impairment

Autism isn’t a single disease, but a full spectrum of diverse symptoms that may be expressed heterogeneously in different affected individuals. One commonly observed component of this ‘broader autism phenotype’ are language deficits, which can likewise range from the diminished capacity to correctly interpret social cues and embedded meaning in spoken language to a complete lack of verbal expression.

Helen Tager-Flusberg presented work that explores the roots of this heterogeneity, comparing ASD-affected individuals whose structural language skills are essentially intact (autism language normal; ALN) and who fall at the Asperger syndrome end of the ASD spectrum with those suffering from more severe spoken language deficits (autism language impaired; ALI). In 2001, she conducted a study in which 89 ALN and ALI children performed an array of language tests, and noted impairments in vocabulary, syntax and semantics within the ALI group. Intriguingly, this profile closely resembled that previously described for subjects diagnosed with specific language impairment (SLI).

Individuals with SLI tend to perform poorly on two standardized language tests: nonsense word repetition and the obligatory marking of verb tense. Tager-Flusberg demonstrated that ALI children show similar impairments in nonsense word repetition trials, with performance declining significantly as
word length increases from two to three to four nonsense syllables. No such deficits were observed in ALN children. Likewise, ALI children were nearly twice as likely as ALN children to omit verb morphology changes required to indicate past or third-person tense in sentences. [2]

**Mapping linguistic problems**

Speech production is dependent on Broca’s area in the frontal lobe, and growth and development of this area is normally localized asymmetrically to the left hemisphere. A 2002 magnetic resonance imaging study by Martha Herbert and colleagues showed that the brains of autistic patients typically lack this asymmetry or show reversed asymmetry in this area, while also showing exaggerated left hemisphere asymmetry in the planum temporale, at the core of Wernicke’s area in the posterior temporal lobe. [3] Similar profiles of brain asymmetry have also been observed in SLI subjects. Tager-Flusberg’s group performed a subsequent study that subdivided autistic subjects into ALI and ALN groups, and found that the characteristics observed in Herbert’s study generally tended to be associated with ALI individual. [4]

Given the seemingly important contribution of long-range connectivity deficits to ASD, her group has subsequently applied diffusion tensor imaging (DTI) to examine alterations in the arcuate fasciculus, the primary tract that connects Broca’s and Wernicke’s areas. No clear differences emerged between control subjects and children with ASD, but when the latter group was subdivided based on linguistic ability, it became apparent that connectivity was significantly diminished in ALI individuals, and the extent of this connectivity was in turn correlated with performance on nonsense word repetition tests. Previous work with functional MRI (fMRI) has similarly suggested diminished connectivity, with reduced correlation of activation between the two primary language centers.

**The language endophenotype**

Given the elevated risk of ASD for siblings of an autistic child, it is reasonable to expect a quantifiable language phenotype among close relations within affected families. Tager-Flusberg found that this was indeed the case, with a clear dependence on the severity of the language deficits observed in the autistic child. [5] Siblings of ALI children show lower language and reading scores, and both parents and siblings of ASD children are more likely to exhibit symptoms of language disorders such as SLI or dyslexia. There is also some evidence for maternal transmission; notably, a study by Geschwind’s team has revealed a mutation in the language-associated CNTNAP2 gene that appears to be maternally transmitted, and Tager-Flusberg’s team is currently investigating this potential connection.

Importantly, the asymmetries observed in the language centers of ASD-affected children were also apparent in their siblings, with reduction in Broca’s area and enlargement in Wernicke’s. Collectively, these data support the hypothesis that this asymmetry and associated language impairments represent an endophenotype for ASD.

This raises the question of how early in infant development these changes become apparent, and Tager-Flusberg’s group has partnered with Charles Nelson’s team at Children’s Hospital in Boston to address this issue. She presented some initial data from trials in which infants were repeatedly
presented with a ‘da’ sound or, less frequently, a ‘ta’ (a ‘native contrast’) or Hindi ‘ta’ sound (a ‘non-native contrast’). Six-month-old infants can readily distinguish each sound, but by 12 months no longer discriminate between ‘da’ and ‘ta’. ERP measurements indicated a lack of asymmetry in both low- and high-risk 6-month-olds in response to the speech stimuli, with lateralization and increased left-hemisphere response becoming apparent in low-risk infants by 9 months. This asymmetry is largely absent in high-risk children at this same age.

ASD was not universally diagnosed in infants exhibiting this lack of asymmetry, even at the age of 18 months, supporting its classification as an autism endophenotype. Nevertheless, the data suggest a developmental window at 7–9 months of age when this developmental abnormality can potentially be detected and monitored as a risk sign for subsequent development of ASD. The characterization in the near future of genetic markers associated with this atypical language center development should also prove valuable in this regard.

Integrating Neuropsychology, Development, Behavior and Treatment for Early Autism

Speaker:
Sally Rogers, University of California at Davis, M.I.N.D. Institute

Highlights:
- Causal understanding of autism is shifting from a cognition-centered model to a more biological model, where symptoms are linked directly to abnormalities in brain structure and connectivity.
- Complex behaviors such as joint attention and imitation require long-range integration of multiple brain areas, which is typically impaired in ASD.
- Children build these circuits through exploration and interaction, and interventions that stimulate this behavior through ‘naturalistic teaching’ may most effectively address ASD diverse symptoms.
- Interventions based on the Early Start Denver Model (ESDM) incorporate positive social, emotional, linguistic and motor training in the context of child-directed play interactions.
- Initial data indicate that ESDM interventions can promote notable cognitive and linguistic gains in young children with ASD.

ASD is manifest differently in early childhood than it is in school-aged children, and Sally Rogers described how the various cognitive impairments observed in affected 2-to-5-year-olds can be loosely grouped in terms of ‘clusters’ of social, emotional, action-oriented, linguistic, perceptual and learning deficits.

The roots of the problem

Research from the early 1990s put forward a model for autism in which the origins of these symptoms were best understood in terms of how various cognitive functions are affected by biological and environmental factors. Accordingly, it might be expected that treatment strategies that selectively target the above-mentioned ‘problem areas’ should have a positive impact on any associated symptoms, and some subsequent research has provided support for this approach. For example, teaching imitation to children with ASD can lead to improvements in their capacity for symbolic play, joint attention, and receptive and expressive language. “There is something to this—that these difficulties in early childhood may not be individual problem areas,” said Rogers, “and we may not have to teach every single thing to a child.”
Nevertheless, an alternative model has emerged more recently, in which ASD-related dysfunctions are directly tied to abnormalities in the structure and connectedness of specific brain regions. Rogers cited Geschwind’s presentation from the morning session and the growing body of evidence that a limited capacity for long-range circuit formation—the sort of connections that are essential to the integration of brain functions—can have profound negative effects on higher-order skills. She also cited another type of circuit-building problem related to malfunctions in the ‘pruning’ activity described by Lichtman, with new studies suggesting that the autistic brain may also be characterized by excessive connectedness and disorganization at the local level. “Too many connections are a bad thing, not a good thing,” she said. “We need a cleaner system.”

**Repairing the circuitry**

She illustrated the importance of efficient circuit building with the example of imitation behavior, which relies on long-range signal relays that begin at the visual system, transit through multiple mirror neuron centers, and terminate in the motor system. Accordingly, this is one of the behaviors typically impaired in children with an ASD, and studies have shown that autistic children engaged in an imitation task exhibit brain activity levels that are both reduced and more highly localized relative to their unaffected peers, even among high-functioning children.

“Babies sculpt their own brains through their own experiences,’ said Rogers”

On the other hand, Rogers also emphasized the importance of early learning as a means for forging and strengthening these essential neural networks. “Babies sculpt their own brains through their own experiences,” she said. As such, a brain-oriented model of autism calls for the development of interventions that can effectively bolster circuits that are likely to be less robust in children affected by ASD. Discrete Trial Training, in which children engage in repeated exercises in a relatively distraction-free environment that improves attention and focus, is an example of such a strategy, and is rooted in the principles of Applied Behavior Analysis (ABA). Although time-consuming, this approach has consistently proven effective for targeting individual deficits related to ASD.

There are other alternatives, however, and interventions based on ‘naturalistic teaching’ have also shown strong promise. In this model, the child steers the general direction of the intervention through their choices of activity and attention focus, while the adult participates and inserts pre-planned teaching activities during the course of play. “The interaction looks more like what most of us would do with our own young children,” said Rogers.

**Getting an ‘Early Start’**

Here Rogers expanded on the work described earlier in the afternoon by Dawson, pertaining to initial data from interventions based on their Early Start Denver Model. She presented video depicting a child-adult exchange from a typical ESDM session, which incorporates a diverse array of stimuli and reinforcements, including verbal and social interaction, eye contact, motor activity and positive emotional feedback. “Many more connections are happening, and many more brain areas are being stimulated,” says Rogers. “With the affect and reward system, you can see it in [the child’s] face.”

ESDM integrates social and communicative elements from the Denver Model with the turn-taking, choice and reinforcement aspects of Pivotal Response Training (PRT), as well as the fundamental teaching principles of ABA. Rogers emphasized that the primary objective is to target the diverse
neuropsychological areas affected in early-stage ASD, using play interactions as a context for embedding developmentally meaningful training exercises. The hope in working with younger autistic children is that this training will prove more effective in fueling skill acquisition among these children and help them to catch up with their typically-developing peers. Above all, ESDM is anchored in the recognition that children learn actively, by doing and participating and interacting, and endeavors to integrate physical and mental learning in parallel.

She presented additional data from the randomized controlled trial from the University of Washington cited earlier by Dawson, [1] which compared metrics of child development among children who had received essentially equivalent amounts of weekly intervention time either by ESDM or from therapeutic resources in their community. They observed a marked improvement in IQ among the ESDM group; at the start of the trial, 70% of the children receiving ESDM met diagnostic criteria for intellectual disability, but after two years of intervention only 30% of children could still be thusly categorized. Considerable linguistic gains were also apparent—every child in the ESDM group was verbal by the end of the trial, and 88% of these four-year-olds had acquired spontaneous useful speech, with the capacity to form flexible phrases with nouns, verbs and objects. "We’re hoping to get to 90%," said Rogers.

She concluded that these findings illustrate the power of early experience and learning in the acquisition of physical, mental and cognitive skills, and that ESDM and similar interventions based on an ‘integrative’ approach should prove highly valuable in stimulating formation of essential neural networks in young autistic children.

A Parent-Mediated Intervention Increases Responsive Behaviors among Parents of Children with Autism

Speaker:
Michael Siller, Hunter College, CUNY

Highlights:
- The limited ability of young children with ASD to enter into a joint attention focus contributes to their deficits in language development.
- Joint attention can be facilitated through maternal synchronization, in which the mother uses ‘responsive language’ that relates to objects or activities that already have a child’s attention.
- A recently-developed intervention strategy has demonstrated the capacity to train parents in the use of responsive language and thereby enhance maternal synchronization.
- Future studies will examine the extent to which these enhancements further improve language development in young children with ASD.

Learning together

Early language learning is a collaborative process entailing the establishment of a joint attentional focus, in which a child and adult are both attending to the same object or task in parallel. Without entering such a state, it becomes exceedingly difficult for children to effectively pair words with their meanings.

Children aged between 15 and 19 months are typically able to recognize the focus of another person’s attention, and thereby
associate a label with that object. Before this age, according to Michael Siller, language learning depends on the parental establishment of this joint attention. “What you hear a lot is parents labeling objects to which the child is already attending or commenting on actions or intentions or goals that the child is pursuing,” he said.

Accordingly, the joint attention deficits observed in children with ASD can further undermine their language development, and longitudinal studies from Siller and UCLA collaborator Marian Sigman have shown that a child’s capacity for joint attention correlates directly with their subsequent acquisition of language skills. [1] Their study also suggested that autistic children benefit from high levels of maternal synchronization, where the mother routinely makes use of responsive language to talk about and describe the objects and actions to which a child is attending, reducing the severity of their language deficits.

In an effort to more directly characterize the benefits of this synchronization, Siller and colleagues have been developing an intervention strategy that helps to train parents in the effective use of responsive language with their children. He presented data from a recently completed randomized controlled trial, the objectives of which were to confirm that such an intervention could successfully be designed and whether this strategy would prove effective at stimulating language development in children with ASD.

They developed a program based on in-home training, with twelve sessions centering around both parent-child and interventionist-child interaction and incorporating conventional teaching, live modeling and coaching. Sessions are recorded on video and subsequently reviewed, enabling parents and interventionists to work together to identify successes and challenges encountered in each session.

Although no change was observed in the control group, the experimental group showed highly significant improvements in maternal synchronization at exit relative to intake, showing that the designed intervention is apparently successful at training parents in the effective use of responsive language.

However, further analysis of the initial data is required to confirm the extent of long-term language gains resulting from this enhanced synchronization, and Siller and colleagues are currently reviewing the one-year follow-up data. In parallel, his group is partnering with Connie Kasari’s team at UCLA to determine the potential benefits of applying the same intervention to still-younger children, by working with a cohort of high-risk toddlers aged between 18 and 30 months.

**Teaching parents how to talk**

Thirteen subjects participated in a pilot study to guide the development of the intervention, after which Siller’s team partnered with the California Regional Centers to recruit 70 families from throughout the Los Angeles area for the randomized controlled trial. All children in the trial were six years of age or younger, with a clinical diagnosis of ASD (confirmed based on both ADOS and ADI) and severe language impairment. 25 of these 70 children had no words at all, and only 14 had sufficient language development to complete an image-labeling exercise. The selected families accurately reflected the ethnic diversity of the local community based on recent Census data, with the majority of the children either Hispanic or white.

At the start of the trial, 36 families were randomly assigned to the experimental group and 34 were designated as controls; of these, 34 and 30 children respectively completed the study. The average
span of participation was 5.7 months, and Siller’s team recorded three ten-minute sessions of mother-child interaction for each family at intake and exit, both in the home and in the laboratory, analyzing each in order to quantify the degree of responsive language observed. They subsequently determined maternal synchronization based on the percentage of the mother’s communications that focused on their child’s attention and activities relative to the percentage of time that the child was engaged in play with provided toys.

Epidemiology and the Changing Paradigm of Autism Spectrum Disorders

Speaker: 
Marshelyn Yeargin-Allsopp, Centers for Disease Control and Prevention (CDC)

Highlights:
- Effective medical surveillance of trends in ASD prevalence has been confounded by numerous factors, including several major changes in clinical descriptions and diagnostic standards.
- However, available data strongly indicate that the last few decades have seen a dramatic increase in prevalence from around 4–5 cases per 10,000 to 6 cases per 1,000.
- The CDC Autism and Developmental Disabilities Monitoring (ADDM) Network uses multiple source record review to accurately quantify ASD prevalence at numerous sites nationwide.
- Data collected by ADDM between 2002 and 2006 reveals a considerable increase in ASD prevalence across all geographic and racial cohorts, and estimates a current prevalence of 1 in 110 children.
- Changes in record-keeping and diagnosis have contributed somewhat to this rise, but further research is still needed to identify other significant factors.

A shift in prevalence

Marshelyn Yeargin-Allsopp concluded the day’s talks with a review of ongoing efforts at CDC to quantify and determine contributing factors to changes in the prevalence of ASDs across the United States.

She began by outlining some of the factors that have confounded previous efforts to accurately measure incidence, the rate at which new cases of a given condition appear within a specified population. Most of these relate to the quality of the measurement criteria, including quantification of onset based on diagnosis at a relatively late age (averaging 4–6 years), failure to confirm diagnoses over the course of a study and the use of inaccurate or outdated diagnostic standards.

This last factor is also a crucial consideration in attempts to measure prevalence—the number of instances of a particular condition at a set point in time or during a particular period. Yeargin-Allsopp offered a brief overview of how these standards have changed from when Leo Kanner first described the basic autistic profile in 1956, through the reclassification in 1980 of this disorder as a developmental disability rather than a mental illness, up to the publication in the 1990s of the World Health Organization’s ICD-10 and the American Psychiatric Association’s DSM-IV, which both provide a considerably broadened description of ASDs that includes high-functioning variants such as Asperger syndrome.

Prevalence rates have increased in parallel with the implementation of these broader, more nuanced
diagnostic standards, and this has made it challenging to understand changes in prevalence over time. In recent years, this increase has become particularly dramatic, with reported prevalence rates soaring from 4–5 cases in 10,000 individuals prior to the 1990s to as high as 6 cases per 1,000 individuals. At the same time, available data regarding prevalence trends are limited and yield contradictory conclusions.

Following the paper trail

Yeargin-Allsopp’s team at CDC is making use of multiple source record review in their efforts to examine these trends; this entails the collection of data related to developmental disabilities in children from community, medical, educational and social service agencies, followed by analysis of these records in order to identify potential flags for ASD. The resulting evaluations are in turn examined by autism experts, who assist in the validation of individual cases.

Since the mid-1990s, CDC has been using this strategy to monitor ASD, along with other developmental disorders, among 8-year-olds in the five counties of metropolitan Atlanta; this age represents the peak prevalence for all various disorders being studied. Their data revealed a prevalence of 6.5 per 1,000 in the year 2000 [1]—considerably higher than other disorders such as cerebral palsy, hearing loss or visual impairment.

Congress subsequently expanded the funding for this program and the Autism and Developmental Disabilities Monitoring (ADDM) Network now encompasses multiple sites nationwide. As with the Atlanta program, surveillance at all locations incorporates records from multiple health and education sources, with all cases subject to review and confirmation by clinicians using DSM-IV criteria. “Our results have really become the standard for setting ASD prevalence estimates for the US,” said Yeargin-Allsopp.

2002 surveillance data from 14 different sites monitored nearly 10% of American children for ASD, [2] and the CDC noted an average prevalence of 6.6 per 1,000—a measurement that informs the 1:150 statistic that has been cited throughout the day. Based on these measurements, approximately 560,000 Americans under the age of 21 are affected by an ASD.

This past December, CDC published findings based on monitoring data collected from 11 sites in 2006, [3] which suggest a still-higher prevalence of 1 in 110 children: essentially a 57% increase since 2002. These data also reflect the commonly observed disparity between boys and girls—boys are more than four times as likely to be diagnosed with an ASD—and mirror estimates obtained from similar surveillance efforts in Asia and Europe. Most of these children had been documented with a developmental disorder by the age of 3, but the average age of ASD diagnosis was considerably later, at 4 and a half years of age. “We obviously still have a lot of work to do in terms of identifying children with these behaviors early,” said Yeargin-Allsopp.

Understanding the trends

“More aggressive investigation will be necessary to identify risk factors, accelerate diagnosis and effectively deliver treatment”

Beyond the generally observed increase in prevalence across sites between 2002 and 2006, there was an especially notable 91% increase in prevalence among Hispanic children, and Yeargin-Allsopp suggests that this may reflect focused efforts to address a history of under-diagnosis in this group.

In general, however, the basis for this dramatic increase in prevalence remains unclear, although a number of potentially
contributing factors are apparent. For example, the researchers had access to more records, and in many cases, these were of better quality. In addition, some sites improved their capacity for early diagnosis and for recognition of higher-functioning children with ASD who may lack clear cognitive deficits. None of these factors is adequate to fully explain these prevalence trends, however, and more aggressive investigation will clearly be necessary to identify risk factors, accelerate diagnosis, and effectively deliver treatment and support to ASD-affected children and their families.

Plans are now underway at CDC to expand their health surveillance activities to examine prevalence among both children under the age of 8 and adults, and to attempt to characterize the association of ASD with known comorbidities such as Fragile X Syndrome and attention-deficit hyperactivity disorder. Yeargin-Allsopp adds that her group also intends to examine prevalence in the developing world and among immigrant populations within the US, such as Somali families living in Minnesota. “The bottom line [is that] we need to continue working with government and non-government partners to take a comprehensive approach to ASD surveillance and research,” she said.

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Epidemiology and the Changing Paradigm of Autism Spectrum Disorders


Keynote Speakers

Daniel Geschwind, MD, PhD
UCLA School of Medicine

Daniel Geschwind is the Gordon and Virginia MacDonald Distinguished Professor of Neurology, Psychiatry and Human Genetics, and Director of the Neurogenetics Program and Center for Autism Research and Treatment at UCLA. He obtained an A.B. degree in Psychology and Chemistry at Dartmouth College; and his M.D. and Ph.D. degrees at Yale University School of Medicine. He completed his neurology residency at UCLA in 1995, where he has remained following training, joining the faculty in 1997. He also serves as the Co-Director of the UCLA Center for Neurobehavioral Genetics, within the Semel Institute. Dr. Geschwind has published more than 100 papers and review articles and serves on the editorial boards of the journals Neurobiology of Disease (Associate Editor); Biological Psychiatry (Deputy Editor); Neurogenetics; and Current Genomics, as well as on several review committees and scientific advisory boards, including the March of Dimes, the Cure Autism Now Foundation, the Faculty of 1000 Medicine, and the Society for Neuroscience’s Program Committee. He received the Derek Denny-Brown Neurological Scholar Award from the American Neurological Association in 2004. Dr. Geschwind's laboratory works broadly within the field of neurogenetics and over the last 5 years has focused these efforts increasingly on autism spectrum disorders. Overall, three primary areas of research in neurogenetics are encompassed -- autism and language; focal neurodegenerative syndromes; and the structural/molecular basis of human cognitive specializations. In each of these independent but overlapping domains, his laboratory has used genetics and what is now sometimes referred to as a functional genomic approach. He and his collaborators have engaged in a multi-pronged strategy, from studying normal human and animal model brain patterning, to diseases where language and social communication are disrupted (such as autism).
Geraldine Dawson, Ph.D.
Autism Speaks Foundation

Geraldine Dawson became Autism Speaks' first Chief Science Officer in January of 2008. In this role, Dawson serves as the scientific leader of Autism Speaks, working with the scientific community, stakeholders, and science staff to shape, expand, and communicate the foundation's scientific vision and strategy. Dawson is also Research Professor of Psychiatry at the University of North Carolina at Chapel Hill and Adjunct Professor in the Department of Psychiatry at Columbia University.

Prior to joining Autism Speaks, Dawson was Professor of Psychology and Psychiatry at the University of Washington (UW) and Founding Director of the UW Autism Center, which has been designated an NIH Center of Excellence since 1996. While at the University, Dawson led a multi-disciplinary autism research program focusing on genetics, neuroimaging, diagnosis, and treatment. Dawson's own research has been in the areas of early detection and treatment of autism, early patterns of brain dysfunction (electrophysiology), and more recently, development of endophenotypes for autism genetic studies. Dawson received continuous NIH funding for her research from 1980 until 2008 when she left UW to join Autism Speaks. Dawson's scientific achievements include discovering that autism symptoms could be recognized during infancy, defining the earliest manifestations of autism, pioneering the use of event-related brain potentials to study early brain dysfunction in autism, development of behavioral and electrophysiological endophenotypes in genetic studies of autism, and development and evaluation of the Early Start Denver Model, an intervention for infants and toddlers with autism. Dawson has published over 180 scientific articles and chapters and co-edited or authored a number of books about autism spectrum disorder and brain development, including Autism Spectrum Disorders; Human Behavior, Learning, and the Developing Brain; and A Parent's Guide to Asperger Syndrome and High-Functioning Autism. She has received over 50 grants supporting her research, including 17 research grants from NIH. From 2000-07, Dawson founded and directed University of Washington Autism Center's multi-disciplinary clinical services program, which is the largest of its kind in the northwestern United States. A strong advocate for families, Dawson has testified before the U.S. Senate on behalf of individuals with autism and played a key role on the Washington State Autism Task Force.

Dawson earned a Ph.D. in developmental and child clinical psychology from the University of Washington. After graduate school, she studied as a postdoctoral fellow at the Neuropsychiatric Institute at UCLA and, a year later, accepted a position as Assistant Professor at University of North Carolina in Chapel Hill. In 1985, she returned to the University of Washington as a faculty member, where she continued her research on autism and practiced as a clinical psychologist specializing in autism until she accepted her current position at Autism Speaks. She currently resides in North Carolina with her husband and daughter.

Speakers

Jeffrey Lichtman, MD, PhD
Harvard University

Jeff Lichtman has an AB from Bowdoin (1973), and an M.D. and Ph.D. from Washington University (1980) where he worked until 2004, most recently as Professor of Neurobiology. In 2004 he moved to Harvard where he is a Professor in the Department of Molecular and Cellular Biology. He is also a member of the newly established Center for Brain Science. Lichtman’s research interests revolve around the question of how mammalian brains accommodate information based on their early experiences. He has focused on the dramatic rewiring of neural connections that takes place in early
postnatal development. This work has required development of techniques to visualize the patterns of connections in the nervous system and how they are altered over time.

**Hollis T. Cline, PhD**  
The Scripps Research Institute

Hollis T. Cline, Ph.D., is a professor at the Scripps Research Institute in San Diego. She received a Ph.D. in Neurobiology from the University of California, Berkeley, in 1985. Using time-lapse imaging, electrophysiology, and molecular genetic techniques, Cline developed an experimental system to assess cellular and molecular mechanisms underlying plasticity in response to visual stimulation in living animals. She is using her Pioneer Award to launch a large-scale project to understand the architecture, development, and plasticity of brain circuits. Cline is a member of the Board of Scientific Counselors of the National Institute of Neurological Disorders and Stroke and was recently a Council member of the Society for Neuroscience.

**Jason Dictenberg, PhD**  
Hunter College, City University of New York

Jason Dictenberg, Ph.D. is an Assistant Professor of Biological Sciences at Hunter College and the Graduate Center, City University of New York. He received his BA from Brandeis University with Honors (1993) and a Ph.D. from the University of Massachusetts Medical School (2000). He completed a post-doctoral fellowship at Albert Einstein College of Medicine where his research demonstrated that the dynamics of mRNA transport to synapses were defective in the hippocampus of the Fragile X syndrome mouse. His research interests focus on the role of mRNA transport and translation within neuronal dendrites and at synapses, and the dysregulation of this process in diseases of cognitive function. His laboratory is studying how activity regulated expression of dendritic mRNAs influences synapse development and morphologic plasticity. Emphasis is placed on the visualization of single mRNA dynamics within dendrites of living neurons and the subsequent translation of these mRNAs in response to synaptic stimulation. These approaches are being developed using super-resolution quantitative digital microscopic techniques coupled with novel in vivo methods for spatial and temporal control of light-activated gene expression. Ultimately this research will highlight how dendritic mRNAs are regulated in the processes of synaptogenesis and long-term synaptic changes that underlie plasticity, and defects that give rise to alterations in learning and memory that result in neurological disease. Dr. Dictenberg is the recipient of grants from the NIH and NSF to study the role of mRNA transport and translation in synapse development.

**Christopher Walsh, MD, PhD**  
Harvard University

Christopher Walsh, MD, PhD, is widely regarded as the nation’s leading neurogeneticist. His research is illuminating the causes of devastating developmental disorders such as autism and providing insight into the normal growth and functioning of the human brain. Among his laboratory’s research interests are autism and microcephaly, a condition in which the brain fails to achieve normal growth, resulting in cognitive delay and other serious neurological problems. Some of the genes associated with microcephaly are also linked with an elevated risk of developing cancer and immune system disorders. Dr. Walsh’s laboratory has identified more than 500 families with different forms of developmental disability from around the world and has discovered more than a dozen novel disease genes associated with their disorders. Most recently, his lab identified half a-dozen genetic mutations associated with autism that suggest a new, promising approach to treatment. Identifying these genes vital to developing clinical DNA tests and prenatal screening methodologies, which make it possible for physicians to offer better genetic counseling for families. In addition to their gene-finding studies, Dr.
Walsh and colleagues carry out painstaking research to understand the basic biological functions of the genes they have identified, with the aim of applying this knowledge to develop new therapies. A Howard Hughes Medical Institute Investigator, Dr. Walsh has received many awards for his work, including the Research Award from the American Epilepsy Society, the Dreifuss Penny Award from the American Academy of Neurology, and the Derek Denny-Brown and Jacoby Awards from the American Neurological Association. Dr. Walsh received both his MD and PhD from the University of Chicago and completed his residency in Neurology at Massachusetts General Hospital.

Mirella Dapretto, PhD  
University of California, Los Angeles

Dr. Dapretto is presently appointed as Associate Professor in the UCLA Dept. of Psychiatry & Biobehavioral Sciences. She received a Ph.D. in Developmental Psychology from UCLA and later acquired expertise in functional magnetic resonance imaging (fMRI) as a postdoctoral fellow at the UCLA Ahmanson-Lovelace Brain Mapping Center. Using neuroimaging techniques and an interdisciplinary approach, Dr. Dapretto’s research examines the neural representation of language and social cognition in both the adult and typically-developing brain, as well as in developmental disorders such as autism. Dr. Dapretto has been the recipient of several awards, including an NIH grant to study the neural representation of language in typical development, and several grants (funded by Cure Autism Now, the National Alliance for Autism Research, and Autism Speaks) to study the neural basis of the socio-communicative impairments observed in autism spectrum disorders. Her work has been published in high-profile scientific journals such as Neuron, Brain, Nature Neuroscience, and Archives of General Psychiatry. Currently, Dr. Dapretto is the Principal Investigator of the imaging project within the NIH funded Autism Center of Excellence at UCLA.

Helen Tager-Flusberg, PhD  
Boston University

Dr. Tager-Flusberg is currently Professor in the Department of Psychology at Boston University, and in the Department of Anatomy & Neurobiology at Boston University School of Medicine. She received her doctorate in Experimental Psychology from Harvard University, and then held appointments at the University of Massachusetts and the Eunice Kennedy Shriver Center before going to Boston University in 2001. Her research, which is currently funded by grants from the NIH, Autism Speaks, and the Simons Foundation focuses on early neurobehavioral markers and developmental trajectories of infants at risk for autism or SLI; and neurocognitive profiles of language and social phenotypes in autism, Williams syndrome and other disorders. She has edited 4 books and written over 150 peer-reviewed papers and chapters, and is the Associate Editor for 3 journals. She has presented her research at universities, conferences and workshops to professional and community groups.

Sally Rogers, PhD  
University of California, Davis

Sally J. Rogers is a developmental psychologist and a Professor of Psychiatry at the M.I.N.D. Institute, University of California Davis. She is the principal investigator of several autism research projects, including one of the ten NIMH/NICHD funded Autism Centers of Excellence (ACE) network projects, involving a multi-site controlled trial of an infant-toddler treatment for autism, with her collaborators Cathy Lord at University of Michigan and Annette Estes at University of Washington. She is also the director of an interdisciplinary postdoctoral training grant for autism researchers. She is involved at the international level in major clinical and research activities involving autism, including membership in the executive board of the International Society for Autism Research, an editor of the journal Autism
Research, and a member of the Autism, PDD, and other Developmental Disorders workgroup for the DSM V.

She received her Ph.D. from Ohio State University, with a specialization in Mental Retardation and Developmental Disabilities. She has spent her career studying cognitive and social development in young children with disabilities. She has published over 150 papers, books, and chapters on topics including cognitive development in children with profound mental retardation, cognitive and social development of blind infants, symptoms of toddlers with Fragile X Syndrome, as well as numerous papers on clinical and developmental aspects of autism. She has been very interested in imitation problems in autism for many years and has made seminal contributions to this line of autism research, including a recent book. Her current research focuses in two areas: on developing effective interventions for infants and toddlers with autism that families and professionals can deliver, and on earliest identification of autism in infancy, which she carries out with her colleague, Sally Ozonoff. In addition to research, she is also a clinician, providing evaluation, treatment, and consultation to infants, children, and adults with autism and their families. The intervention model that she developed with Geri Dawson and other colleagues at University of Colorado Health Sciences Center, University of Washington, and University of California Davis – the Denver Model and the Early Start - is internationally known and the treatment manual and instrumentation for this approach has been recently published.

Michael Siller, PhD
Hunter College, City University of New York

Dr. Siller is an Assistant Professor in the Psychology Department at Hunter College of the City University of New York (CUNY). He attended graduate school at the University of California at Los Angeles, where he obtained both his M.A. (2001) and Ph.D. (2006) in Developmental Psychology. His doctoral work was acknowledged with the Millard Madsen Distinguished Dissertation Award. Dr. Siller also attended the Free University of Berlin in Germany where he gained an M.A. degree (Diplom Psychologe) with an emphasis in Clinical Psychology (1999). He has presented and published internationally on the development of social and communication skills in young children. Dr. Siller is particularly interested in how parent-child play interactions contribute to the social, emotional, and communication development of young children with autism spectrum disorders. Currently, he collaborates with Dr. Sally Rogers (M.I.N.D. Institute, UC Davis), co-directing the Autism Speaks Toddler Treatment Network.

The initial aim of Dr. Siller’s research was to develop a novel measure of parental communication that captures responsive parental behaviors, and also takes into account the unique challenges that parents of young children with autism face during interactions with their children. He first used this measure in a cross-sectional study comparing parental communication patterns across different diagnostic groups (Siller and Sigman, 2002). Contrary to previous findings, this research showed that mothers of children with autism were as responsive to their children’s focus of attention and ongoing activity as mothers of typically developing children or children with mixed developmental delays. In light of this finding, Dr. Siller conducted two prospective longitudinal studies to evaluate the link between individual differences in parental communication and children’s subsequent gains in communication skills (Siller and Sigman, 2002, 2008).

This research provided the first pair of studies to show that responsive parental behaviors reliably predict the long-term (16-year) language outcomes of children with autism. His recent research has progressed from naturalistic to experimental designs where subjects are randomly assigned to different treatment conditions. Dr. Siller initiated two intervention studies designed to provide an experimental test of the direction of effects linking responsive parental behaviors with the development of
communication skills in children with autism. The first randomized trial involved 70 pre-verbal children with autism between 2½ and 6½ years of age (Siller, Hutman and Sigman, 2007). Early results show that his experimental parent education program is efficacious for increasing responsive behaviors among parents of young children with autism. In addition, he is currently collaborating with Dr. Connie Kasari (Department of Education, UCLA) to evaluate whether the same parent education program can also be effective for promoting the communicative behaviors of toddlers (18 to 30 months) who are at “high risk” for Autism Spectrum Disorder.

Marshelyn Yeargin-Allsopp, MD, FAAP
Centers for Disease Control & Prevention

Marshelyn Yeargin-Allsopp, M.D. - Medical Epidemiologist; Chief, Developmental Disabilities Branch; National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention. Dr. Yeargin-Allsopp received her B.A. degree in Biology from Sweet Briar College and M.D. degree from Emory University. She completed an internship and residency in Pediatrics at Montefiore Hospital, Bronx, New York. She was on the faculty of the Albert Einstein College of Medicine and completed a fellowship in Developmental Pediatrics at the Rose F. Kennedy Center of Yeshiva University, the Albert Einstein College of Medicine. She is board-certified in Pediatrics and Neurodevelopmental Disabilities. Dr. Yeargin-Allsopp joined CDC in 1981 as an Epidemic Intelligence Service Officer and completed a Preventive Medicine Residency in 1984. Since coming to CDC, she has designed and implemented the first U.S. population-based study of developmental disabilities in school-age children in an urban area. It has served as the basis for a CDC population-based developmental disabilities surveillance system, the Autism and Developmental Disabilities Monitoring (ADDMD) network and a CDC epidemiologic research study, Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE). Dr. Yeargin-Allsopp is an Adjunct Assistant Professor of Pediatrics at the Emory University School of Medicine; she was one of the original members of the State of Georgia Interagency Coordinating Council for Early Intervention Services (for children from birth-2 years) and is the medical director of the Clayton County Early Intervention Program in metropolitan Atlanta. She is a past member of the Scientific Advisory Board and Scientific Affairs Committee for Autism Speaks and a past member of the Medical Advisory Board for the NIH-funded CPEA and STAART (Autism) Centers. She is a member of the Medical Advisory Board for Reaching for the Stars, a parent advocacy group for children with cerebral palsy and was previously a member of the Board of Directors for the Marcus Autism Center, a program in Atlanta that provides services to individuals with developmental disabilities. She is the Chair of the Interagency Coordinating Committee for the National Children’s Study, a large government-funded project to prospectively follow 100,000 children from before birth to early adulthood, to study a range of environmental and social risk factors and health and developmental outcomes. Dr. Yeargin-Allsopp was the CDC liaison to the American Academy of Pediatrics (AAP) Committee on Children with Disabilities from 1997 to 2004 and was a member of the AAP Autism Expert Panel until 2007. She was the 2006 recipient of the C. Anderson Aldrich Award of the AAP Section on Developmental and Behavioral Pediatrics and the 2008 recipient of the Arnold J. Capute award of the Council on Children with Disabilities of the AAP. Dr. Yeargin-Allsopp has presented internationally and published extensively on the epidemiology of developmental disabilities, including autism and cerebral palsy.

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