Autism Spectrum Disorders Research

at the National Institute of Mental Health

FACT SHEET

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Autism spectrum disorders (ASD), a broad continuum of brain illnesses that includes Asperger's syndrome, share common genetic roots and essential clinical and behavioral features, although they differ in severity and age of onset. Autism, the most severe of these pervasive developmental disorders, typically begins in early childhood and impairs thinking, feeling, language, and the ability to relate to others.

From one to six in 1,000 Americans suffer from ASDs,[1,2] with some recent studies citing dramatic apparent increases in prevalence in certain locales. Boys with the disorders outnumber girls three or four to one. Within the first few years of life, children with ASDs fail to develop normal social interaction and communication and show restricted, repetitive, or stereotyped behaviors and interests.

Families coping with ASDs are searching for answers about causes, diagnosis, prevention, and treatment. The National Institute of Mental Health's (NIMH) investment in autism-related science has quadrupled over the past 7 years—from $9.4 million in FY 1997 to $36.2 million in FY 2002. The research is supported through grants and contracts with investigators at university medical centers and in the Institute's own laboratories in Bethesda, MD. In addition, new Institute initiatives aimed at advancing basic knowledge of brain development and genetics hold promise for understanding complex behavioral disorders like autism. NIMH's autism-related research ranges from efforts to improve awareness, diagnosis and

An NIMH Snapshot

The National Institute of Mental Health (NIMH) is one of 27 components of the National Institutes of Health (NIH), the Federal Government's principal biomedical and behavioral research agency. NIH is part of the U.S. Department of Health and Human Services. The FY 2003 budget for NIMH is $1.3 billion.

NIMH Mission

The NIMH mission is to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. This public health mandate demands that we harness powerful scientific tools to achieve better understanding, treatment, and eventually, prevention of these disabling conditions that affect millions of Americans.

To fulfill its mission, the Institute:

- conducts research on mental disorders and the underlying basic science of brain and behavior;
- supports research on these topics at universities and hospitals around the United States;
- collects, analyzes, and disseminates information on the causes, occurrence, and treatment of mental illnesses;
- supports the training of more than 1,000 scientists to carry out basic and clinical research; and
- communicates information to scientists, the public, the news media, and primary care and mental health professionals about mental illnesses, the brain, mental health, and research in these areas.

treatment, to studies involving brain imaging, tissue banks, animal models, genetics, developmental neurobiology, and neuropsychology.

Implementing the Children's Health Act of 2000

As part of the Children's Health Act of 2000,[3] Congress designated the NIMH to take the lead in expanding, intensifying and coordinating NIH's expanding autism research effort, which totaled nearly $74 million in 2002. NIMH has implemented this landmark legislation, in collaboration with the four other Institutes represented on the NIH Autism Coordinating Committee (NIH/ACC): National Institute of Child Health and Human Development (NICHD), National Institute of Neurological Disorders and Stroke (NINDS), National Institute on Deafness and Other Communication Disorders (NIDCD), and National Institute of Environmental Health Sciences (NIEHS)[4]

NIMH, on behalf of the Department of Health and Human Services (DHHS), also convenes the Interagency Autism Coordinating Committee (IACC), which serves as a forum where Federal agencies and public members can share information about their autism-related activities. In addition to the NIH/ACC members, this panel includes representatives from several DHHS agencies and the Department of Education. The IACC also includes four public members, family members or guardians of people with autism or spectrum disorders.[5]

Studies to Advance Autism Research and Treatment (STAART) Network

Foremost among the Children's Health Act's provisions is a collaborative effort to support development of several broadly based "Centers of Excellence in Autism Research." In response, the five NIH/ACC Institutes have jointly established the Studies to Advance Autism Research and Treatment (STAART) Network. This project is building new infrastructure for autism research by bringing together critical masses of expertise and resources at eight dedicated research centers across the country. The Centers are conducting basic and clinical research, including investigations into causes, diagnosis, early detection, prevention, and treatment. They include research in the fields of developmental neurobiology, genetics, clinical developmental psychology, and psychopharmacology. Interdisciplinary collaborations, including the recruitment of outstanding investigators who had previously not worked in the autism field, are being funded in stages over the next several years.

Grants totaling $65 million over five years were funded in Fall 2002 and Spring 2003 to support STAART Centers at the following sites: [6,7]

- University of North Carolina, Chapel Hill
- Yale University
- University of Washington
- University of California, Los Angeles
- Mount Sinai Medical School
- Kennedy Krieger Institute, Baltimore
- Boston University
- University of Rochester, New York

Each center is pursuing its own particular mix of studies. For example, at the Kennedy Krieger Institute and four collaborating area institutions, a team of 27 researchers—psychiatrists, neuropsychologists, psychologists, speech-language pathologists, developmental pediatricians and neuroscientists—are examining motor and communication impairments in autism, to find out what goes wrong in the developing brain, with an eye to early identification and intervention. Spurred by evidence of a serotonin abnormality in autism, investigators are studying animals deficient in the chemical messenger to discover its role in establishing connections between neurons.

Among other STAART Center studies currently underway, researchers at Yale University are examining eye tracking in children with autism age 5-12, as well in toddlers. They are studying how a child sees a social situation, relative to his or her level of social competence. Investigators there are also using functional brain imaging to assess the effectiveness of a computer-assisted intervention to improve facial identification and facial expression in autism. A study of relatives of individuals with autism and Down syndrome at the University of North Carolina is looking for patterns of thinking about social situations and "executive functioning" (planning, impulse control and reasoning) that might provide clues to psychological characteristics shared in common among families with these highly heritable disorders. A brain imaging study seeks to discover the neural roots of social and emotional processes as well as executive functioning and ritualistic-repetitive behaviors in adults and very young children with autism.[8]

Public Input

The Children's Health Act of 2000 mandates that the NIH make available information about its autism activities and facilitate public feedback to the NIH. Communications Directors, Public Liaison Officers, and other staff from the NIH/ACC regularly engage with representatives of autism advocacy groups to exchange information and stay in touch via an internet web site and a list-serve. Members of the autism advocacy community also serve as public participants on NIMH scientific review committees. A searchable information clearinghouse for all NIH autism-related activities is posted on the National Library of Medicine's MedlinePlus web site (http://medlineplus.nlm.nih.gov/nih.gov/medlineplus/autism.html). This links to several resources within the DHHS, including NIMH's autism web page (http://www.nimh.nih.gov/publicat/autism.cfm).

Brain Tissue and Genetics Resources

The Children's Health Act of 2000 also calls on NIMH to take the lead in expanding a program under which samples of tissues and genetic materials are donated, collected, preserved, and made available for autism research. Post-mortem brain tissue, which has been very scarce for the study of autism, offers a unique, high-resolution window into the inner workings of brain cells. For example, by using radioactive tracers on thinly sliced sections of brain tissue, scientists can detect and pinpoint abnormal activity of genes within cells. Only with access to brain tissue can the underlying neuropathology of autism be uncovered. To take advantage of emerging opportunities

for discovery in post-mortem tissue made possible by the new molecular methodologies, NIMH, in collaboration with the autism community and other NIH Institutes, is stepping up efforts to establish brain bank collections to study autism. For example, NIMH, NINDS and NIDCD are mounting a joint effort to develop a National Autism Brain Bank at the Harvard Brain Tissue Resource Center, which is primarily funded by NIMH and NINDS. It will store and disseminate postmortem human brain specimens for the study of autism.[9]

Diagnosis, Training, and Early Identification

People with ASDs show a broad range of impairment, with great variability in clinical symptoms and levels of functioning. For example, some people with autism have normal intelligence and develop good basic language skills, while others lag intellectually and develop little or no language. A common diagnostic scheme for assessing the complex social and communication deficits that constitute key features of the disorder has been a critical prerequisite to scientific progress.

NIMH has supported research that has raised the quality and standardization of screening and diagnosis in autism. Standard diagnostic interviews and observational methods developed through this research have become a national and international "gold standard," ensuring that what is diagnosed in one research center is comparable to that diagnosed in another. The Institute funds a series of annual workshops for training researchers in the use of these tools, and is funding further investigation of measurement tools.[10,11]

NIMH also supports research aimed at improving early diagnosis of autism. Institute-supported studies have demonstrated that a reliable diagnosis of autism spectrum can be made at age 2.[12] Yet, the age of onset remains elusive. Some children seem to develop normally for a couple of years and then regress; for example, they may lose language skills after developing a small vocabulary. Others may be affected from birth, but in such subtle ways that diagnosis is delayed. Earlier identification of children destined to develop symptoms could hold clues to the underlying neuropathology and would also facilitate early intervention. NIMH is funding studies that focus on young children at heightened risk for the disorder, such as younger siblings of children with autism.[13,14,15]

Brain Imaging

Non-invasive brain imaging techniques, such as MRI (magnetic resonance imaging), offer great potential for advancing understanding of the neural basis of emotional and intellectual deficits in autism and other childhood neuropsychiatric disorders. However, scientists currently have little data on normal brain function and development to compare with data from individuals with autism. Such norms have been lacking for brain imaging studies, leading to non-comparable findings and excessive duplication in scanning control subjects. Therefore, NIMH is co-sponsoring, with NICHD, NIDA and NINDS, a $28 million initiative that is using aMRI (anatomic magnetic resonance imaging), DTI (diffusion tensor imaging), and MRS (magnetic resonance spectroscopy) to create the world's first such large-scale database on normal brain development in children.[16]

The NIH MRI Study of Normal Brain Development is cataloging the structural development of the brain, by age and sex, with seven major research centers scanning more than 500 infants, children, and adolescents. Children age five and older are being followed up with additional scans and clinical and behavioral reassessments at 2-year intervals. Younger children are being re-scanned at more frequent intervals—3-12 months—to capture more rapid brain maturational changes occurring at these ages.

This study will permit the normal growth curves of brain structures to be charted, revealing the development of circuitry for language, thinking, and other functions. Individual brains differ enough that only broad generalizations can be made from comparisons of different individuals at different ages. But following the same brains as they mature allows scientists a much more detailed view of developmental changes. By comparing scans of children with neuropsychiatric disorders with this normative data, researchers will be able to determine the timing and developmental course of brain structural changes in childhood disorders. These databases, being developed by an NIMH-funded data analysis center, will ultimately facilitate early diagnosis and differentiation of various forms of autism. It will also speed the development of targeted treatments and evaluations of their effects.

The promise of such a normative brain database for turning up clues about childhood brain disorders was recently illustrated in a similar, but smaller-scale, NIMH intramural study.[17] In this first longitudinal structural MRI study to track individual children's developing brains, the researchers were surprised to discover a second wave of overproduction of gray matter (neurons) just prior to puberty. Possibly related to the influence of surging sex hormones, this thickening peaks at around age 11 in girls, 12 in boys, after which the gray matter actually thins some. Prior to this study, scientists had thought that the brain overproduced gray matter for a brief period in early development (in the womb and for about the first 18 months of life) and then underwent just one bout of pruning. The gray matter growth spurt predominates in the frontal lobe, the seat of executive functions. This type of normative data will help researchers contrast typical growth with that in autism spectrum disorders. A wave of abnormal brain enlargement seen in MRI studies of young children with autism follows a back-to-front pattern, similar to a wave of abnormal gray matter loss seen in childhood onset schizophrenia. This may suggest a process in which the timing and trajectory of various abnormalities parallels clinical outcome.[18, 38]

In other brain imaging studies, researchers using MRI and MRS are searching for brain anatomical and biochemical abnormalities that may underlie impaired social communication in children with autism. One fMRI study is looking for malfunctioning brain circuits associated with impaired thinking about human relationships, a problem seen in autism. While in the scanner, subjects view animated cartoons designed to challenge their ability to understand a social situation. High-functioning individuals with autism are being scanned to sort out the neural circuitry of social versus mechanical knowledge .[19, 20]

Yet another series of MRI studies is pinpointing brain structural abnormalities

associated with the severity of attention deficits in people with autism.[21] For example, the researchers have shown that decreased volume in an area of the brain's parietal lobe correlates with the degree of behavioral impairment in detecting stimuli located outside a principal focus of visual attention.

A project at the University of North Carolina has been assessing the relation between brain anatomy and autism through MRI scans of very young children with autism.[22] The aim is to get a better picture of the development and timing of the brain enlargement that occurs in autism between 18 and 35 months. To relate these findings to another developmental disorder of known origin, the researchers have joined forces with colleagues at Stanford University to similarly follow the brain development of children with Fragile X syndrome.[23, 24] These studies will illuminate genetic and environmental factors that influence normal and abnormal brain development and may help to clarify subtypes of autism.

Animal Models

Studies in monkeys hold great potential for understanding autism, since their brains resemble those of humans thus offering valuable clues. For example, NIMH-funded investigators are continuing to examine monkeys in which early injury to the brain's limbic system, or emotional hub, interfered with the establishment of social and emotional bonds.[25] Experiments in monkeys by NIMH intramural scientists found that loss in infancy of two key limbic structures, the amygdala and hippocampus, results in social and emotional abnormalities strikingly similar to autism, in both nature and time course, by 6 months of age. The monkeys with brain lesions, like some autistic children, showed an absence of social interactions, lack of normal facial expressions and body language, and stereotyped behaviors. Also as in autism, the problems emerged only after early infancy and remained permanent. Other monkeys in which a lower part of the temporal lobe was removed developed milder symptoms that substantially abated as they grew older. This study, combined with clinical findings, point to the limbic system structures as likely sites of damage in autism.[26] Such behavioral and neuroanatomical research may help to pinpoint brain circuit abnormalities in autism and ultimately lead to intervention strategies. Findings relevant to autism may also emerge from planned studies of proteins in the animal brain.

Assuming there is a developmental abnormality in autism, due to a gene defect or gene/ environment interaction, some genes are likely to turn on too much or too little—or in the wrong place. This may interfere with the migration and wiring of embryonic brain cells during early development, or with the way cells function. In collaboration with other NIH Institutes and the private sector, NIMH is mounting efforts to expand the set of available tools for discovering such molecular mistakes.

For example, studies in mice are identifying the neural basis of complex behaviors. The mouse has become a critical model in studying human disease because scientists have access to many specially bred strains—each expressing distinctive physiological and behavioral characteristics—and know an enormous amount about mouse genetics. Rapidly-evolving technologies now make it possible to insert, knock out, or mutate mouse genes,

quickly breed a generation that expresses the change, and then see how it affects behavior. When autism-linked genes are discovered, they will be inserted and expressed in mice to find out what they do at the molecular, cellular, and behavioral levels. Researchers will be able to track a wiring abnormality, a cell migration abnormality, or other anomaly that may lead to symptoms in humans.

Clinical Genetics

While it is known that heredity plays a major role in complex behavioral disorders like autism, the identification of specific genes that confer vulnerability to such disorders has proven extremely difficult. Detecting multiple genes, each contributing only a small effect, requires large sample sizes and powerful technologies that can associate genetic variations with disease and pinpoint candidate genes. And even after human disease vulnerability genes are found, sophisticated techniques will be needed to find out what turns them on, what brain components they code for, and how they affect behavior. Although by no means assured, the prospect of acquiring such molecular knowledge holds great hope for the engineering of new therapies.

Evidence suggests that some family members of people with autism may share with them milder, but qualitatively similar, behavioral characteristics of autism.[27] For example, they may have mild social, language or reading problems. A multi-site team of NIMH-supported investigators has been studying such families to characterize these behavioral traits in hopes of discovering sites in the genome associated with them. In the latest phase of these studies, neuropsychological characteristics of relatives of individuals with autism and autism spectrum will be compared with those of people with injuries to brain areas implicated in autism, such as the amygdala and frontal cortex. Patterns of co-occurrence of the characteristics will be examined in individuals and families.[28]

Four previously undetected chromosomal sites strongly linked to autism have been discovered by the largest and methodologically most sophisticated genome-wide screens to date, funded, in part, by NIMH. Two studies, led by investigators at Columbia University and the University of Oxford, add regions on chromosomes 2, 5, 8, and 17 to a growing list of areas likely harboring autism-predisposing genes. They also add to previous evidence implicating areas on chromosomes 7, 16 and 19.[29,30]

Although one chromosomal region, 7q, had turned up consistently in such screens, no specific candidate gene there had yet been pinpointed until NIMH-funded researchers, led by a team at the University of Iowa, discovered that variants of a particular gene in the 7q region, expressed in human thalamus, may be associated with autism susceptibility.[31] It is a member of a family of genes that influences brain development.

To increase the likelihood of finding genes for autism, researchers are increasing the statistical power of human data sets. One genome-wide screen of autism vulnerability genes in 110 families showed suggestive evidence for linkage to ASD on several chromosomes. In a follow-up analysis, the researchers increased the sample size threefold while holding the study design constant, so that 345 families (each with at least two siblings affected with autism or ASD), were included. The most significant findings were on chromosome

17q conspicuously near the gene that codes for the serotonin transporter and on 5p. Analyses from this largest data set studied to date implicate brain serotonin systems in autism. This finding is congruent with those from other studies which show evidence of elevated blood serotonin levels both in patients with autism and in their unaffected first-degree relatives. Studies also show that drugs that selectively target 5-HTT can ameliorate some autism-related symptoms. Serotonin-related neural circuits may thus provide targets for new drug development.[32]

Continued progress in molecular genetic studies of autism will require very large sample sizes, and the pooling of ever larger numbers of families. In addition, future studies likely will require the identification and characterization of autism-related traits correlated with liability to produce disease. NIMH is supporting efforts to reach out to families to build a library of DNA samples and clinical data that can be broadly distributed to researchers through the NIMH Human Genetics Initiative (http://www.nimhgenetics.org/). For example, in March of 2002 NIMH announced the awarding of a grant totaling more than $6 million, over five years, to researchers at the University of California, Los Angeles, for a major expansion of the Autism Genetic Resource Exchange (AGRE) gene bank, a collaborative effort with the citizens group Cure Autism Now (CAN). The goal is to add 300 more families to this resource, which conducts 2-hour in-home screenings of families that have more than one member diagnosed with autism, PDD or Asperger's syndrome.[33] A similarly ambitious $5 million public/private collaboration between the National Alliance for Autism Research (NAAR) and NIMH, NICHD, NINDS, NIDCD was recently announced. The NAAR Autism Genome Project is also focused on finding genes associated with the autism spectrum disorders.

Using the AGRE data set, researchers at Rutgers University recently discovered a strong association between a gene in the 7q region and autism. Among 167 affected families, children with autism were twice as likely as unaffected children to have inherited a particular variant of a gene called ENGRAILED 2. The team is now attempting to replicate the finding in a much larger sample, using NIMH-funded data sets funded in part by NIMH.[34]

Developmental Neurobiology

To function properly, the brain must be wired correctly during critical periods in early development. Mistakes in this process, resulting in circuitry gone awry, are hypothesized to occur in neuro-developmental disorders like autism. NIMH-funded researchers recently developed a way to discover the normal wiring diagram of the mammalian brain.[35] The technique, a type of "gene trap," provides a shortcut for identifying—from among the tangled trillions of neural connections—just the machinery involved in brain wiring. The trick for finding the needle in a haystack: attach a molecular tag to the needle. Through genetic engineering, lines of mice are bred to express telltale mutations. Brain neurons harboring particular wiring molecules are revealed by a blue tint, while their tentacle-like extensions, or axons, are colored purple.

By breeding strains of mice in which particular genes are knocked-out, other Institute-funded researchers have been discovering the molecular machinery of the

guidance systems used by such migrating embryonic neurons. When they knocked-out the cell's antennae for receiving vital signals from guidance chemicals, the tentacle-like axons failed to make the proper connections.[36]

After reviewing evidence pointing to abnormal brain development in autism, researchers at the University of California, supported in part by NIMH, have proposed that the disorder stems from mechanisms gone awry that normally regulate brain growth. This "growth dysregulation hypothesis" holds that the anatomical abnormalities seen in autism are caused by genetic defects in brain growth factors. Due to abnormal timing in the starting and stopping of growth in neurons and supportive tissue, there is premature overgrowth in some brain structures and reduced growth or excessive cell loss in others, the researchers suggest.[37] Although the head size and brains of children with autism are slightly smaller than normal at birth, they undergo a spurt of excessive brain growth soon thereafter. Increased head circumference by the end of the first year predicted an enlarged cerebrum and cerebellum by 2 to 5 years of age. Sudden, rapid head growth in an infant may signal for risk of developing autism, the researchers propose.[38]

Neuropsychology

NIMH-supported neuropsychologists are dissecting the nature of cognitive deficits in autism and related disorders. Since identification of the syndrome more than 60 years ago, clinicians and researchers have been intrigued with the uneven ability profiles of individuals with autism. While many affected individuals show generalized deficits, many also show areas of intact functioning. The nature of these deficits and strengths, their relationship to clinical symptoms, implications for treatment, and implications for underlying neurobiology, are the focus of these studies.

Adults with autism show more executive function deficits than those with other developmental disabilities. Executive functions include the ability to plan ahead, work toward a goal and to hold a mental representation "on-line" in working memory. To see if such deficits might underlie the syndrome, NIMH-funded researchers at the University of Denver compared the performance of preschoolers with autism with age-matched controls on eight executive function tasks. Surprisingly, the children with autism performed as well or better than the control group, suggesting that developmental lags in this area are not specific to autism. A second study that tracked children's progress in performing a spatial reversal task over a year found no evidence that children with autism were growing into an executive deficit over time. Rather, the children without autism seemed to be growing out of a deficit. The two groups seemed to be on diverging developmental trajectories. These results cast doubt on the notion that autism stems exclusively from executive function deficits.[39]

Co-occurring Disorders

In addition to cognitive impairments, individuals with autism and other ASDs often suffer from multiple and severe mental and emotional problems. These include impulse-control disorders, obsessive-compulsive disorder, mood and anxiety disorders, mental retardation, and genetic disorders such as Fragile X. Such co-existing problems start early in life, are chronic, and

account for a substantial portion of outpatient, inpatient and residential services. They present immense challenges to clinicians and families, and the complexity of the psychopathology presents enormous research challenges. NIMH is developing and testing treatment and rehabilitative interventions for such co-occurring psychopathology.[40] Individuals with autism may also have co-occurring seizures and tuberous sclerosis, a genetic disorder that causes benign tumors to form in many different organs, primarily in the brain, eyes, heart, kidney, skin and lungs.

A key set of proteins involved in synaptic plasticity and neuronal growth, some of them likely implicated in ASDs, has been discovered by an NIMH-funded scientific team. Researchers at the University of Pennsylvania and the University of Illinois developed a new technique that revealed, in living neurons, a swath of secondary damage caused by the primary protein defect in Fragile X syndrome, the most common inherited form of mental retardation. Mental retardation is common in people with autism, and the new findings suggest that ASDs too may be traceable to this protein pathway. Gene knockout mice modeling the protein defect showed abnormalities in the distribution and quantities of some of the affected secondary proteins and the genetic material that makes them. A melding of genomics and proteomics, the new method, called Antibody Positioned RNA Amplification (APRA), can be applied in similar studies of other systems and cells.[41]

Defective fragile X mental retardation protein (FMRP) can have devastating effects because as an "RNA binding protein" it influences many other proteins in critical brain centers, like the hippocampus, a memory hub. FMRP regulates the synthesis and transport of a bevy of here to fore unknown associated proteins. Like a dispatcher in a truck depot, FMRP manages the shuttling of these "cargo proteins" from the cell's nucleus to supply the needs of its working parts, or cytoplasm. Much of the cargo turns out to be the genetic material (RNA) that makes proteins vital to synaptic maturation and communication between neurons—which breaks down if the 'dispatcher' can't do its job.

To discover FMRP's cargo proteins in cultured mouse hippocampal neurons, the researchers devised an intricate methodology (APRA) that takes advantage of the specific affinity that antibodies and short strands of genetic material have for particular genes and proteins. They joined an antibody that binds to FMRP with genetic material that, in turn, binds to genes associated with FMRP. The antibody positions the molecular probe close to the FMRP cargo so that it can be detected. Among genes expressed in the human brain, about 60 percent detected by the probe were directly associated with FMRP—again, many involved in synaptic plasticity and neuronal maturation.

Since some people with Fragile X syndrome show autistic behavior, the researchers suspected that some FMRP cargo proteins might also be associated with autism. Among the 81 proteins, 15 mapped to the same chromosomal locations as candidate autism genes. Mutations in some of the genes that code for these proteins may contribute to autism and other disorders characterized by autistic-like social impairment and stereotyped behavior.

Treatment

Both psychosocial and pharmacological interventions can improve the behavioral

and cognitive functioning of individuals with ASDs.[42] The increasing use of psychotropic medications to treat symptoms of autism and other childhood-onset psychiatric disorders has spotlighted an urgent need for more studies of such drugs in children. To meet this need, NIMH established a network of Research Units on Pediatric Psychopharmacology (RUPPs) in 1997 that combined expertise in psychopharmacology and psychiatry at several research sites. The network was expanded to include psychosocial interventions with the funding of additional network projects called the RUPP-PI (Research Units on Pediatric Psychopharmacology and Psychosocial Interventions) network. The RUPP and RUPP-PI networks are intended to become a national resource that will expedite clinical trials in children.[43, 44, 45] They include five groups specifically funded to evaluate treatments for autism. Studies are examining dose range and regimen of medications, and their mechanisms of action, safety, efficacy, and effects on cognition, behavior, and development. The RUPP network is nearing completion of a study examining the efficacy of methylphenidate for treating hyperactivity and impulsivity in children and adolescents with a variety of behavioral disorders. In one recent study, risperidone, one of a newer class of anti-psychotic medications, was successful and well tolerated for the treatment of serious behavioral disturbance in children with autism aged 5-17.[46]

The RUPP-PI network has launched a multi-site study investigating the effect of combined parent training and medication treatment on disruptive behavior in children with autism spectrum disorders. The study will test whether adding a program to teach parents behavior management techniques to a regimen of risperidone will add to treatment response and/or maintain treatment effects after discontinuation of the medication.[47, 48, 49]

Among other studies of psychosocial treatments in autism, two NIMH-funded research teams are evaluating parent training interventions that are tailored to the particular characteristics of the child and family. The investigators have demonstrated that an individualized approach enhances the effectiveness of their Pivotal Response Model, and that this, in turn, leads to positive changes in parents' confidence and feelings of empowerment.[50, 51, 52] The investigators are continuing their line of research on interventions development with a study investigating the efficacy of visual augmentation strategies for teaching communication skills to nonverbal children with autism. [53,54,55]

The NIH Autism Coordinating Committee (NIH/ACC) coordinates efforts of NIMH, NICHD, NINDS, NIDCD, and NIEHS to facilitate research on interventions for individuals with autism and autism spectrum disorders. In November 2000, six grants were funded in response to an RFA (Request for Applications)[56] for innovative methods and feasibility studies. These projects included behavioral and pharmacological treatments and are nearing completion. The STAART Centers funded in 2002 and 2003 (described above) include eight treatment projects that are in development or underway. Foci of the intervention projects include efficacy of early interventions, efficacy of treatments for social deficits, efficacy trials for pharmacotherapy, and understanding the variability of response to treatments. Through these and other initiatives, the

Institutes hope to encourage multi-disciplinary partnerships to develop and improve treatments for individuals with autism spectrum disorders.

The NIH/ACC sponsored a workshop "Research on Psychosocial and Behavioral Interventions in Autism: Confronting the Methodological Challenges" in September 2002.[37] The purpose of the meeting was to review the state-of-the-science with regard to psychosocial, behavioral, and educational interventions for children with autism; to examine the barriers to progress in the field; and to discuss potential strategies for overcoming the barriers. An outcome of the meeting was the formation of ongoing working groups of scientists focusing on methodology and design issues.

Services

As part of its initiative on Child and Adolescent Interdisciplinary Research Networks, NIMH awarded a grant in FY03 to the University of California-Davis, "Enhancing Mental Health Services to Children with Autism." This innovative effort will create, for the first time, a formal, interdisciplinary research network of faculty and community representatives focused on an understudied population, children with autism and their families in rural communities. The network will review barriers and develop guidelines for implementing telehealth technologies such as clinical telemedicine, distance learning, and information distribution for the delivery of high quality, empirically supported, coordinated mental health services.

NIH Collaboration

NIMH supports research on autism in collaboration with the National Institute of Child Health and Human Development, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, and the National Institute of Environmental Health Sciences.

The Broad NIMH Research Program

NIMH supports and conducts a broad-based, multidisciplinary program of scientific inquiry aimed at improving the diagnosis, prevention, and treatment of mental disorders in people of all ages. Increasingly the public, as well as health care professionals, are recognizing these disorders as real and treatable medical illnesses of the brain. Still, there is a need for more research that examines in greater depth the relationships among genetic, behavioral, developmental, social, and other factors to find the causes of these illnesses. NIMH is meeting this need through a series of research initiatives.

- **NIMH Human Genetics Initiative**

This project has compiled a large repository of clinical information and DNA obtained from families affected by schizophrenia, bipolar disorder, autism, Alzheimer's disease, and other mental disorders. Qualified scientists are given access to these data and genetic materials in order to characterize the genetic bases of mental disorders. See http://www.nimh.nih.gov/research/geneticsintiative.cfm for more information.

- **Neuroinformatics: Human Brain Project**

This Federal effort is using state-of-the-art computer science technologies to organize the immense amount of data being generated through neuroscience and related disciplines, and to make this information readily accessible through the World Wide Web for simultaneous study by interested investigators. Because the scope of the Human Brain Project extends to all facets of brain and behavioral research and includes a range of technology sciences, this initiative is sponsored, in a coordinated fashion, by fifteen Federal organizations across four Federal agencies: the National Institutes of Health, National Aeronautics and Space Administration, National Science Foundation, and U.S. Department of Energy. For additional detailed information see http://www.nimh.nih.gov/neuroinformatics/index.cfm.

- **Prevention Research Initiative**

Prevention research can be broadly characterized as seeking to understand the development and expression of mental illness throughout the course of life so that appropriate interventions can be designed and applied in order to prevent mental disorders and promote mental health. Advances in biomedical, behavioral, and cognitive sciences led NIMH to formulate a plan, *Priorities for Prevention Research at NIMH* (http://www.nimh.nih.gov/publist/984321.htm), which marries these sciences to prevention efforts. Focusing on the expansion of prevention research to include the prevention of relapse, disability, and co-occurring conditions, the plan provides a blueprint for NIMH prevention research in the years to come.

Key Areas of NIMH Research

In total, NIMH supports more than 2,000 research grants and contracts at universities and other institutions across the nation and overseas. It also conducts basic research and clinical studies at its own facilities on the National Institutes of Health campus in Bethesda, MD, and elsewhere. Key areas of NIMH research include:

- basic research on behavior, emotion, and cognition to provide a knowledge base for a better understanding of mental illnesses;
- basic sciences, including cellular and molecular biology, developmental neurobiology, neurochemistry, neurogenetics, and neuropharmacology, to provide essential information about the anatomical and chemical basis of brain function and brain disorders;
- neuroscience and behavioral aspects of acquired immune deficiency syndrome (AIDS) and behavioral strategies to reduce the spread of human immunodeficiency virus (HIV);
- clinical trials to test interventions to treat, prevent, and reduce the frequency of mental disorders and their disabling consequences;
- mental health services research, including mental health economics and improved methods of services delivery;
- co-occurrence among mental disorders and with substance abuse and other medical conditions, such as depression and heart disease;
- the prevalence of mental disorders;
- risk factors for mental disorders and protective factors against them;
- suicide, suicidal behavior, risk and protective factors, and preventive interventions;
- differences in mental health and

mental illness among special populations;

- children and adolescents who suffer from or who are at risk for serious mental disorders and learning disabilities;
- aging and mental health, including the impact of caregiving;
- responses to terrorist acts and major traumatic events; and
- psychotherapies and pharmacotherapies for specific disorders.

For More Information

The NIMH Office of Communications carries out educational activities, such as the *Real Men Real Depression* campaign (http://menanddepression.nimh.nih.gov), and publishes and distributes research reports, press releases, fact sheets, and informational materials intended for researchers, health care providers, and the general public. All of these materials, and this fact sheet, are in the public domain and may be copied or reproduced without permission from the Institute, although citation of NIMH as the source is appreciated. Materials may be downloaded directly from the NIMH Web site, or hard copies may be ordered through the mail.

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