The National Alliance for Autism Research (NAAR) is the first organization in the country dedicated to funding and accelerating biomedical research to unravel the mysteries of autism and find a cure. Founded in 1994 by parents of children with autism concerned about the limited amount of funding available for autism research, NAAR was created in a spirit of optimism and excitement over the opportunities for accelerating the pace of autism research. This spirit continues to inspire and guide the organization today, enabled by recent advances in the neurosciences and other scientific fields.

Our Mission

The mission of NAAR is to fund, promote, and accelerate biomedical research and science-based approaches that seek to determine the causes, prevention, effective treatments and, ultimately, a cure for autism spectrum disorders. This mission includes providing grants to researchers for innovative pilot studies; mentor-based fellowships to recruit new investigators to focus on autism; and funding larger, collaborative research programs that have the potential to yield major scientific advances in autism research.
NAAR 2005 Research Awards

NAAR is proud to announce it committed a record $8.3 million to fund a variety of projects in autism research in 2005. This funding commitment includes research grants and fellowships in the United States, Canada, and Europe as well as expansion of the Autism Tissue Program, High Risk Baby Sibling Autism Research Project, and the Autism Genome Project.

The fellowships and pilot studies listed in this publication received $6.5 million in awards and represent a core element of NAAR’s research program. These programs focus on a wide range of disciplines including genetics, neuroscience, neuroimaging and neuropathology, animal models, environmental exposures, gene-environment interactions, diagnosis, early identification, and intervention.

The 2005 research awards constitute the largest single-year commitment to biomedical autism research that NAAR has made in its 11-year history. Including the 2005 research awards, NAAR has now committed $30.2 million to fund over 270 research projects, fellowships, and programs—more than any other non-governmental organization worldwide.

Mentor-Based Fellowships

NAAR’s Mentor-Based Fellowship Program provides the valuable resources to support and encourage the development of young scientists who benefit from the mentorship of prominent researchers. Both pre- and post-doctoral candidates have the opportunity to become experienced clinicians, launch independent research, assume teaching roles, and join departments around the world that presently have no representation in autism research.

Cause/Genetics

These studies focus on examining changes in gene expression in children with autism spectrum disorders.

Mentor: Claudia Bagni, Ph.D.
Fellow: Caroline Lacoux
University of Rome “Tor Vergata” Fondazione Santa Lucia, IRCCS, Rome

Molecular Studies of the ASD (Autistic Spectrum Disorder)

Summary: Fragile X Syndrome (FXS) is an X-linked disorder that causes a reduction in levels of the fragile x mental retardation protein (FMRP). There are a number of similarities in individuals with FXS and autism spectrum disorders, and approximately 25% of patients with the Fragile X Syndrome exhibit autistic-type behaviors. Therefore, the study of the FMRP target genes could offer important insights into the genetic basis of autism. Drs. Bagni and Lacoux plan on studying the genes that regulate this protein to better understand the molecular pathways that may also play a role in autism. Specifically, the Bagni lab will be targeting on an mRNA located in neurons that is linked to FMRP.

What this means to individuals with autism: These studies may help clarify the genetic influences in autism. Finding genes involved in autism susceptibility and learning how they contribute to disease development will provide information that could lead to more effective treatments and interventions.

Mentor: Janine LaSalle, Ph.D.
Fellow: Sailaja Peddada
University of California, Davis School of Medicine

Investigation of Novel MeCP2 Target Genes Regulating Neuronal Maturation in Autism-Spectrum Disorders

Summary: One approach to understand the genetics of autism is to characterize the genes and pathways responsible for syndromes with defined genetic basis with common features of autism, including seizures, stereotyped behavior, and social avoidance, thereby leading to discovery of potential clues to the more complex disorder of autism. Rett syndrome (RTT) is the only subtype of autism-spectrum disorders with a known genetic cause. This research will further investigate the gene identified in RTT, (MeCP2). The goal is to further characterize the effect of alterations in MeCP2 expression on the ID gene family of transcriptional regulators and to determine the functional relevance of these genes in the development of autism, Rett syndrome, and normal neuronal development.

What this means to individuals with autism: Rett’s Syndrome shows similar clinical characteristics of autism, especially in the early phases of the disease. A better understanding of the effects
of mutations of the MeCP2 protein will help scientists determine the cause of these behavioral similarities. These results are expected to increase the understanding of the molecular pathogenesis of autism spectrum disorder so genes that control behaviors similar to the two disorders can be uncovered.

Mentor: Samuel Pleasure, M.D., Ph.D.
Fellow: Jennifer Lynn Freese, Ph.D.
University of California, San Francisco
The Role of Frizzled9 in Hippocampal and Cortical Development

Summary: Williams Syndrome is a rare genetic condition resulting from a deletion of genetic material on chromosome #7. Because some symptoms of this disorder, including developmental delays and seizures, are similar to ASD, this suggests that the two disorders may share a similar cause. Dr. Pleasure’s lab has been studying one gene located on chromosome #7 called Frizzled9. Mice with mutations of this gene have profound visuospatial learning deficits, altered seizure threshold and a reduction in the number of cells in the hippocampus. Therefore, it is possible that Frizzled9 function is critical in Williams Syndrome and possibly ASD. Recent data indicates that genes in the same family as Frizzled9 may control neuronal shape, size, and connections between neurons in the developing and adult brain. Dr. Pleasure’s lab plans to examine the neuroanatomy and connectivity of the hippocampus and neocortex in Frizzled9 mutants. In addition, they will generate mouse mutants to allow the understanding of relative roles of Frizzled9 in neuronal function during development and in adulthood

What this means to individuals with autism: By examining genes that are associated with disorders that show behavioral similarities to autism, researchers can better determine the individual contribution of genetic influences in ASD. Using a conditional knockout model can allow scientists to study behavioral function when this gene is missing, and if the behaviors recovered when the gene is re-expressed during adulthood. This will provide insight into the genetic contribution of Frizzled9 in ASD to better explain the causes.

Mentor: John Rubenstein, M.D., Ph.D.
Fellow: Ugo Borello, Ph.D.
University of California, San Francisco
The Role of Frizzled9 in Hippocampal and Cortical Development

Summary: The cerebral cortex (the part of the brain responsible for perception of sensations, learning, reasoning) is thought to be a principle location for the defects underlying autism. By studying the role that specific genes (Fgf and Wnt) play in the development of the cerebral cortex, Drs. Borello and Rubenstein hope to gain insight into the genes’ interactions and how they affect the developing cortex, and the cognitive and mood abnormalities observed in autism. Using an animal model in which these genes are not expressed properly, these scientists can determine how each contributes to normal cortical development and consequences of abnormal expression.

What this means to individuals with autism: This study will help discover the role of certain genes in the neurodevelopment of autism. Finding genes involved in autism susceptibility and learning how they contribute to disease development will provide information that could lead to more effective treatments and interventions.

Mentor: Peter Scheiffele, Ph.D.
Fellow: Ben Cheh
Columbia University
Consequences of neuroligin mutations on synapse formation and behavior

Summary: The cellular and genetic defects that cause the behavioral and cognitive abnormalities in individuals with autism are unknown. However, recent studies have revealed that mutations in a family of neuronal cell adhesion molecules called neuroligins are associated with autism and Asperger syndrome. Drs. Scheiffele and Cheh will study the inactivation and loss of neuroligins in neurons to determine the role of these molecules on neuron shape and function. The researchers will use tools developed on cells in a dish to generate a mouse model that permits testing behavioral consequences of neuroligin function during development and in the adult animal.

What this means to individuals with autism: As mutations in neuroligins have been associated with autism, this study will demonstrate the neurobiological and behavioral function of this gene. In this way, scientists will gain a better understanding of the role that this molecule plays in autism spectrum disorders.

Mentor: George Wagner, Ph.D.
Fellow: Michele Cheh, Rutgers University
Animal Model of Autism Using Engrailed2 Knockout Mice

Summary: Autism is a neurobiological disorder whose primary symptoms include impaired communication and social interaction with restricted or repetitive motor movements. As recent studies have shown an association with a specific mutation of the engrailed 2 gene with autism spectrum disorders, Dr. Wagner’s lab will examine behavioral development in a mouse model where this gene is not expressed. In this way, animals will be tested on these core domains of behavior, including those behaviors that are affected by brain areas that do not function properly in individuals affected with autism.

What this means to individuals with autism: By using animal models, researchers are able to determine the effects of single
mutations in gene expression with specific behavioral deficits. These studies will help determine the function of the engrailed 2 gene on behavioral development so that the role of this gene in autism spectrum disorders can be examined more closely.

Mentor: Christopher Walsh, M.D., Ph.D.
Fellow: Seung-Yun Yoo, Ph.D.
Beth Israel Deaconess Medical Center, Harvard Medical School, HHMI

Identification of gene(s) involved in autosomal recessive autism

Summary: Previous studies have shown that large family size, coupled with strong ancestral lineage in Arabic families of the Middle East, make it possible to recognize recessively inherited neurological disorders in this population. The goal of this study is to use these families to map and identify autism genes in order to better understand their classification, pathogenesis, and potential treatments. Drs. Walsh and Yoo have been collecting genetic material from related families with autistic children from the Arabic populations of the Middle East. As some of these genetic mutations may be isolated to smaller groups of Arabic populations, this endeavor provides a unique opportunity to facilitate precise gene mapping. The later goals of the study is to identify the novel autism gene(s) and sequence these candidates from autism patients of the Autism Genetic Resource Exchange (AGRE) to confirm the importance of a causative gene for autism and to determine whether the same gene may cause autism in a more genetically diverse population.

What this means to individuals with autism: This study will investigate the genetic causes of autism. Finding genes involved in autism susceptibility and learning how they contribute to disease development will provide information that could lead to effective treatments and interventions.

Mentor: Stephanie White, Ph.D.
Fellow: Julie Miller, Ph.D.
University of California, Los Angeles

Molecular targets for socially-learned vocalization

Summary: Unfortunately, there is little understanding of the basic cellular and molecular processes underlying human speech and language, which are profoundly affected in autism spectrum disorders. Many factors make it difficult to identify the neural mechanisms that underlie vocal learning humans. Fortunately, songbirds offer the potential to identify socially-sensitive neural mechanisms for vocal-learning, including human speech. Songbirds, like humans, learn their vocalizations and share key aspects with human speech. These studies will use songbirds to reveal the basic neural mechanisms that underlie vocal learning and identify gene targets for vocal learning. In further studies, molecules identified in the songbird will be compared to those identified in human brains to assess their role in human speech and language.

What this means to individuals with autism: Animal models of speech and language are essential to study the potential causes of disorders in this area of functioning. These studies will help explain the mechanisms of language development in individuals with autism, which will allow researchers to understand potential causes of ASD.

Mentor: Darragh Devine, Ph.D.
Fellow: Amber Muehlmann
University of Florida

Self-Injurious Behavior: Pharmacotherapy in an Animal Model

Summary: A debilitating behavior sometimes exhibited in autism is self-injurious behavior (SIB), which consists of complex repetitive movements that produce physical injury (e.g. head-banging, face-punching, self-biting). While research has yielded behavioral treatment strategies that are effective for many individuals, there are also self-injurers who are resistant to behavioral interventions. There is evidence that drug therapy may be a valuable adjunct to behavioral treatment, but there is little information available to guide the selection of appropriate drug treatments. Using a model of drug-induced self-injury in rats, this study will screen and evaluate the potential effectiveness of the drugs valproate, topiramate, memantine, and nifedipine for treatment of SIB.

What this means to individuals with autism: By studying the effectiveness of these drugs in rat models, a pre-screening strategy will be developed so that potential drug therapies can be evaluated before they are attempted in human self-injurers. The effectiveness of all four drugs will yield information about the neurobiological basis of SIB and help guide ongoing neurobiological investigations into the treatment strategies for self-injurious behavior.

Mentor: Margaret Fahnestock, Ph.D.
Fellow: Lisa Lagrou
McMaster University

Mechanism of Neurotransmitter Dysregulation in Autism

Summary: Proper neurochemical balance during development is crucial to normal brain function. Previous studies have linked a dysregulation in blood levels of serotonin, dopamine and norepinephrine in individuals with ASD, however, the mechanism of these alterations has not yet been well characterized.
Recently, studying post-mortem brain tissue, Dr. Fahnestock’s lab demonstrated a reduction in expression of the 5HT2a receptor, providing a mechanism for elevated serotonin levels in autism. In this next set of studies, this reduction in 5HT2a receptor expression will be studied further by examining the gene responsible for how this protein is expressed. Furthermore, Drs. Fahnestock and Lagrou will determine if individuals with autism exhibit abnormal amounts of enzymes that synthesize these neurotransmitters, providing a better understanding of the etiology and symptomatology of autistic disorder at the molecular level.

**What this means to individuals with autism:** The results of these studies will aid the development of diagnostic tests, identify candidate genes for additional genetic studies, and suggest new drug avenues for treatment.

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**Cause-Gene/Environment**

These research projects focus on how the interaction between genetic makeup and responses to environmental exposures may lead to autism spectrum disorders.

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**Mentor:** Jane Adams, Ph.D.
**Fellow:** Jennifer Gaven, Ph.D.
**University of Massachusetts, Boston**

*Early Markers of Autism and Social-Cognitive Processing in Infants Exposed to Valproic Acid During Prenatal Development*

**Summary:** The use of drugs to control epilepsy (such as valproic acid) during pregnancy has been suggested to increase the risk for autism spectrum disorders in offspring. Thus far, data on autism risk has been based primarily on case reports, retrospective sample studies, and suggestions from animal research. This study will assess the developmental outcomes in a group of infants prenatally exposed to VPA, as well as a comparison group of infants matched by age, maternal age and demographic characteristics. It will also examine the effects of prenatal VPA exposure on motor, mental, and social-emotional development, as well as social-cognitive processing.

**What this means to individuals with autism:** This study will help clarify if there is indeed an increased risk of autism in children exposed to valproic acid in-utero. Determination of environmental or pharmaceutical contributions to autism will contribute to development of better animal models and intervention strategies to prevent VPA associated cases of autism.

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**Mentor:** Dorothy Bishop, D. Phil.
**Fellow:** Andrew Whitehouse, Ph.D.
**Oxford University**

*Electrophysiological and Behavioral studies of Phonological Short-Term Memory: A Comparison with Specific Language Impairment*

**Summary:** Specific Language Impairment (SLI) is a selective disorder in which a child develops along normal lines, except in the area of verbal language, where skills lag behind those of other children of the same age. In autistic disorder, communication difficulties encompass both verbal and nonverbal aspects and are associated with problems in socialization and behavioral repertoire. Whether these similarities represent a subgroup of children with autism who share a core heritable language deficit with SLI, or whether this is merely a superficial behavioral similarity with a different underlying cause, remains unclear. This study will use non-invasive electrophysiological (recordings of electrical activity of the brain) and behavioral methods, including short-term memory, to investigate the relationship between SLI and autism. This will enable the researchers to understand if behavioral similarities of autism and SLI are indicative of the same underlying neurobiological cause.

**What this means to individuals with autism:** Determining the exact relationship between SLI and autism has important implications for describing the autism phenotype and allowing better understanding of the language impairments seen in autism. In addition, results of this study will help determine more successful communication-intervention techniques.
Cognitive Ability

This research works toward understanding the specific behavioral deficits of individuals with autism spectrum disorder and how they relate to brain function.

Mentor: Mark Strauss, Ph.D.
Fellow: Keiran Rump
University of Pittsburgh

The Recognition of Emotional Expression by Children and Adults With Autism

Summary: One of the most basic cognitive processes in children and adults is the ability to form categories and recognize existing categories with regards to objects, faces, and facial expression. The research in Dr. Strauss’s lab suggests that there are critical and perhaps very early deficits in these basic cognitive abilities in individuals who have autism spectrum disorders. This critical and basic ability begins to develop in the first year of life and allows infants to discriminate male from female faces, recognize people, and identify basic objects prior to knowing verbal labels. In order to learn language, typically developing infants must first be able to abstract and learn basic categorical information about both object categories (e.g., dogs, cats, chairs) and people (e.g., gender, facial expressions, age). Such basic cognitive deficits may manifest as clinical deficits in language, social, and repetitive behaviors typically demonstrated by individuals with autism.

What this means to individuals with autism: Dr. Strauss and Ms. Rump will examine the ability of individuals with autism to form categories in different cognitive domains. These results could have a profound impact on understanding delays in both linguistic and social development in children with autism and perhaps serve as a very early diagnostic tool for detecting autism.

Mentor: Helen Tager-Flusberg, Ph.D.
Fellow: Ruth Grossman, Ph.D.
Boston University

Behavioral and Brain Imaging Studies of Verbal/Non-Verbal Integration in Autism

Summary: Some individuals with autism show apparently normal language skills. However, they display difficulty following conversation, making everyday discourse a challenge. The current study will examine if the source of these communication problems stems from an inability to integrate verbal and non-verbal information (such as facial expression) in a conversation. Children and adolescents with autism will be tested for their ability to understand sentences that are preceded by an emotionally expressive cue. This behavioral testing will be coupled with functional magnetic resonance imaging that will determine which areas of the brain are activated with and without this priming technique in both individuals with autism and those not affected.

What this means to individuals with autism: These studies will shed light on some of the core deficits in social communication in individuals with autism and advance understanding of the neurobiological basis of these deficits.

Mentor: Rita Valentino, Ph.D.
Fellow: Steven Leiser, Ph.D.
The Children’s Hospital of Philadelphia

Sensory Response Dysregulation

Summary: This study will investigate how the brain processes sensory information and how this impacts on attention. It is recognized that sensory processing is abnormal in autism, as evidenced by both hypo and hypersensitivity to tactile stimulus such as touch. This study will focus on a specific system of nerves in the brain, the locus coeruleus (LC)-norepinephrine (NE) system, that projects...
to sensory regions of the cortex and modulates sensory information processing. This system also functions to maintain arousal and set the mode of attention between focused and scanning. These studies will use a rat model in which LC-NE activity will be selectively manipulated and the response of cortical sensory neurons to auditory stimuli will be determined. Drs. Valentino and Leiser will examine how changes in neuronal responses translate to behavior in an attention task.

**What this means to individuals with autism:** This study will help determine how the brain receives and processes sensory input, the impact of stress- and pain-related substances on this function, and how this translates to behaviors requiring attention. This knowledge will help researchers understand sensory abnormalities that are prevalent in autism and potentially lead to more advanced treatment.

**Diagnosis/Identification**

Scientists in this area are developing ways to improve diagnostic markers for earlier identification.

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**Mentor:** Geraldine Dawson, Ph.D.
**Fellow:** Raphael Bernier
**University of Washington**

**Role of mirror neurons in the imitation deficits in autism**

**Summary:** Imitation is a critical way in which people learn to relate to others socially. In individuals with autism, imitation has consistently been shown to be impaired. A class of neurons, called mirror neurons, provides a possible neurological mechanism for imitation ability because these neurons activate both when an action is observed and when it is executed. Using non-invasive EEG technology, Dr. Dawson’s group intends to study mirror neuron activity and correlate that activity with tasks which target imitation ability. The primary goal of this study is to investigate whether there is evidence of mirror neuron dysfunction in autism and parents of autistic individuals.

**What this means to individuals with autism:** By studying both affected individuals and first-degree relatives of individuals with autism, a better understanding of the complex broader autism phenotype can be examined. Furthermore, a neurobiological mechanism behind specific impairments seen in those with the autism phenotype will aid in better diagnostic and treatment paradigms.

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**Mentor:** Pat Mirenda, Ph.D.
**Fellow:** Karen Bopp, Ph.D.
**University of British Columbia**

**Relationships Between Prelinguistic Communicative Behaviors and Early Intervention Outcomes in Young Children with Autism**

**Summary:** Studies have shown that some children with autism progress significantly in the area of cognition and language, while others show little or no improvement. This research will investigate how the language skills of children with autism develop over time and what predicts which children will do better than others. Specifically, the research will examine data collected at multiple time periods during development to determine the predictive value of early communication, joint attention, cognitive, social, and imitative skills on later social development. This study will also examine the effects of early behavioral intervention on language development.

**What this means to individuals with autism:** This research will allow investigators to create a software program that clinicians can use to examine early word production as part of language development. The results will not only provide essential information regarding prognosis, but will also provide a better understanding of individual characteristics for better early intervention programs.
Mentor: Joseph Piven, M.D.
Fellow: Matt Mosconi
University of North Carolina at Chapel Hill
Social Perception in Young Children with Autism

**Summary:** Abnormalities in the size and molecular structure of the amygdala have been linked to autism spectrum disorders. Drs. Piven and Mosconi will conduct a series of studies to examine the development of the amygdala, a brain structure associated with understanding facial expressions and communicative gestures (e.g., shifts in eye gaze). This research also will focus on the relationship between amygdala abnormalities and social deficits in autism. Using magnetic resonance imaging (MRI), as well as cognitive and behavioral data, these studies will examine amygdala growth in children with and without autism and the relationship between amygdala volumes and social behavior in children with autism.

**What this means to individuals with autism:** This study will help determine how the development the amygdala affects social perception in young children with autism. This will help researchers understand social deficits that are prevalent in autism and potentially lead to more advanced treatment by targeting functioning of this brain area.

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Mentor: Helen Tager-Flusberg, Ph.D.
Fellow: Kristen Lindgren
Boston University
Functional Connectivity of Language Areas in Autism and Specific Language Impairment

**Summary:** Dr. Tager-Flusberg and her predoctoral fellow will be investigating how the brain processes language in children with autism. Children with autism with both normal and impaired language abilities will be tested for their ability to make linguistic and non-linguistic judgments about sentences. An example of a non-linguistic task would ask: Are the words presented in upper-case or lower-case letters? A linguistic question would be asked: Is the word representative of something positive/nice or negative/bad? Past research has found that tasks that require understanding of the meaning of language activate brain regions located in the left hemisphere. This experiment will test whether the same patterns of activation are found in children with autism and also examine the connectivity of different areas of the brain.

**What this means to individuals with autism:** This research will help expand understanding of the cognitive and neural mechanisms that underlie the communicative deficits in high-functioning individuals with autism. Results will help better understand the cognitive and neural mechanisms that underlie the communicative deficits in high-functioning individuals with autism.

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Mentor: Chandan Vaidya, Ph.D
Fellow: Kelley Anne Barnes
Georgetown University.
fMRI of Implicit Learning in Childhood Autism

**Summary:** Social rules are learned by explicit instruction coupled with repeated experience to those rules. Through this process, individuals become sensitive to predictable regularities in their environment without being consciously unaware of them. This forms a powerful mechanism of learning, termed implicit learning, which is known to underlie acquisition of higher cognitive functions such as language and social intuition. This project will study implicit learning mechanisms in individuals with autism, using functional magnetic resonance imaging to identify the brain systems at fault and determine their relation to social deficits.

**What this means to individuals with autism:** This research will discover new basic knowledge about implicit learning in individuals with autism. By learning about how the brain functions during implicit learning, interventions that target impairments in social interaction and social relationships can be better developed for those with both high and low functioning autism.

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**Pilot Studies**

At the core of NAAR’s mission is funding grants that enable researchers to conduct pilot studies in autism research, which can then be leveraged into larger, multi-year grants from the National Institutes of Health (NIH) and other sources. While NAAR has expanded the scope of its research agenda, the ongoing funding of pilot studies remains central to our mission.

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**Cause-Gene/Environment**

These research projects focus on how the interaction between genetic makeup and responses to environmental exposures may lead to autism spectrum disorders.

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Peter McCaffery, Ph.D.
UMMS/E. K. Shriver Center
Disruption of Organization of the Cerebral Cortex by Retinoic Acid

**Summary:** Dysfunction of the cerebral cortex is likely to be a significant contributor to the pathogenesis of autism. One mechanism by which changes in cortical function may occur is by too much activity, leading to “overexcitation.” This may be caused by a dysregulation in systems that normally turn off neurons. In this study, Dr. McCaffery and associates will investigate the influence of retinoic acid, which inhibits the migration of neurons.
of specific neurons to the cortex and so would reduce the number of neurons that regulate brain activity. Retinoic acid has been suggested as one possible candidate of an environmental input that, in excess, may result in some features of autistic pathology. Fetal exposure to retinoic acid can occur through the use of a number of drugs that can influence the levels or potency of retinoic acid, including Accutane, alcohol, or valproate.

What this means to individuals with autism: Studying the effects of pharmaceutical agents and teratogens on brain development will help illustrate the mechanisms by which environmental factors may contribute to the neuropathology of autism.

Craig Newschaffer, Ph.D.  
Johns Hopkins School of Public Health  
Autism, Autoimmunity and the Environment  

Summary: There is some evidence regarding an association between autism and autoimmunity, but the nature of this connection is still unclear. At the same time, given apparent upsurges in autism prevalence, interest into environmental risk factors continues to build. Because autism pathology likely begins early in development, the prenatal period is a critical time window for exposures to environmental risk factors. This study will look at two potentially related factors contributing to the fetal environment: maternal antibody levels and chemical exposures during pregnancy. The results of this research will add to the understanding of immunologic and environmental risk factors in autism.

What this means to individuals with autism: A reliable biomarker to enhance diagnosis of autism has not yet been well characterized or established. This study will explore autoantibodies as potential biomarkers of autism risk and will link biomarker data with ecologic data on environmental exposures.

Harvey Singer, M.D.  
Johns Hopkins University School of Medicine  
Autoimmune Abnormalities in Autism: A Family Study  

Summary: Several theories have been proposed based on the presence of antineurononal antibodies (ANAb) in individuals with autism. One study suggests that autism may be caused by the placental transfer of antibodies that, in turn, interfere with the development of the fetal brain. A second hypothesis suggests that identifying antibodies against specific central nervous system (CNS) proteins is essential in providing clues about the underlying pathophysiology. In order to further investigate the possibility of placental transfer of antibodies as a cause for autism, Dr. Singer's research will compare antibody levels in mothers of children with autism to those of unaffected children. He will also study both adult and fetal postmortem brain tissue to look at differentiation based on developmental factors.

What this means to individuals with autism: The identification of autoimmune abnormalities can aid in the definition of the autism phenotype, and provide new insight for physiologic mechanisms behind the cause of autism as well as potential preventative therapy.

Robert Vogt, Ph.D.  
Newborn Screening Branch, Centers for Disease Control  
Immune Biomarkers in Serum and Newborn Dried Blood Spots  

Summary: At present, there are no biological tests that can be performed to diagnose autism. This study will help develop methods and establish reference ranges for measuring immune biomarkers in infants, children, and mothers that could aid in early recognition and diagnosis of autism. The researchers will investigate if autism may be caused by immune and inflammatory reactions that influence neural development during gestation and infancy. They will use the microbead suspension array (MSA), which is a flexible, highly sensitive assay system that can be used to measure multiple biomarkers simultaneously from a very small sample, such as a drop of blood. Dr. Vogt and his colleagues hope to develop a panel of reliable, transferable laboratory methods for measuring selected biological markers of the immune system in serum and dried blood spots (DBS).

What this means to individuals with autism: This study will help establish tests and reference ranges that are readily transferable to other laboratories, so that all research and public health investigators can make use of them. Ideally, these population-based research activities will implicate specific environmental triggers of autism and help lead to preventive measures.

George Wagner, Ph.D.  
Rutgers University  
Animal Model of Autism Using Engrailed2 Knockout Mice  

Summary: Autism is a neurobiological disorder with primary symptoms include impaired communication and social interaction with restricted or repetitive motor movements. Dr. Wagner and his colleagues have developed a model that examines the neurobehavioral development of mice in three core areas: motor, cognitive, and social. As the EN2 gene has been shown to be associated with autism, Dr. Wagner's lab will examine behavioral development in a mouse model where this gene is not expressed. Furthermore, the effects of two environmental toxicants, VPA and DEHP will be examined to determine if this gene confers susceptibility to environmental exposures. He predicts that disruption of the En2 gene will alter the developmental path of the brain and lead to widespread behavioral changes that may be made worse in the presence of these toxicants.
What this means to individuals with autism: These studies may help clarify the genetic, neurobiological and environmental influences in autism. Finding genes involved in autism susceptibility and learning how they contribute to disease development will provide information that could lead to more effective treatments and interventions.

Cause/Neurobiology

Researchers in this field investigate neurobiological mechanisms in the causes of autism spectrum disorders.

Richard Courtemanche, Ph.D.
Concordia University
Dynamic Network Activity in the Cerebellum for Expectancy: Normal and Abnormal Networks Based on Neurochemistry

Summary: Autism has part of its roots in the improper development of certain cells in the cerebellum. This brain structure, long thought to be exclusively involved in movement, is now considered to have a particular role in attention, sensation, and even thinking, supporting the rest of the brain with its remarkable capacities. Recent studies in animals have shown that a particular pattern of electrical activity in the cerebellar cortex could explain part of the problems in directing attention, and ultimately a reluctance to socially interact, as seen in autism spectrum disorders. Using a mouse model, researchers will investigate how the cerebellum chemically operates to better process incoming information and generate responses.

What this means to individuals with autism: By understanding more about chemical functions in the brain, researchers can develop new drugs and other methods to treat and diagnose abnormal cerebellar processing, such as seen in autism.

Ludise Malkova, Ph.D.
Georgetown University
Socioemotional Dysfunction and Midbrain-Amygdala Circuitry

Summary: Dr. Malkova’s group will focus on identifying the neural substrates in the brain that are responsible for the abnormal socioemotional behavior that is present in autism spectrum disorders. Working with nonhuman primates, the researchers will perform tests to gain an understanding of the functional relationship between the amygdala-derived and colliculus-derived regulation of defensive and aggressive emotional tone to reveal new targets for both etiology and therapeutic intervention for autism. Using this framework, this group will investigate if functional network disruptions, as opposed to purely structural lesions, are responsible for triggering autistic symptoms in primates.

Sacha Nelson, M.D., Ph.D.
Brandeis University
Cortical Circuit Abnormalities in Mouse Models of Rett Syndrome

Summary: Rett Syndrome is a pervasive developmental disorder commonly associated with autistic behavior, which has been linked to a reduction in expression of the gene which codes for MeCP2. MeCP2 is a protein that binds to methylated DNA, and abnormal expression of this gene leads to changes in the complexity of neuronal connections. In a mouse model, abnormal MeCP2 function during development has been shown to lead to impairments in maturation. Research has shown that females with one abnormal and one normal copy of the gene initially develop normally, but then regress after 6-18 months, losing linguistic and cognitive abilities, and showing reduced social interaction. The biological mechanisms of how altered MeCP2 function leads to autistic behavior and other symptoms are not understood. In this study, Dr. Nelson and his colleagues will use a mouse model to investigate the biological link between MeCP2 function, cortical activity and autism.

What this means to individuals with autism: Studying diseases with similar phenotypes to autism with a known genetic mutation will help researchers better understand the role of candidate genes to symptom severity and onset. This will help simplify assays of gene therapy and other intervention strategies.

Samuel Pleasure, M.D., Ph.D.
University of California San Francisco
Chemotactic Regulation of Cajal-Retzius Cell Migration

Summary: Recent evidence suggests that autism spectrum disorders are likely to be in part caused by subtle disorders of the way cells in the cerebral cortex are organized, particularly at the stage when cells are elaborating dendrites and refining axonal projections. One type of cell that regulates migration and organization of cortical neurons are termed Cajal-Retzius (CR) cells. These CR cells secrete the glycoprotein reelin, the expression of which is dysregulated in some individuals with autism. This group at UCSF will investigate how these neurons migrate, the factors that control the proper migration migration of these cells during neural development, and the effects of certain signaling molecules on proper migration.
What this means to individuals with autism: The study of Cajal-Retzius cells will help increase understanding of the neurobiological mechanisms of brain development and neuronal migration and organization. This understanding is crucial to find effective treatment and prevention strategies.

Douglas Portman, Ph.D.
University of Rochester School of Medicine and Dentistry
Genetic Control of Sexual Dimorphism in the Nervous System: A Nematode Model for Genetic Mechanisms in Autism

Summary: One of the many mysteries regarding autism is its highly biased sex ratio: approximately 75-80% of individuals with autism are male. Though the development of autism is strongly influenced by genetic factors, no obvious linkage of autism susceptibility genes to sex chromosomes has been found that might explain this biased ratio. Dr. Portman and his colleagues will use a unique animal model to identify and characterize the genetic factors that masculinize the animal nervous system. They will investigate which factors account for the male predisposition to autism and if genetic mutations in these genes directly confer increased autism susceptibility.

What this means to individuals with autism: This study will use an innovative approach to understand the genetic and sex-specific components of the development of autism, ultimately providing potential opportunities for novel diagnostic and therapeutic tools.

Payam Rezaie, Ph.D.
Open University, United Kingdom
Examining Alterations in Cortical Neuronal Subpopulations and Synaptic Proteins in Autism

Summary: Together with Dr. Schmitz’s group, Dr. Rezaie and his colleagues will more precisely examine specific types of neurons in the cerebral cortex to determine which of these develop abnormally. Using postmortem tissue, Dr. Rezaie will focus on a two specific cell types: pyramidal neurons (which connect to other parts of the brain) and interneurons (which regulate their activity). In addition, the ability of these neurons to connect to one another will be examined on a cellular level by targeting specific proteins that affect the ability and efficiency of cells to interact with each other. Together, these experiments will build a more comprehensive picture of the cellular basis of alterations affecting the cerebral cortex in autism.

What this means to individuals with autism: This innovative work will represent a fundamental addition to the existing knowledge of the neurobiology of autism and form a basis on which to develop and investigate experimental models of the disorder. Furthermore, this study will work toward an integration of different aspects of the neurobiology of autism (glial, neuronal and synaptic), for development of better treatments.

Mirjana Savatic, M.D., Ph.D
Stony Brook University
Nitric Oxide and Synaptic Plasticity: Implications for Autism

Summary: A consistent observation in individuals with autism is the presence of a greater total brain volume that develops during the first few years of life. In this study, Dr. Savatic and Dr. Enikolopov will explore the role of nitric oxide (NO), a molecule that is involved in brain development and regulation of synapse formation, patterning, and plasticity. It has been suggested that NO might be involved in the development of autism, as some of the behaviors found in autism have been observed in animal studies when NO synthase (NOS) activity has been suppressed. The researchers will investigate if NO deficiency results in the production of more neurons, leading to a larger brain.

What this means to individuals with autism: This project will help clarify the role of nitric oxide as a potential causative factor in autism, leading to the development of new therapeutic interventions.

Flora Vaccarino, Ph.D.
Yale University
Molecular Mechanisms of Cerebral Cortical Overgrowth

Summary: The majority of children with autism show altered pattern of brain growth, with accelerated production of white and gray matter in the cerebral cortex and cerebellum during the first years of life. Dr. Vaccarino and her colleagues will investigate whether an unusually high rate of production of neural cells at this time in development causes behavioral abnormalities. Using a mouse model, researchers will mimic neural cell overproduction in the cerebral cortex by the overexpression of a growth factor gene, FGF2, at selective stages of prenatal or early postnatal development. They will investigate whether increasing FGF2 expression will produce increased neuronal output in the respective regions. Preliminary data has shown that increased neural cell number in the cerebral cortex induced by FGF2 injections is associated with fear for novelty, a primary feature of autism.

What this means to individuals with autism: By providing an animal model with the overproduction of cells in laminar structures (key characteristics of autism), investigators may be able to understand how increased cell number may have a negative impact on cognitive functions. This work may lay the founda-
tions for understanding how these abnormalities could be treated or reversed in individuals with autism.

Linda Van Aelst, Ph.D.
Cold Spring Harbor Laboratory
Role of the X-Linked Mental Retardation Protein Oligophrenin-1 in Neuronal Development and Function

Summary: In this study, Dr. Van Aelst and her colleagues will focus on a molecule called oligophrenin-1. The altered expression of this molecule has been associated with mental retardation, impaired language skills, and motor development delays. To understand the role of oligophrenin-1 in the brain and how loss of oligophrenin-1 results in the above phenotypes, Dr. Van Aelst’s group will experimentally decrease the levels of oligophrenin-1 protein in neurons and examine how this affects the shape and function of developing neurons. They will examine what impact loss of oligophrenin-1 has on the size, shape and communication of neurons in an areas of the brain which have been shown to be affected in individuals with autism.

What this means to individuals with autism: While mutations in the expression of multiple genes are most likely involved in autism spectrum disorders, scientists can only learn about the function of each gene while studying each individually. The isolation and characterization of relevant genes and a better understanding of the mechanisms that control brain development are imperative to help explain the processes that contribute to autism.

Donald Wilson, Ph.D.
University of Oklahoma
Functional Consequences of Sensory Gating Deficits

Summary: Sensory gating is the ability of the brain to filter irrelevant or redundant sensory input in order to allow individuals to devote the right amount of attention toward more important stimuli. An example of good sensory gating is the ability to be aware of background sounds or odors while still focusing on a dinner conversation. Impairments in proper sensory gating have been established in schizophrenia and described in individuals with autism spectrum disorder. Dr. Wilson’s lab has established a rodent model of sensory gating in the olfactory system, which is how this species engages in social communication. Using this model, the effects of abnormal sensory gating on social development will be examined, and a mechanism by which sensory gating deficits are altered will be established.

What this means to individuals with autism: One area of research that has not been adequately studied is the ongoing cognitive and neural effects of altered interaction with sensory stimuli during development. This study will examine these effects and also use an innovative animal model to examine the cellular mechanism by which irrelevant sensory information is filtered.

Matthew Anderson, M.D., Ph.D.
Beth Israel Medical Center / Harvard Medical School
Modeling Human Neuroligin-3 Autism in Mice

Summary: Recent work has demonstrated that some males with autism spectrum disorder have a mutation in the NLGN3 gene, a member of a family of genes implicated in synapse formation (the way cells in the brain communicate with each other). This discovery provides the first clue to discovering what cellular mechanisms may underlie autism. A newly developed genetic tool that makes use of the DNA modifying enzyme, Cre recombinase, now enables the Anderson lab to delete or express genes in specific cell types of the adult brain. Using this technique, Dr. Anderson and his colleagues will systematically delete NLGN3 from the major brain cell types to determine which cells cause functional defects that may explain the symptoms of autism spectrum disorders.

What this means to individuals with autism: Identifying the cellular localization and functions of NLGN3 in the intact brain will redirect future biomedical research efforts into the cellular basis for autism and help focus efforts towards developing therapies to treat the disorder.

John Constantino, M.D.
Washington University School of Medicine
Replication of Quantitative Linkage Findings in a New Sample of Genotyped (but Not Yet Phenotyped) Autism Pedigrees

Summary: Although autism is largely an inherited disorder, the specific genes that cause most cases of the disorder remain unknown. Previous genetic studies of autism have primarily involved affected pairs of siblings, but because affected sib pairs are relatively rare, this limits the sample size that can be used to search for genes for autism. In order to increase both the size of the sample and its power to detect genes, Dr. Constantino will use a quantitative approach in which genetic markers are related not just to presence or absence of the disorder, but to the degree of symptom severity that each individual manifests. Researchers will obtain quantitative assessments of autistic social impairment in all of the siblings in each family involved.
Joshua Corbin, Ph.D.
Georgetown University
*Genetic and Cellular Basis of Amygdala Development*

**Summary:** While it is known that more than one brain region is affected in autism, research has shown that dysfunction of the brain region known as the amygdala contributes to many of the behavioral abnormalities associated with autism. The amygdala performs a broad range of important functions, including modulating conditioned responses to fearful stimuli and regulating distinct aspects of emotional memory and social behavior. Currently, little is known regarding the early development of this complex structure. Using a mouse model, Dr. Corbin will investigate the genetic and cellular basis for the development of the amygdala. This understanding of normal amygdala development will provide a context to understand the underlying abnormal developmental mechanisms that contribute to autism.

**What this means to individuals with autism:** By learning more about the development of specific brain abnormalities, researchers can help identify how they contribute to disease development and provide information that could lead to more effective treatments and interventions.

James Millonig, Ph.D.
University of Medicine and Dentistry of NJ
*Genetic and Functional Analysis of ENGRAILED 2, a Cerebellar Patterning Gene*

**Summary:** In collaboration with Linda Brzustowicz's group at Rutgers University, Dr. Millonig's group has demonstrated that certain variants of the gene ENGRAILED 2 (EN2) are inherited more frequently in autistic individuals than unaffected siblings. The goal of this study is to identify specific changes in the DNA sequence that are inherited in a manner consistent with "mutations" and determine whether these variations in the gene affect the expression or function of EN2. Alterations in the expression of EN2 may explain cerebellar defects, which are some of the most prevalent morphological abnormalities associated with autism.

**What this means to individuals with autism:** These studies will help determine whether EN2 acts as an autism susceptibility gene, which could provide important insight into the genetic and developmental basis of autism.

Antonio Persico, M.D.
Univ. Campus Bio-Medico, Lab of Mol Psychiatry & Neurogenetics
*Addressing the Pathophysiology of Endophenotypes in Autism: Megalencephaly, Hyperserotoninemia, and Peptiduria*

**Summary:** Certain genetic characteristics have been identified in individuals with autism. Researchers have identified specific subgroups of autistic patients who present with elevated serotonin blood levels, loss of specific peptides in the urine, and enlarged head circumference. These three “markers” are believed to be closely related to underlying genetic variants of autism. This study will conduct research into these three marker areas in individuals with autism and their family members. The researchers will also perform genetic linkage/association studies to investigate strong candidate genes likely involved in the biological processes underlying these marker areas.

**What this means to individuals with autism:** The identification and characterization of changes at the DNA level either causing autism, conferring vulnerability, or explaining “marker” features associated with this disease will enhance understanding of the neurobiological bases of autism. This may lead to earlier and more reliable diagnoses as well as new treatment strategies.

Vijaya Ramesh, Ph.D.
Massachusetts General Hospital
*Pam as a Candidate Gene for Autism*

**Summary:** Tuberous sclerosis complex, commonly known as TSC, is an inherited disease that results in neurological complications including seizures, mental retardation, and autism. Features of autism spectrum disorders are reported to be present in 25-50% of individuals with TSC. Researchers have found that mutations in the two genes involved in TSC disrupt the functions of hamartin and tuberin, resulting in TSC and associated neurological symptoms. Dr. Ramesh and his associates have identified a protein known as *Pam* as a partner of tuberin and hamartin. *Pam* is known to have distinct functions in the nervous system as well as a crucial role in brain development and neuronal connectivity. This study will investigate the role that *Pam* plays in autism through its interaction with hamartin and tuberin and through its critical function in neurons.

**What this means to individuals with autism:** By examining the involvement of *Pam* in autism, this research will provide...
new clues for understanding the genes responsible for autism in TSC as well as autism in individuals without TSC.

James Rand, Ph.D.
Oklahoma Medical Research Foundation
Molecular and Cellular Mechanisms of Neuroligin-Mediated Synaptogenesis

Summary: Recent research has demonstrated an association between autism and mutations in genes encoding a family of proteins called neuroligins. There are 4 neuroligin-encoding genes in humans, and mutations disrupting the NLGN3 and NLGN4 genes (both of which are on the X-chromosome) are associated with autism. Altered expression of these two genes may contribute to perturbations in the way neurons communicate with each other and how they interact, leading to neuron “miswiring.” Using a simple model system, Dr. Rand and his associates will further investigate the molecular genetics, cell biology, and interactions of neuroligins to determine their role in the development of autism.

What this means to individuals with autism: Identifying genes involved in autism susceptibility and learning how they contribute to disease development will provide information that could lead to more effective treatments and interventions.

Epidemiology

These studies investigate the original developmental characteristics of autism.

Roy Grinker, Ph.D.
The George Washington University
The Prevalence of Autistic Spectrum Disorder (ASD) in Korean School-Aged Children

Summary: While studies regarding the prevalence of autism have been conducted in the U.S., Canada, and other select countries around the world, no research of the kind has been done in South Korea. Dr. Grinker and his associates will conduct the first epidemiological study of autism in South Korea, screening and assessing children from the city of Jinju to ascertain the prevalence of autism among all children born between 1994 and 1999. In addition, the study will investigate social attitudes about autism and patterns of service utilization among Korean children with autism. The investigators will also explore the suggestion that many Korean children with autism are likely to have their first clinical evaluation at an age (before two) earlier than those suggested in Western and Japanese studies.

What this means to individuals with autism: This research will contribute to autism prevalence studies done worldwide and help set the stage for future international collaboration as part of a global network of autism research. Investigating the prevalence of autism in different areas of the world will illustrate examples of possible environmental and cultural issues that may play a role in the diagnosis of autism spectrum disorders.

Diagnosis/Identification

Scientists in this area are developing ways to improve diagnostic markers for earlier identification.

Guido Gerig, Ph.D.
University of North Carolina Chapel Hill
Quantitative White Matter Analysis of Early Brain Development in Autism

Summary: Several studies have reported a difference in brain size in individuals with autism during early development. Dr. Gerig will collaborate with investigators at UNC and will use diffuse tensor imaging to study brain size from 2 to 4 years of age, covering a period of time before autism is normally diagnosed. His lab will focus on white matter in the brain, which is responsible for communication between cells. In addition, his lab will develop new techniques to analyze differences in white matter during development and make these new technologies freely available to other researchers.

What this means to individuals with autism: This study will improve understanding of early brain development in autism and how it correlates to cognitive ability and behavioral severity. The findings will help develop innovative clinical applications for better interventions at earlier ages.

Jana Iverson, Ph.D.
University of Pittsburgh
Early Identification of Autism: Developmental Trajectories in Communicative and Motor Skills in Siblings of Children with Autism

Summary: The NAAR High Risk BabySibling Autism Research Project is an ongoing project designed to enable clinicians to make a more definitive diagnosis of autism earlier than ever before by identifying behavioral and biological markers for autism. Currently, siblings of children with autism are observed from age 5-18 months. This next study will allow Dr. Iverson to continue to observe these children from ages 21-36 months. These later observations on these children will include further validation of possible early autism indicators in relation to
diagnostic status at 36 months; documentation of Sibling Group developmental trajectories, including any regressions that may occur in language, gesture, imitation, play, motor skills, and communication abilities; and comparison of data obtained from the Sibling group to parallel data from a No-Known-Risk group to assess variations in frequency of occurrence and age of onset, and/or atypicalities of form that may distinguish individual children at heightened risk for autism from those with no known risk.

What this means for individuals with autism: This study is designed to determine what signs predict later diagnosis for autism spectrum disorder. With the ability to diagnose children earlier, children at risk for developing ASD can be placed in intervention programs that will improve their developmental outcomes.

Andrea Jackowski, Ph.D.
Yale University - Child Study Center

_Brain Morphometry in Newborns at Risk for Autism: an MRI Study_

Summary: Dr. Jackowski and her colleagues at Yale will also be studying the difference in head size and white matter changes through development using non-invasive imaging techniques. However, her lab plans to study these measures even earlier in development. Using a group of children who are identified as ‘at risk’ because of an already existing familial diagnosis (i.e. high risk baby siblings), Dr. Jackowski’s group will examine brain size and white matter changes through development from birth through diagnosis.

What this means to individuals with autism: The combination of brain structural and connectivity imaging data from the first week of life will help investigators determine the neurobiological causes of autism and aid in developing treatments at the earliest stage of life.

Beth Malow, M.D., M.S.
Vanderbilt University

_Defining the Physiological and Behavioral Components of Insomnia in Children with Autism Spectrum Disorders_

Summary: Many children with autism do not sleep well at night. Lack of a good night’s sleep can cause children to be more irritable, hyperactive, or aggressive during the day. The purpose of this research study is to figure out why children with autism do not sleep well. Researchers will ask parents to complete questionnaires about their children’s sleep and keep diaries of their sleep patterns. Children may also wear a wrist-watch-like sleep monitor or take part in sleep studies in the home or hospital laboratory.

What this means to individuals with autism: If researchers can determine why children with autism do not sleep well, they can find ways to help these children sleep better at night. Improving sleep in children with autism may help reduce challenging behaviors, improve daytime functioning and reduce stress in the families caring for these children.

Sara Webb, Ph.D.
University of Washington

_Linking Cerebellar Pathology to Functioning in Individuals with Autism: Implications for Translational Research_

Summary: Abnormalities in the structure and function of the brainstem are well documented in autism. The focus of this proposal is to investigate the existence and nature of deficits in the functioning in the brainstem and cerebellum by examining behaviors that are regulated by the proper function of these areas. These behavioral tests include information processing and eye movements. These results will be integrated with images of these structures to link abnormalities in the structure of the cerebellum with specific behavioral impairments.

What this means to individuals with autism: By learning more about specific brain abnormalities, researchers can help identify how they contribute to disease development. Furthermore, this
study will further define the phenotype of autism, using measures of cerebellar and brainstem functioning in humans that can be used in translational research to test animal models of autism.

Nurit Yirmiya, Ph.D.
The Hebrew University of Jerusalem
The Development of Siblings of Children with Autism at Age 7 Years

Summary: It has been shown that young children with autism can benefit greatly from specialized early intervention programs to improve cognitive, social, and behavioral development. Therefore, early identification of autism is crucial to help early social and communicative skills progress. Currently, studies targeting young siblings of children with autism (who are genetically at risk of developing autism and other related impairments) are in progress at the Hebrew University of Jerusalem. The researchers’ data has indicated that most siblings develop well during infancy and young childhood, but about 20% of siblings do indeed begin to show broad autism genetic characteristics. This research will reevaluate children in the study at the age of 7 years to track the developmental paths of the participants.

What this means to individuals with autism: Early identification of autism in children can lead to earlier intervention therapies and programs, which can improve the social and communication skills of individuals with autism.

Cause/Neurochemistry

These research projects help determine how neurochemistry contributes to autism spectrum disorders.

Gary Rudnick, Ph.D.
Yale University School of Medicine
Mutation associated with Asperger’s Syndrome – Effect on Amine Transporter Regulation

Summary: A rare mutation in the gene encoding the serotonin transporter (SERT) was found to be associated with a group of psychiatric disorders including Asperger’s syndrome. The serotonin transporter regulates the duration and amount of neurotransmitter in the inside and outside of the cell and is the target of drugs, like Prozac, used to treat autism spectrum disorders. Dr. Rudnick plans to investigate whether this mutation also affects the function of transporters for norepinephrine and dopamine. These studies will be performed with human cells in culture that will be manipulated to express mutant forms of the transporters for serotonin, norepinephrine and dopamine. Dr. Rudnick’s lab has years of experience with this type of system, and has high expectation of interesting results. Because of the similarities in structure and function between these transporters, these studies will examine their contribution to the cause of autistic spectrum disorders.

What this means to individuals with autism: A specific mutation in the SERT might be the genetic basis for some mental disorders or for the lack of responses to therapeutic drugs by some patients. This experiment will examine the functional consequences of a specific genetic mutation, leading to more effective pharmacological interventions.

Patricia Whitaker-Azmitia, Ph.D.
SUNY at Stony Brook
Serotonin, Oxytocin and Social Behaviors

Summary: Research has shown that some individuals with autism have an increased level of serotonin in their blood, termed hyperserotonemia. During fetal and early brain development, these elevated levels of serotonin can lead to a reduction in a neuropeptide called oxytocin. Oxytocin has been shown to be altered in some individuals with autism and has been associated in animal models with social and maternal bonding.
This study will develop a mouse model of hyperserotonemia to examine changes in serotonin and oxytocin levels in the brain during development. The animals will be tested at various ages to see if changes in serotonin terminals and the neuropeptide oxytocin will affect social behavior.

**What this means to individuals with autism:** By investigating serotonin and oxytocin levels in the brain, researchers can help determine which chemical changes affect social behavior in individuals with autism. This can lead to potential treatments, including those that increase the brain activity of oxytocin.

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**Cognitive Ability**

This research works toward understanding the specific behavioral deficits of individuals with autism spectrum disorder and how they relate to brain function.

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**Michal Assaf, M.D.**
**Olin Neuropsychiatry Research Center / IOL / Yale School of Medicine**

**Neuronal Correlates of Implicit Social Interaction in Autism Spectrum Disorders: A Functional MRI Study**

**Summary:** Individuals with autism spectrum disorders share a common core dysfunction of social communication skills. This dysfunction is widely believed to be a symptom of impaired implicit mentalizing. Mentalizing can be defined as the ability to predict others’ behavior by attributing states of mind (such as thoughts and feelings) to them. This research will explore the neuronal network that processes implicit mentalizing and the neuropathology that underlies this social cognitive deficit. While participants are involved in a naturalistic and competitive social two-player game, Dr. Assaf and his colleagues will use functional MRI (fMRI) to measure activation patterns in the brain network that help promote implicit mentalizing.

**What this means to individuals with autism:** This study will improve understanding of the biology underlying the core deficit of social impairment in autism and help pave the way for future research (including genetic) that advances the development of new treatment tools for autism.

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**Kim Dalton, Ph.D.**
**University of Wisconsin**

**Multisensory Integration of Visual and Vocal Emotional Cues in Autism: A Brain fMRI Study**

**Summary:** A core feature of individuals with autism is the profound impairment of social and emotional communication skills. Evidence suggests that the social/emotional deficits associated with autism have their basis in dysfunction of affective neural circuitry, suggesting that autism is a disorder of the “social brain.” Dr. Dalton and her colleagues will further investigate findings of abnormalities in the central circuitry of emotion and emotion regulation during emotional face and voice processing and integration. Using state-of-the-art eye-tracking and brain neuroimaging techniques, this research will build on a model of the neural circuitry underlying social/emotional dysfunction in autism and evaluate the association of these deficits with patterns of multisensory integration and functional connectivity.

**What this means to individuals with autism:** A clear understanding of the underlying mechanisms responsible for the social/emotional deficits in autism is necessary in order to develop highly effective evidence-based practice critical in assisting individuals with autism to succeed in society.

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**Daniel Levitin, Ph.D.**
**McGill University, Canada**

**Quantifying the Extent of Emotional Processing in Autism: Converging Evidence from Music Processing and Central Coherence Theory**

**Summary:** Early evidence indicates that autistic children may perceive emotion in music, either through the whole melody or when groups of notes are played. If this is true, it would provide evidence of an emotional skill that is spared in autism. Dr. Levitin and his colleagues at McGill University have examined these skills in individuals with Williams Syndrome and will be developing novel paradigms and methods to conduct studies to investigate the processing of musical emotion and musical structure in individuals with autism. This will be done by quantifying and characterizing the nature of emotional processing with respect to music. In addition, the extent to which individuals with autism spectrum disorders use auditory vs. visual cues to respond to music will be examined.

**What this means to individuals with autism:** The results will significantly advance theories of cognitive and emotional processing in autism and will have tangible benefits for the clinical community. Immediate applications will include assisting learning programs and aiding behavioral modification.
Diana Robins, Ph.D.
Georgia State University
Perception of Emotional Cues from Facial Expression and Affective Prosody using fMRI

Summary: Individuals with autism experience difficulty engaging in social interaction, and the struggle to understand the emotions expressed by other people is one aspect of this social disability. This project will test emotion processing in individuals with autism by using short movies. Participants will watch the movies and judge whether the emotion heard in the actor’s tone of voice matches the emotion seen on the actor’s face. During the study, participants will undergo brain imaging to identify those areas of the brain that are highly active as the person engages in emotion processing. Preliminary research suggests that individuals with autism do not show the same patterns of brain activation to the emotional movies as typically developing individuals. This research will examine these differences in more detail, in order to better understand the brain activity that underlies the difficulty individuals with autism experience when they process emotions.

What this means to individuals with autism: These studies will help researchers identify brain areas that consistently show differences between ASD and non-ASD. These results may then be used to develop better interventions and treatments.

Latha Soorya, Ph.D.
Mt. Sinai School of Medicine
Mediators of Motor Skills in Adolescents & Adults with ASD

Summary: Research shows that individuals with autism have difficulty with a variety of motor skills including both basic (such as balance) and complex motor tasks (such as three-part sequenced actions). To further investigate the specificity and nature of the motor skills impairments found in autism, Dr. Soorya and colleagues will perform a comparison of motor functioning in individuals with high functioning autism, Asperger’s disorder, attention deficit hyperactivity disorder, and those without disabilities. In order to examine the nature and impact of motor impairments, assessments of neurological and cognitive function will also be made.

What this means to individuals with autism: Clarifying the nature of motor deficits in autism can have broad implications for understanding the disorder, improving treatment specificity, and for improving overall functional outcomes.

Interdisciplinary

These studies are bridging the clinical and basic sciences to link methods in the laboratory with clinical practice.

Christoph Schmitz, M.D.
Maastricht University, Netherlands
Cytoarchitectural Alterations in the Cerebral Cortex in Autism

Summary: Dr. Schmitz’s lab has been studying the neuropathological characteristics of autism for many years. His group has reported abnormalities in size, number, and organization of neurons in the cerebral cortex. This current study will utilize novel tools to view the organization of cells in the cortex in three dimensions, specifically examining the connectivity of neurons between different areas of the cortex. Furthermore, his lab will compare these changes with those of a current animal model of autism: in utero maternal influenza virus exposure.

What this means to individuals with autism: The results of the proposed project will contribute to a better understanding of the neuropathology of autism using software which will be made available to the research community. In addition, this study will investigate the validity of an animal model of autism where environmental factors play a key role.

John Welsh, Ph.D.
Oregon Health & Science University
—and—
Timothy Roberts, Ph.D.
Children’s Hospital/University of Toronto
Electrophysiological Signatures: An Intermediate Phenotype for Autism

Summary: Autism is characterized by a range of clinical and behavioral symptoms. This presents a challenge to the design of experimental or animal models of autism necessary for understanding the causes and developing effective interventions or prevention measures. In order to tighten the relationship between clinical and experimental findings, Drs. Welsh and Roberts have initiated a collaboration that will link changes in brain wave activity in animal models with those seen in the clinic. In order to do this, these two scientists at different research institutions will relate invasive electrophysiological recordings in the rodent brain (Dr. Welsh) to non-invasive magnetoencephalographic recordings during speech and sounds (Dr. Roberts) in children with diagnoses of autism spectrum disorders. These researchers received funding as part of a new interdisciplinary funding mechanism designed to bridge the clinical and basic sciences in autism spectrum disorders.

What this means to individuals with autism: By directly comparing electrophysiological recordings from rodents and that of children with autism, these researchers hope to improve both animal models and clinical assessments. Furthermore, these experiments will unify experimental research and clinical studies to better define the autism phenotype.