An intensive early intervention program for very young children with autism, some as young as 18 months, is highly effective for improving IQ, language ability and social interaction, a comprehensive study has found.

The study, published late in 2009 in the journal Pediatrics, described the first rigorous, controlled examination of the Early Start Denver Model, an intensive early intervention program appropriate for children with autism who are younger than 2½ years. This program combines applied behavioral analysis teaching methods with developmental relationship-based approaches.

“Infant brains are quite malleable, so, with this therapy, we’re trying to capitalize on the infant brain’s potential for learning in order to limit autism’s deleterious effects and to improve their outcomes,” says study co-author Sally Rogers, a M.I.N.D. Institute researcher and professor of psychiatry and behavioral sciences.

The Early Start Denver Model (Denver-model) integrates relationship, developmental, and systematic teaching practices from the behavioral sciences. It was originally developed by Rogers, study co-author Geraldine Dawson, and their collaborators at the M.I.N.D. Institute, University of Washington, and University of Colorado Health Sciences Center.

In the study, participants were separated into two groups, one that received 20 hours per week of Denver-model intervention and another that was referred to community-based programs for therapy. At the conclusion of the study, the IQs of the children in the intervention group had improved by an average of approximately 18 points,
Newborn screening for fragile X

Led by Flora Tassone, UC Davis M.I.N.D. Institute researchers are in the second of a five-year, $2.3 million study using a blood spot test they developed to screen as many as 30,000 infants for the fragile X mutation, laying the groundwork for universal newborn screening for the single most common inherited cause of mental retardation.

“Identification of the condition in early infancy would allow families to seek crucial early intervention services for their children that we hope will mitigate the disabling effects of the disorder,” said Tassone, research biochemist in the Department of Biochemistry and Molecular Medicine and a researcher with the M.I.N.D. Institute.

The test was developed by Tassone and Paul Hagerman, professor of biochemistry and molecular medicine. It uses small drops of blood drawn from male and female infants taken after birth to evaluate the status of the fragile X gene.

The study is part of a larger grant from the National Institutes of Health to the Fragile X Research Center at the Center for Human Development and Disability at the University of Washington. The grant, funding studies at several institutions, is examining various aspects of fragile X gene function. The M.I.N.D. Institute newborn screening study is being conducted in cooperation with Rush University Medical Center in Chicago.

Tassone’s research focuses on understanding the genetic basis of neurodevelopmental disorders, including fragile X syndrome and autism spectrum disorders, with specific emphasis on the identification of susceptibility genes and their interactions with environmental factors.

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compared to a little more than four points in the comparison group.

“It’s unlikely that these differences are due to the Denver-model group receiving more hours of intervention, since the children in the community sample averaged almost as many hours of therapy a week,” said Rogers. “We believe that the Denver-model children made more progress because they were involved in carefully structured teaching and a relationship-based approach to learning, with many learning opportunities embedded in their play.”

Before clinicians can be confident that it is a powerful intervention, this model should be tested by others, Rogers said. That replication is now being conducted by Rogers at the M.I.N.D. Institute and by colleagues at the University of Washington and University of Michigan in a study funded by the National Institute of Mental Health and the National Institute of Child Health and Development (NICHD).

“We’re looking for children ages 12 to 24 months with an autism spectrum disorder for this new study,” says Rogers. “The Pediatrics study involved the youngest group thus far reported on, down to 18 months, and the current study reaches down to an even younger group — which leads to the question: ‘Just how early can we begin to intervene for autism, or autism risk?’”

To that end, her team has just been funded by NICHD to develop and test a preventive intervention for 6- to 11-month-olds at risk of autism spectrum disorder. “For this study, we’re looking for infants in the Sacramento area whose parents are worried about their children’s social responsiveness and the possibility that they might be developing autism.”

Families interested in either study are encouraged to contact Rogers or Beth Goodlin-Jones at (916) 703-0280.
Psychopharmacology advances in fragile X syndrome

Researchers at the UC Davis M.I.N.D. Institute are at the epicenter of a whirlwind of basic science research into psychopharmacological treatments for the most common inherited cause of intellectual disability, fragile X syndrome.

“This is a most exciting time for those of us studying fragile X,” said Randi Hagerman, a developmental and behavioral pediatrician and the medical director of the M.I.N.D. Institute. “We’re on the cusp of finding effective drugs to mitigate fragile X syndrome’s devastating impacts.”

In a pilot study reported in the Journal of Medical Genetics, researchers at the M.I.N.D. Institute and Rush University Medical Center, Chicago, have found that an oral drug called fenobam calms behavior and reduces hyperactivity and anxiety in patients with fragile X. These effects are similar to those found in previous studies in mice. One important role of the brain protein that is missing in fragile X syndrome (FMRP) is to offset the activity of a brain receptor protein called mGluR5 (short for metabotropic glutamate subtype 5). Fenobam acts as an mGluR5 antagonist, substituting for FMRP and checking the activity of mGluR5. The institute also is studying a second mGluR5 antagonist in a phase II trial investigating the drug’s safety and efficacy.

Two studies involving memantine, a novel class of Alzheimer’s disease medication that acts on the glutamatergic system by blocking certain glutamate receptors, also are underway. A trial studying potential uses of memantine for autism is funded by Forest Laboratories. The National Institutes of Health has funded a memantine study for people with fragile X premutation who have FXTAS.

The National Fragile X Foundation recently funded a trial of the antibiotic minocycline in adults with fragile X. This antibiotic is a potent inhibitor of matrix metalloproteinase 9 (mmp-9), a protein that delays the maturation of neuronal synapses.

“Minocycline lowers mmp-9 in the animal model, allowing the synapses to mature, and we’re very hopeful that it will have beneficial effects on children and adolescents with fragile X syndrome,” Hagerman said.

New clinic gives hope to patients with chromosome 22q11.2 deletion syndrome

A unique new clinic at the M.I.N.D. Institute has given new hope to families and children with chromosome 22q11.2 deletion syndrome, a poorly recognized and often misunderstood condition caused by the most common genetic deletion in human beings.

Chromosome 22q11.2 deletion syndrome (22q11.2DS) occurs when a small segment of the long arm of chromosome 22 is lost during prenatal development. It affects one in 4,000 people worldwide and is linked to more than 180 physical, psychological and behavioral anomalies, including congenital heart defects, cleft palate or other insufficiencies.

Children with the deletion also are at increased risk of attention-deficit/hyperactivity disorder, autism spectrum disorder, obsessive-compulsive disorder and, in adulthood, schizophrenia.

“Working together as an integrated team of researchers and clinicians, we’ve begun to gain a new and far more holistic understanding of the children we study and the families in which they live,” said Tony Simon, the clinic’s founder and an associate professor of psychiatry and behavioral sciences.

“The clinic has led us to consider the entire family as a context for each child’s development, including how their parents and siblings cope and interact not only with them but also with their teachers, doctors and other providers.”

Established in 2008, the clinic has provided a much appreciated clinical resource for families of...
Developing targeted treatments for FXTAS

Researchers at the UC Davis M.I.N.D. Institute are at the forefront of new initiatives to find targeted interventions for fragile X-associated tremor/ataxia syndrome, or FXTAS, a progressive neurodegenerative condition that causes tremor, balance problems, and dementia in older men and women with a mutated form of the fragile X gene.

The research is spearheaded by Randi Hagerman, a pediatrician and M.I.N.D. Institute medical director, and Paul Hagerman, a professor of biochemistry and molecular medicine and director of the NeuroTherapeutics Research Institute (NTRI). The Hagemans identified FXTAS in the late 90s as resulting from the same gene that causes fragile X syndrome, through research on grandfathers of children with fragile X.

NTRI has found a new connection that takes researchers back to the study of children: people with FXTAS have neurodegenerative problems as children, with symptoms such as emotional or intellectual problems.

“The expanded repeat is causing dysregulation in these cells at a very young age,” said Paul Hagerman. “This explains why some of the children who are carriers, those with 55 – 200 repeats, may have problems as youngsters and degenerative changes later in life. NTRI has enabled us to close the circle from children to grandparents and back to children again.”

Until now, no controlled trials of medications specifically for the treatment of FXTAS have been conducted. In 2007, Paul Hagerman and his team received $21.8 million from the National Institutes of Health to develop FXTAS treatments. The five-year grant established NTRI, which is at the hub of an international research consortium focusing on FXTAS.

“We want to understand all aspects of how FMR1 gene mutations function, not only in FXTAS but also in diseases of the young, such as autism — the full-life spectrum of this disorder,” said Hagerman. “If our aspirations are fulfilled, we will eventually be able to develop effective treatments for all the diseases tied to FMR1.”

The NTRI roster includes several research teams sharing the goal of achieving and measuring targeted therapeutic responses in FXTAS.

Isaac Pessah, professor of molecular biosciences, along with Paul Hagerman, are using neuronal cell models to design and test novel therapeutic agents for FXTAS and pre-FXTAS cellular dysregulation.

Robert Berman, professor of neurological surgery, is leading a team that is building mouse models of the human genetic disorder to study the progression of FXTAS and eventually deter-
mine whether candidate medications alter the course of the disorder. Working with researchers at the Erasmus Medical Center in Rotterdam, Netherlands, and at the University of California, San Diego, Berman is creating a mouse model that will permit the mutant \textit{FMR1} gene to be turned on or off under experimental control. These researchers have also identified behavioral features in the mouse model that parallel behaviors in humans with FXTAS and will be a boon when drug trials appropriate for mice begin.

Randi Hagerman’s group is leading clinical trials, along with neuroimaging and other electrophysiological tests of the brain changes associated with FXTAS, to assess treatment effectiveness. The initial emphasis has been on the identification and assessment of various candidate therapeutic agents that might attenuate the effects of the RNA produced from the genes with expanded repeats.

Finally, Tony Simon, professor of psychiatry, and Susan Rivera, professor of psychology, are actively investigating the cognitive changes that occur in younger adults who may go on to develop FXTAS, and are relating their findings to the underlying molecular abnormalities that occur in this disease process.

Along with UC Davis Health System and Erasmus Medical Center, other consortium partners are the University of California, San Diego, the University of Colorado Health Sciences Center, and Scripps Research Institute.

Paul Hagerman explained that current treatment for FXTAS is empirical, based on anecdotal experience and on knowledge of what treatments work for other disorders. Several classes of medications are available to treat symptoms like tremor or balance problems, including the medications primidone, beta-blockers, carbidopa and levodopa. These have been reported anecdotally to benefit patients with FXTAS, as well. “However, the goal of our research is targeted treatment for this specific disorder; treatment that gets at the basis of the disease,” said Hagerman.

That’s good news for FXTAS sufferers who often had difficulty obtaining an accurate diagnosis, let alone treatment. Previously, affected individuals routinely were given other, descriptive diagnoses, such as “atypical Parkinson’s disease” and in many cases saw multiple neurologists in vain efforts to seek an accurate diagnosis. With NTRI’s contributions, those days are numbered, and effective treatments are on the horizon.

More information about FXTAS is available on the NTRI web site, \url{www.ucdmc.ucdavis.edu/NTRI}, and on the National Fragile X Foundation web site, \url{www.fragilex.org}
Virtual reality: an intervention for autism

Peter Mundy believes that because the brain continues to develop until a person is 18, intervention through adolescence is both a moral and neurodevelopmental imperative.

Mundy, the Lisa Capps Chair for Neurodevelopmental Disorders and Education, is a professor of education and of psychiatry and behavioral sciences, and the director of educational research at the M.I.N.D. Institute.

One goal of Mundy’s educational research efforts is to find new ways to help high-functioning children with autism. Thirty to 45 percent of persons with autism are high functioning. Most attend schools where they may spend part of their time in the classroom with typically developing children, and they want to fit in. To that end, Mundy is leading a promising research project testing virtual reality that he hopes will teach these children to make eye contact more readily.

“Looking at other people, and especially making eye contact, improves social communication and social learning,” said Mundy. “Making eye contact while talking can be difficult for many people. This is especially true for children with autism spectrum disorders.”

The project, created in collaboration with UC Davis postdoctoral scholar William Jarrold and groups at the University of Southern California and Stanford University, brings study participants into the research laboratory and places them before a computer screen. The glasses they wear allow a computer to track their head movements and determine where their gaze falls. Then they’re asked to read aloud and periodically look at each of three faces on the screen — or they’ll disappear.

“We’re exploring the use of virtual reality methods to help children with autism practice and feel more comfortable with looking at other people while talking,” Mundy said.

Mundy’s group has recruited 40 children aged 8 to 18 years to take part in the experiment. If the approach works, it could be adapted to multiple training protocols. Most importantly, such experiments help expand knowledge about the adolescent brain in general.

“We are just beginning to learn how the ability to talk and make eye contact changes and develops between 8 and 18 years of age in all children,” Mundy said.
Developing novel, integrated treatments for ADHD

Julie Schweitzer, an associate professor of psychiatry and behavioral sciences and researcher in attention-deficit/hyperactivity disorder (ADHD) at the M.I.N.D. Institute, is leading an innovative examination of therapies for individuals with ADHD. ADHD is the most common psychiatric disorder in childhood, affecting 3 to 5 percent of school-aged children in the United States. It is also a chronic illness that requires long-term management strategies.

More than their peers, children with ADHD tend to act impulsively and daydream.

Schweitzer’s team is teasing out what makes children with ADHD different. Their many research tools include:

- measurements of pupil size, an indicator of norepinephrine levels;
- functional magnetic resonance imaging (fMRI) scans, measuring changes in brain activity during cognitive tasks related to deficits associated with ADHD;
- event-related potential, a variation on EEG, focusing on electrical activity in the brain in response to a task (diagram above); and
- diagnostic behavioral measurements

“We’re measuring differences in brain functioning in relation to cognitive and emotional demands in subtypes of ADHD,” Schweitzer said. “Ultimately, we’re searching for targets for cognitive, educational and pharmacological therapies.”

Last summer, Schweitzer co-authored a paper published in the journal Pediatrics showing a link between attention problems, seen as early as kindergarten, and high school reading and mathematics achievement. Children’s inability to pay attention when they started school had the strongest negative effect on academic performance at the end of high school, regardless of their IQ. These results showed that early attention problems predict poor performance later in reading and mathematics.

Schweitzer’s basic research findings may shed light on what leads to these deficits in academic functioning. In a recent Child Neuropsychology study, she found that children with ADHD show more variable or inconsistent response times on memory tasks compared with typically developing peers. The study may explain why attention in a classroom may be fine one moment and poor at another, but cumulatively results in long-term negative effects on learning in the classroom.

Her team’s related study, published last year in the journal Brain Research, extended these findings with brain imaging data. Using fMRI, they found that in participants with ADHD neural activity in brain regions that should be less active when performing attention-demanding tasks remained high.

Schweitzer and her collaborators are testing a number of potential treatments for ADHD, including computerized training and comparing telemedicine versus face-to-face parent training. They’ve partnered with the Sacramento Unified School District in a project testing the effectiveness of parent workshops in increasing implementation of ADHD treatment recommendations.

The best outcome of this novel work, Schweitzer said, would be “identifying the underlying biological deficits associated with ADHD, so that we can develop targeted treatments and thereby improve the lives of people with ADHD and their families.”
The founding vision of the M.I.N.D Institute was a translational research enterprise whose scientists would endeavor to understand the biological underpinnings of neurodevelopmental disorders in order to create innovative prevention, treatments, and cures. While much of the work at the Institute is directed at understanding genetic, neurobiological, environmental and immunological causes of neurodevelopmental disorders, this issue of M.I.N.D. Matters highlights some of our ongoing treatment efforts. Current investigations of fragile X syndrome are an outstanding example of this. Randi and Paul Hagerman, colleague Flora Tassone, and others have capitalized on the known genetic and neurobiological factors of this disorder to launch biological detection and treatment studies of affected individuals, both young and old. Their interdisciplinary approach provides a model for similar efforts with other disorders.

While the targets for biological intervention in autism spectrum disorders are much less clear, innovative behavioral therapies developed by Sally Rogers and colleagues provide benefits in cognitive function and quality of life that are now being applied to children at risk for autism, even prior to definitive diagnosis. Director of Educational Research Peter Mundy is exploring the use of virtual reality techniques to help higher functioning individuals with autism become more comfortable and effective in carrying out social interactions. M.I.N.D. Institute scientist Julie Schweitzer has developed a multidisciplinary approach to understanding the underlying deficits in attention deficit hyperactivity disorder as a precursor to attempting various targeted interventions. Finally, Tony Simon has established an interdisciplinary clinic dedicated to research and treatment of individuals with chromosome 22q11.2 deletion syndrome. Using cognitive neuroscience approaches, his team is attempting to understand the cognitive deficits of this disorder with the ultimate goal of developing video gamelike therapies to reverse some of the disability. This is done in the context of a whole family approach to caring for the subjects in his studies.

This issue of M.I.N.D. Matters is in no way an exhaustive summary of the efforts of M.I.N.D Institute scientists and clinicians to develop the most innovative and effective treatments. But, it provides clear evidence that the commitment to prevention, treatment and cure is alive and well at the M.I.N.D. Institute.