NIH Centers of Excellence

Autism Centers of Excellence

Overview

Why the ACE Were Established
Recent studies suggest that autism spectrum disorders (ASD) may affect approximately 1 in 150 children in the United States. Because of the urgent need to better understand the causes of ASD and develop treatments for these serious and disabling disorders, Congress passed the Combating Autism Act of 2006 (Pub. L. No. 109-416), which emphasized the need for expanding research and improving coordination among NIH Centers of Excellence focused on ASD. The new Autism Centers of Excellence (ACE), scheduled for funding in FYs 2007 and 2008, will focus on identifying the causes of ASD and developing new and improved treatments.

Under the new ACE program, NIH will consolidate two existing programs in autism research, the Collaborative Programs of Excellence in Autism (CPEA) and Studies to Advance Autism Research and Treatment (STAART). NIH launched the CPEA program in 1997 to support significant, collaborative research on the possible causes of autism, including genetic, immunological, and environmental factors. In 2000, Congress passed the Children’s Health Act (Pub. L. No. 106-310), which called on NIH to expand, intensify, and coordinate autism research activities, and to establish at least five Centers of Excellence for autism research. In response, the five NIH institutes participating in the NIH Autism Coordinating Committee (NIH ACC)—NICHD, the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Mental Health (NIMH), and NINDS—launched the STAART Centers Program to unite expertise, infrastructure, and resources focused on major questions about autism, including treatment research.

Although the CPEA and STAART programs collaborate extensively and will be consolidated under the new ACE program, the CPEA is not congressionally mandated. Therefore, this report will focus on the goals, activities, and accomplishments of the congressionally mandated NIH Centers of Excellence for autism research, namely the STAART and ACE Programs (see Tables 4-6 and 4-7).

How the Centers Function Within the NIH Framework
The Children’s Health Act of 2000 also established an Interagency Autism Coordinating Committee (IACC), which includes Federal agencies and members of the public appointed by the Secretary of the U.S. Department of Health and Human Services (HHS). At the request of Congress, the IACC developed an Autism Research Matrix in 2003. The matrix serves as a guiding framework for directing autism research funded by NIH. ACE grantees will focus on the goals of the Autism Research Matrix, particularly in the areas of identifying causes of ASD and developing treatments.

The NIH ACC conceptualized the program goals of the STAART and ACE programs, and the ICs share responsibilities

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30 For more information, see http://www.cdc.gov/MMWR/preview/mmwrhtml/ss5601a2.htm
for administration and oversight. For example, NIMH administers the individual STAART centers, and NICHD administers the Data Coordinating Center (DCC). Thus, there is input from multiple ICs in managing these programs, which are funded through cooperative agreements. Grants that support centers affiliated with the ACE program are administered through a program officer and grants management officer at the awarding IC. The STAART and ACE programs represent less than a quarter of the total NIH commitment to autism research. The rest is distributed across contracts, grants of many types, and cooperative agreements.

**Description of Disease or Condition**

Autism was first described in 1943 by Leo Kanner as a disorder “characterized by extreme aloneness and a desire for the preservation of sameness, with a variety of behavioral (cognitive, affective) symptoms derived from them.” Over time, the description of this complex neurodevelopmental disorder has broadened. ASD includes a group of developmental disorders of early childhood that vary in severity, share common clinical features, and persist throughout the lifetime of the individual. These disorders share the core clinical characteristics of impairment in verbal and nonverbal communication skills and social interactions, and restricted, repetitive, and stereotyped patterns of behavior. ASD ranges in severity; “classic” autistic disorder is the most disabling, whereas others, such as Asperger’s disorder, have fewer or milder symptoms. Among children at the more severe end of this spectrum, mental retardation, seizures, and self-injurious behaviors are common.

Symptoms of ASD often are first identified by a child’s primary caregivers. There may be delays or plateaus in a child’s attainment of developmental milestones, such as the onset of speech. In some cases, the first signs of an ASD occur in young children who appear to regress after they seem to have been developing normally. For most children, the diagnosis of an ASD can be reliably made by age 3. The current diagnostic criteria and classifications of ASD represent progress in identifying a core set of developmental symptoms that, in the past, might have been diagnosed differently because the criteria were more narrowly defined than they are today.

**Burden of Illness**

ASD causes tremendous economic and social burdens for families and society at large. Although ASD varies greatly in character and severity, it occurs in all ethnic and socioeconomic groups and affects every age group. Currently, there is no coherent and comprehensive system of care for affected individuals. People with autism may receive private and public services in special education settings, hospitals and university medical centers, and residential treatment facilities, among others.

Some scientists and economists have estimated that the combined direct and indirect costs to care for all Americans with ASD during their lifetimes exceed $34 billion and that each individual accrues approximately $3 million in costs over his or her lifetime. Families often incur large debts related to medical and educational services not covered through public programs or medical insurance. In addition to financial challenges, autism often leads to profound emotional hardships for patients and their families.

Current CDC estimates of the prevalence rate of ASD are as high as 6.7 children per 1,000. The total number of individuals in the United States with an ASD diagnosis is unknown. However, CDC estimates that up to 560,000

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32 Ganz ML. Arch Pediatr Adolesc Med. 2007;161:343-9, PMID: 17404130

33 CDC, 2007
individuals age 21 and younger have an ASD (assuming a prevalence rate of 1 in 150, a birth rate of 4 million children per year in the United States, and a constant prevalence rate over the past 20 years). Prevalence estimates, which refer to the number of affected individuals at a given point in time, have increased markedly since the early 1990s, but it is unclear whether there is also an increase in incidence, a measure of the number of new cases across time in the same population. It is also unclear whether the rise in prevalence is due to factors such as the use of the broader category of ASD or earlier and better diagnosis of ASD. A similar increase in ASD prevalence has occurred in other countries. Boys are approximately four times as likely as girls to have an ASD.34

Scope of NIH Activities: Research and Programmatic
The primary goals of the STAART Centers Program are to support cohesive teams of accomplished biomedical, behavioral, and clinical investigators to pursue common objectives in ASD research, and to establish a research network that is capable of implementing large treatment, diagnostic, genetic, neuroscientific, and other studies of ASD that were previously not feasible. The new ACE program will improve the efficiency of administering the STAART and CPEA centers by consolidating them into one program and will broaden the pool of researchers involved in ASD research.

Each STAART center supports clinical and basic studies, including at least one study focused on treatment. The centers provide core resources that enhance ongoing research by providing critical infrastructure, including centralized patient recruitment and tracking, with standardization of clinical data. The centers are multidisciplinary and include outstanding investigators in related disciplines.

Although the Children’s Health Act of 2000 required a minimum of five centers, NIH funded eight centers because of the exceptional quality of the applications. Scientific investigations of the STAART Centers Program focus on genetics, neurobiology, behavioral interventions, drug therapies, and diagnosis, in accord with the legislation. Each center conducts a unique set of studies, including investigations to determine how parents can better assist children with ASD, research on the neurobiological causes of ASD and the impact of early intervention, and projects to examine the possible role of serotonin in ASD, including a neuroimaging study of serotonin pathways and receptors comparing people with Asperger’s disorder to people with more typical development.

To identify genes that confer susceptibility to the development of autism, STAART centers use and contribute to the NIMH Center for Collaborative Genetic Studies, a repository of DNA, cell cultures, and clinical data that serves as a national resource for researchers studying the genetics of complex mental disorders. This collaborative program, established partly through an innovative public-private partnership, provides a major resource for qualified investigators. Another important resource for studies on ASD is the DCC, which provides data management and statistical support for autism research activities, including those conducted at the STAART centers. The DCC supports pharmacologic, multisite, randomized control trials and works with the data collection and analysis personnel at each center to standardize data forms and formats so that centralized data storage can be accessed.

NIH Funding for FY 2006 and FY 2007
The total funding for autism COEs—STAART Centers (U54s), DCC (U01), and the ACE program, which includes centers (P50s) and networks (R01s)—was $12.8 million and $25.5 million in FY 2006 and FY 2007, respectively.

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34 Fombonne E. J Clin Psychiatry 2005;66 Suppl 10:3-8, PMID: 16401144
Outcomes: FY 2006 and FY 2007 Progress Report

Programmatic and Research Accomplishments
The STAART program is contributing to the understanding of ASD by investigating areas such as early detection, efficacy of early behavioral interventions, neural bases of core features, efficacy trials for pharmacotherapy, genotypic and phenotypic responses to treatment, and identification of susceptibility genes. A few accomplishments of the STAART program are highlighted briefly below.

- Early Detection: The Kennedy Krieger Institute of Johns Hopkins University has conducted a prospective longitudinal study of children who are at high risk for autism because they are younger siblings of children with an ASD. Important implications of this study are that autism screening could be usefully implemented near the first birthday, but screening would need to be repeated near the second birthday to detect children whose development becomes atypical during this interval35.
- Neurological Characteristics: Researchers at other STAART centers are evaluating specific neural mechanisms that perform atypically in people with autism. For example, teams at the University of Washington, Boston University, and the University of Wisconsin have used functional MRI to study face perception, which is altered in people with autism. The researchers found that the integration of perceptual and emotional processing mediated by the fusiform cortex and the amygdala, a specific brain pathway, is altered, which may explain the atypical visual scanning of faces that is characteristic of autism36. Research suggests that other brain pathways, such as those of the basal ganglia, may also contribute to repetitive behaviors, a core symptom of autism37.
- Finding Effective Treatments: To identify a treatment for autism, STAART investigators have collaborated in a multisite study to evaluate the efficacy of a drug that selectively inhibits the activity of serotonin, a neurotransmitter in the brain that may play a role in the repetitive behaviors associated with autism. The study subjects have completed the treatment phase of the trial and preparation for data analysis is under way. A manuscript with results is expected to be submitted for publication in 2008.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of ASD Research
To improve the effectiveness, efficiency, and outcomes of ASD research, the NIH ACC planned the ACE program to address the need for the following:

- Enhanced coordination of ASD Research: Coordination of ASD research is an important priority for all stakeholders. This effort has been spearheaded by the IACC, which facilitates information exchange among the member Federal agencies and patient advocacy groups and coordinates autism-related programs and initiatives.

35 Landa RJ, et al. Arch Gen Psychiatry 2007;64:853-64, PMID: 17606819
• More collaborative studies: Collaborative studies allow ASD researchers to combine data from their diverse samples and increase statistical power for detecting many types of experimental effects.

• Improved data standardization and sharing: In the past, data gathering in autism-related research was separated by format, location, and method of analysis, which makes cross-site data comparisons difficult. The National Database for Autism Research (NDAR) is building on the gains made by the DCC by creating a common data platform for data gathering and analysis. The NDAR will make it easier and faster for researchers to gather, evaluate, and share autism research data from a variety of sources and will allow the seamless integration of data, research tools, and institutions across the United States and internationally. All ACE Centers and Networks will make data contributions to NDAR.

Evaluation Plans
The Combating Autism Act of 2006 expanded the scope of the IACC. In accordance with the new law, the IACC will develop and update annually a summary of research advances in ASD, as well as a strategic plan, and will monitor and make recommendations about Federal ASD-related activities. The priorities and progress of the ACE program will be an integral component of these annual activities.

In 2010, HHS will provide Congress with a progress report on activities related to ASD, to include contributions from the ACE program. The report will discuss information about the incidence of ASD, average age for diagnosis, average age for intervention, effectiveness and outcomes of interventions by subtypes, and effectiveness and outcomes of newly developed intervention strategies for individuals with an ASD. In addition, NIH will consider how best to assess the effectiveness of the ACE Program and will identify ways to improve implementation of the program.

Future Directions
The strategic plan for autism research to be prepared by the IACC will be developed with broad representation from Federal agencies as well as members of the public. In addition, private organizations that support autism research will be invited to participate in the planning process so that coordination will occur across autism funding groups, both public and private.

NIH created the ACE program to maximize coordination and cohesion of NIH-sponsored ASD research efforts and to broaden the pool of researchers involved in ASD research. Early in 2006, NIH solicited proposals for the ACE centers and networks with an application deadline of August 2006. NIH instructed grantees to direct their research projects toward the goals of the Autism Research Matrix, particularly in the areas of etiology and treatment. NIH made seven ACE awards in 2007 and anticipates making four additional awards in 2008.

The NDAR will be needed to achieve several of the goals of the IACC Autism Research Matrix, such as “establish[ing] resources for genotype/phenotype studies (i.e., bioinformatics, genetic repository).” NDAR also will coordinate data with other Federal databases, such as the NIMH Center for Collaborative Genetic Studies, which stores DNA, cell cultures, and clinical data, and serves as a national resource for researchers who study the genetics of complex mental disorders, including autism.