Solving the mysteries of seizures caused by tuberous sclerosis

Epilepsy has many causes, and the seizures that characterize it can range from mild to debilitating or lethal. While these neurological lightning storms may be caused by abnormalities in the brain, the seizures themselves can produce additional brain damage.

A new research affiliate at the Center on Human Development and Disability at the University of Washington, Adriana Emmi, M.D., Ph.D., research assistant professor of neurological surgery, is engaged in basic research to further understand the mechanisms, cellular changes and genetic alterations that underlie control of electrical rhythms in the brain, with the ultimate goal of developing preventive or more focused therapies for seizures.

One of Emmi’s research projects, in collaboration with Philip Schwartzkroin, Ph.D., focuses on seizures produced by a genetic disease that can have devastating effects on many systems in the body: Tuberous sclerosis—also called tuberous sclerosis complex or TSC—is characterized by tumors that grow in the brain and on other vital organs including the kidneys, heart, eyes, lungs and skin.

In the brain, TSC produces cortical tubers—root-like growths for which the disorder is named. Epileptic seizures of all types are an almost universal symptom of TSC, beginning with infantile spasms. One of many perplexing aspects of the disorder is that seizures often originate in areas of the brain away from the tubers.

According to the National Institute of Neurological Disorders and Stroke, approximately half to two-thirds of people with TSC develop developmental disorders, ranging from mild learning disabilities to severe mental retardation. Retardation is highly likely if seizures begin in the first year of life. Severe behavior problems may occur, and some individuals may exhibit autistic behaviors.

TSC is often misdiagnosed and may go unrecognized for years. There is no cure, although symptoms can be treated. With an incidence of about one in 6,000 births, TSC affects at last a million people around the world, in all ethnic groups and in both males and females.

While some individuals may inherit TSC, most cases result from spontaneous mutations in one of two genes: TSC1, on chromosome 9, and TSC2, on chromosome 16. The normal genes produce proteins—hamartin in the case of TSC1 and tuberin in the case of TSC2—that regulate the processes by which nerve cells divide to form new cells with individual characteristics. Without the proteins produced by normal genes, cell division is unregulated and unchecked tumor growth results.

“The connections between the gene mutations and the cortical tubers, and between the tubers and seizure development are unclear,” said Emmi. “How the mutation gives rise to aberrant brain growths is still a puzzle.”

Her research focuses on the mutated TSC2 gene, which has been produced in a genetically manipulated laboratory animal, the “Eker rat,” which carries the same mutation found in humans. The animal model was developed by Raymond Yeung, M.D., UW associate professor of surgery. Other research collaborators are Donald Born, M.D., Ph.D., assistant professor of neuropathology and also a CHDD research affiliate; and Jurgen Wenzel, Ph.D., who like Schwartzkroin is a former UW faculty member now at the University of California at Davis.

“This rat model offers an opportunity to examine how the disease develops, to study the cell types affected by TSC, and to identify some potential targets for therapeutic intervention,” said Emmi. “We know seizures are related to the tuberous malformations, but sometimes seizures appear in areas of the brain where there are no malformations. This is a very big issue, because surgery is one of the therapeutic options. For some children, removing the tubers stops the seizures. But for others, we have to remove...”

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tissue in intact areas of the brain where there are seizures but no tubers. By studying this rat, we are trying to understand the basic mechanisms of the seizures and how the tubers generate seizures at the site, or away from the site, of the malformation."

The Eker rat carries the TSC2 mutation from both sides of its parentage, and thus is characterized as /-/-. Since animals with the +/- genotype do not survive long because of severe disease symptoms, one component of the research involves animals of the +/- genotype, where the mutation is inherited from one parent. This animal survives longer term because it develops the disease in a less severe form.

Seizures are induced in normal and Eker rats by injecting an epileptic agent or by exacerbating the malformations with x-radiation. With anatomical/functional guidance provided by FMRI, electroencephalogram (EEG) recordings are made, with electrodes placed both on the surface and deep within the brain. "The simultaneous use of both EEG and FMRI may offer a greater understanding of the relationship between the malformations and the seizures," said Emmi.

Another component of the research is the characterization of +/- cell properties by extracting fetal brain cells from animals of the /-/- genotype. The goal is to stimulate the cells to replicate and establish cell lines that can be kept in culture for generations. These cells will be transplanted into normal rat brains to determine whether the mutated cells induce tubers to appear, to understand the interval between the appearance of the malformations and the appearance of seizures, and to determine whether the malformations provoke seizures in the intact part of the brain.

"While this is basic research, we hope it will provide some answers for our clinical decisions," said Emmi. "Right now, it's confusing. Do we take the child with these brain malformations to surgery, and if so, at what point and exactly where, in relation to the malformations? Understanding the timing of the seizure activity will give us a very important tool to decide whether a child should have surgery as soon as the malformation appears or before any appearance of seizure, or after the first seizure. One of the goals is to prevent more brain damage caused by severe seizure activity."

While TSC is only one source of epileptic seizures, researchers hope that learning more about it will offer insights into other causes of seizures. "We are trying to understand whether these tubers are unique, or whether they are related to other malformations," said Emmi. "Are anatomical malformations the cause or the result of seizures? We are at an early stage of research into this specific disease. But I would not exclude some very strong relationship between the TSC malformation and seizures caused by other means."

Having enjoyed a dual career as a clinician treating children with epilepsy in Italy, and as a researcher in Canada and the United States, Emmi takes satisfaction in pursuing a basic understanding of epilepsy and other brain ailments, in the hope of someday offering more effective preventive or therapeutic treatments.

Second study coordinates functional imaging and EEG

In another research project, Emmi is collaborating with Dr. Bartholomew Keogh, a senior fellow in radiology in the laboratory of Kenneth Maravilla, M.D., a CHD D research affiliate and director of CH D D’s Neuroscience Core. Using rats and mice, they are developing methods to utilize functional MRI in conjunction with electroencephalography (EEG) to image seizures as they happen.
Functional imaging study shows aberrant right-sided brain activation for language in Down syndrome

Much has been learned about the genetic basis of Down syndrome and its distinctive physical and neuropsychological characteristics, including particular weaknesses in language and short-term memory. However, there has been a lack of information about how the brains of people with Down syndrome actually work. Functional magnetic resonance imaging (fMRI) enables neuroscientists to look at the brain as it performs assigned mental tasks or responds to various stimuli, to determine which areas activate.

CHDD research affiliate Joseph Pinter, M.D., University of Washington assistant professor of neurology and pediatrics, is completing a preliminary study using fMRI to analyze language and memory in young people with Down syndrome (DS). Preliminary results suggest that the language problems may relate to the fact that language tasks are performed by the right side of the brain instead of the usual left.

Before the fMRI studies, Pinter used high-resolution MRI to assess the neuroanatomy of the brain in young people with DS. Among the findings, the hippocampus (important in memory) was noted to be small from a young age, suggesting this was a neurodevelopmental abnormality and not a result of later neurodegeneration due to Alzheimer’s disease, prevalent in adults with DS.

“However, you can only infer so much about brain function from the size of various brain structures, and that was one of the limitations of those earlier studies,” Pinter said. “With these new fMRI studies I am looking to more directly assess the deficits commonly seen in DS.”

DS is characterized by problems with expressive language, similar to deficits seen in people with left hemispheric dysfunction, for example after a stroke. While there is not any particular asymmetry in the brain in DS, dichotic listening studies in the 1980s showed right-sided dominance, instead of the usual left-dominant pattern, suggesting that people with DS might have aberrant right-sided language. “fMRI seemed an ideal way to prove or disprove this finding,” said Pinter.

To assess language and other deficits, he designed four mental tasks to be performed in the scanner by young people with DS and a group of controls.

Elizabeth Aylward, Ph.D., professor of radiology and also a CHDD research affiliate, assisted in the design of the experiments. Coordinator of Experimental Design and Image Analysis for the Brain Imaging component of CHDD’s Neuroscience Core, she has made important contributions in the Down syndrome field, publishing some of the first high-resolution MRI neuroanatomical studies of adults with DS. Pediatric neurology resident Michael Seyffert, M.D., and Katherine Field, a radiology technologist and fifth-year psychology student, also worked on the project.

During the fMRI experiments, the young subjects—four teens with DS—and controls wear modified virtual reality goggles and headphones and lie quietly inside the doughnut-shaped scanner, looking at a succession of pictures of objects as their brains are scanned. When the brain images are computer-manipulated and activations during control tasks are subtracted from those during experimental tasks, composite images show brightly colored patches on a dark brain, pinpointing areas of increased blood flow, a marker of increased neural activity in the highlighted areas.

“The first time through the scanner can be a little overwhelming, even though they’ve practiced these same tasks on the computer,” said Pinter. “People wonder how we can persuade a child with mental retardation to lie still in the scanner. With good preparation, the young people not only cooperated and tried hard, but successfully completed the tasks. They aren’t frightened by the close confines of the scanner but enjoy the experience.”
CHDD researchers study effects of prenatal alcohol exposure using three brain imaging techniques

It has long been known that children whose mothers drink alcohol during pregnancy may be born with fetal alcohol syndrome (FAS), a permanent birth defect syndrome characterized by growth deficiency, a unique cluster of minor facial anomalies, and organic brain damage that results in cognitive and behavioral problems. FAS is the leading known cause of mental retardation in the western world, and is entirely preventable.

However, not all individuals with prenatal alcohol exposure are brain damaged, and not all who have brain damage have FAS. Without the characteristic facial features of FAS, children damaged by prenatal alcohol exposure may go undiagnosed and untreated.

Susan Astley, Ph.D., a research affiliate at the Center on Human Development and Disability, University of Washington associate professor of epidemiology, and director of the Washington State Fetal Alcohol Syndrome Diagnostic and Prevention Network (FAS DPN), has received funding from the National Institute on Alcoholism and Alcohol Abuse (NIAAA) for a research project utilizing three non-invasive imaging techniques to study the brains of children with FAS.

Using magnetic resonance imaging (fMRI), Astley and colleagues will determine whether children who were exposed to alcohol prenatally, with and without FAS, whose central nervous system (CNS) dysfunction ranges from mild to severe, manifest alterations in brain structure, brain chemistry and metabolism.

“Such alterations would give irrefutable evidence of organic brain damage, which in turn would lead to more accurate diagnoses and more appropriate treatment plans,” said Astley.

fMRI provides a picture of brain structure, while fMR provides information on brain chemistry. fMRI assesses regional brain activity while the subject is engaged in an assigned mental task or receiving sensory stimuli.

Investigators include CHDD research affiliates Heather Car- michael Olson, Ph.D., child clinical psychologist; Truman Coggins, Ph.D., speech-language pathologist; Elizabeth Aylward, Ph.D., neuroimaging psychologist; Todd Richards, Ph.D., MRI/ MRS physicist; and Kenneth M Aravilla, M.D., radiologist, as well as Tracy Jirikowic, O.T., and Kimberly Kerns, Ph.D., neuropsychologist.

Earlier studies have demonstrated the usefulness of magnetic resonance imaging and spectroscopy in understanding the effects of prenatal alcohol exposure. In the mid-1990s, Astley and colleagues conducted a pilot study of monkeys exposed prenatally to alcohol. Using MRS, they found that choline levels in the brain—a chemical marker of cell membrane breakdown—rose with increased alcohol exposure and more severe neuropsychological dysfunction.

“We found for the first time some very intriguing results,” said Astley. “We were able to identify alterations in brain chemistry that correlated not only with alcohol exposure but also with neuropsychological measures of cognitive/behavioral dysfunction.” Other studies utilizing fMRI have shown significant reductions in the size of various regions of the brain in individuals with severe FAS.

An important strength of the current study will be the enrollment of subjects who were diagnosed by the University of Washington FAS Diagnostic & Prevention Network (FAS DPN) using the 4-Digit Diagnostic Code. The FAS DPN and 4-Digit Code were created in the mid-1990s by Astley and Sterling Clarren, M.D., UW professor of pediatrics and a CHDD research affiliate.

The 4-Digit Diagnostic Code documents the magnitude of expression of the four key diagnostic features of FAS: growth deficiency, facial anomalies, brain dysfunction and prenatal alcohol exposure. Each feature is ranked separately on a four-point scale, with 1 reflecting absence of the FAS feature, and 4 reflecting strong presence of the feature. Each rank is specifically case-defined to improve diagnostic accuracy and reproducibility.

“We have demonstrated that the 4-Digit Code provides more accurate diagnoses across the full spectrum of outcomes associated with prenatal alcohol exposure,” said Astley. “One of the values of this study is the opportunity to further assess and refine the 4-Digit Diagnostic Code.”

The definition of a “Rank 4 for Brain” is structural or neurologic evidence of brain damage; for example, microcephaly, structural abnormalities documented by CT scan or fMRI, or neurologic disorders of prenatal origin.

However, most of the alcohol-exposed children seen through the FAS DPN do not have evidence of this level of damage. “Families bring children to the clinic not because of facial or growth issues,” said Astley, “but because of concerns about brain function.” A “Rank 3 for Brain” reflects evidence of brain dysfunction documented by standardized psychometric assessments like IQ tests, memory tests and language assessments.

The study will take three years and will involve psychometric assessment and imaging of four groups of children aged 8 to 16:

- 20 with full-blown FAS according to the 4-Digit Code.
- 20 with alcohol exposure and severe cognitive dysfunction, but without the FAS facial features. This was previously called fetal alcohol effect or FAE.

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As the information revolution continues unabated, the increasing sophistication of high-technology devices offers unprecedented access to knowledge. While high-tech access to information and services presents remarkable new opportunities for people with sensory, mobility, learning and other disabilities, technology also presents new challenges for ease of access.

To enhance opportunities for persons with disabilities in educational institutions at all academic levels, a National Center on Accessible Information Technology in Education has been established at the University of Washington. The center, known as AccessIT, is funded with a $3.5 million grant from the National Institute on Disability and Rehabilitation Research (NIDRR).

The center's principal investigator and co-director is Kurt L. Johnson, Ph.D., associate professor of rehabilitation medicine and director of the University of Washington Center for Technology and Disability Studies (UWCTDS) at the Center on Human Development and Disability. Sheryl Burgstahler, Ph.D., director of the UW's DO-IT program (Disabilities, Opportunities, Internetworking and Technology), is a co-director of AccessIT. Dagmar Amtmann, M.A., of the UWCTDS is assistant director.

"As far as we have come with advances in information technology, these advances are not available to everyone, particularly people with disabilities."

-- Kurt Johnson

The explosion of information technology has been a double-edged sword," said Johnson. "We have a wealth of options for acquiring information, but if information technology is not universally accessible, it may shut out people with disabilities.

This center is the culmination of at least a decade of effort at the University of Washington to make information technology accessible and a recognition of the considerable expertise that exists here in the area of making information technology accessible to all."

The new center is coordinating a national effort to assist educational institutions in making education-based electronic and information technology accessible to all students, employees and members of the public, including those with disabilities. Its purview extends to any technology used in educational settings, including computers, software, web pages, telecommunications, fax machines, copiers, printers, kiosks and other equipment.

AccessIT's focus is broad, extending from the K-12 level to universities and other post-secondary educational institutions. The audience includes educators at all levels, policymakers, special education teachers, technical support staff, library staff, students and employees with disabilities, and their families and advocates.

Training and technical assistance is provided primarily through the national network of 10 NIDRR-funded Disability Business Technical Assistance Centers, which were established in response to mandates of the Americans with Disabilities Act.

In addition to training sessions and presentations at major educational, disability and technology conferences, the AccessIT website, www.washington.edu/accessit/index.php, is a primary means of disseminating information. The website features a Knowledge Base, a searchable, expanding database of questions and answers related to accessible electronic and information technology. General topics include computers, distance learning, legal issues, operating systems, office machines, software applications, telecommunications products, video and multimedia products, and web-based information and applications.

Electronic and information technology may be inaccessible to people with disabilities if it provides only one method for users to gain access to or manipulate information. For example, people who are blind cannot read instructions presented only in a visual format; people who are deaf cannot understand content that is presented only aurally; people who are color-blind cannot discriminate between color-coded options; people with specific physical limitations may be unable to use software that requires use of a mouse; and people who use wheelchairs cannot operate a copy machine if the controls are unreachable from a seated position.

"As far as we have come with advances in computing, Internet access, telecommunications and other forms of information technology," said Johnson, "these advances are not available to everyone, particularly people with disabilities who may be unable to read or see displayed information, hear or respond to spoken prompts, or use such devices as a keyboard or computer mouse.

An important focus of AccessIT is web accessibility, given the web's ever-expanding role in communication. While the web offers unprecedented opportunities, it presents new challenges. Web designers and programs often inadvertently create barriers for people.
Faculty members join CHDD as research affiliates

Dr. R. Scott Hansen is a Ph.D. in pharmacology from the University of Washington. He is a research assistant professor of medical genetics. His research focuses on the epigenetic regulation of gene expression, including studies of the mechanisms of normal X chromosome inactivation, the mammalian form of dosage compensation which is critical for normal development; silencing of the FMR1 gene as found in fragile X syndrome (the most common inherited cause of mental retardation); and changes in gene silencing found in the ICF immunodeficiency syndrome (one of the rarest developmental disorders). Analyses of the detailed patterns of methylation, replication timing, histone acetylation, chromatin structure, and gene expression are integral to these studies.

Dr. Martin J. Kushmerick is professor of radiology, bioengineering, physiology and biophysics at the University of Washington, director of nuclear magnetic resonance (NMR) spectroscopy at UW Medical Center and head of the UW’s space medicine team. He holds a Ph.D. in molecular biology and an M.D. from the University of Pennsylvania. Kushmerick uses nuclear magnetic resonance spectroscopy and imaging in metabolic studies. His research interests include the energetics, economy and efficiency of muscle contraction; the adaptation and regulation mechanics in muscle cells and organs; and the integration of mechanisms, molecules to muscle, and design of systems for energy balance. The overall theme is the signaling, regulation and interaction of molecular and cellular mechanisms in metabolism to sustain and restore energy balance in muscle.

Dr. Donna R. Weston is an assistant professor of family and child nursing and director of the University of Washington’s Certificate Program in Infant Mental Health. She has a Ph.D. in developmental psychology from the University of California at Berkeley. Her research focuses on assessing children from birth to three years in the context of their relationships with parents and other important caregivers; on developing instruments to assess the mental health of young children in the first two years of life; and on developing a practical method of documenting children’s growth and development, accomplishments and areas of difficulty, in order to strengthen the relationships between children and their parents and caregivers.

Dr. Sidney M. Gospe, Jr. holds a Ph.D. in physiology and pharmacology and an M.D. from Duke University. He is UW professor of neurology and pediatrics, head of the Division of Pediatric Neurology, and holder of the Herman and Faye Sarkowsky Endowed Chair in Child Neurology. His lab studies the effects of exposure to environmental tobacco smoke on brain development, pre- and postnatally. Estimates show that a third to a half of pregnant women are exposed to secondhand smoke. Studies of active smoking by pregnant women show many ill effects. Limited clinical studies of exposure to secondhand smoke also show adverse effects, including fetal growth retardation and cognitive impairment. Gospe is seeking to determine the effects of exposure to sidestream smoke and whether the infant brain is more vulnerable to environmental tobacco smoke at certain periods of development.

Dr. Therese M. Grant holds a Ph.D. in epidemiology from the University of Washington. A research assistant professor of psychiatry and behavioral sciences, she is principal investigator of the Parent-Child Assistance Program, an intervention model working effectively with high-risk mothers who abuse alcohol and drugs during pregnancy. The program has been replicated at a dozen locations in the United States and Canada. Grant’s research focuses on perinatal substance abuse and the effects of prenatal exposure to drugs and alcohol, fetal alcohol syndrome, development of assessment instruments and intervention strategies, as well as the challenges of community intervention and prevention with high-risk mothers and their children.

Dr. Gwenn Garden, assistant professor of neurology, holds an M.D. and a Ph.D. in physiology and biophysics from the University of Washington. Her research involves the molecular pathogenesis of HIV dementia, employing mouse models that closely resemble the pediatric form of HIV dementia. Her work examines the basic cellular biology of apoptosis (cell death) in the central nervous system, especially glial responses to neuronal injury and apoptosis. Although her work is disease-focused, results of her studies may shed light on important cellular interactions that occur in many other settings, including hypoxic and ischemic injury, trauma, seizures, inherited neurodegenerative disease and mitochondrial disease.
Injecting various agents to provoke and then stop seizures while the animal is in the imaging magnet, they can compare the brain's normal activity with seizure activity, while visualizing areas of the brain with and without anatomical abnormalities.

"We're using different epileptic agents known to activate different areas of the brain," said Emmi. "If we can find the relationship between electrical activity and anatomical changes using both EEG and FMRI, it would be valuable from a research point of view, and applicable to any seizure-related disease.

"The clinical possibilities are also very interesting," she said. "We already study seizures in humans using EEG. While EEG can be accurate, it is limited in its ability to pinpoint the location of a seizure. The FMRI provides imaging correlates of neuronal activity that can be used to study seizures in anatomically distinct areas of the brain. At exactly the same moment, you see the appearance of the seizure as changes in neuronal activation in specific areas of the brain and, possibly, in relation to specific anatomic malformations."

FAS . . . from page 4

• 20 with alcohol exposure and cognitive/behavioral function in the low-normal range, with no FAS facial features.
• A control group of 20 children with no known alcohol exposure and normal development.

"We're trying to better understand to what extent poor performance on standard psychometric assessments indicates underlying organic brain damage caused by alcohol," said Astley. "When a child comes in with prenatal alcohol exposure and a depressed IQ, how do you know his low IQ score is the result of the alcohol? Or that the low IQ is indicative of organic brain damage? This imaging study will allow us to look into some of these questions."

According to Susan Astley, the fetal alcohol syndrome imaging study was funded not only because of the expertise and facilities available at CHDD and the University of Washington, but also because of the large patient population available for enrollment into the study. The Washington State Fetal Alcohol Syndrome Diagnostic and Prevention Network has diagnosed more than 1,500 children in the past nine years. The network is an outgrowth of the FAS clinic at the CHDD.

"The primary goal of the original FAS clinic was to identify women at highest risk for producing children damaged by prenatal alcohol exposure," said Astley. "Every time we diagnosed a child with FAS, we had the potential of identifying a woman who might benefit from primary prevention intervention. When we opened the clinic, the waiting list grew far beyond our capacity."

The Washington State legislature funded clinics at five additional sites around the state, creating the Washington State FAS DPN. "The bill required us to diagnose accurately and reproducibly across all these clinics," said Astley. "Little did they know that had never been accomplished for FAS. The 4-Digit Code was our response, and it is now used internationally."

The FAS DPN has become a training center for professionals across the U.S. and Canada. "More than 50 multidisciplinary clinical teams have been trained, and we're growing at a rate of 8-10 clinics a year," said Astley. "The number is limited only by our ability to train."

Astley credits the FAS DPN's clinical and research expertise in FAS and its large patient population for helping her group win another award, a $1.2 million grant from the Centers for Disease Control to conduct the first randomized control trials in FAS to determine what interventions work best with families and children. CHDD research affiliates Heather Carmichael Olson, Ph.D., Truman Coggins, Ph.D., and Lesley Olswang, Ph.D., are involved in the research, as well as Tracy Jirikowic, O.T.

For more information, visit the FAS DPN web site at http://depts.washington.edu/fasdpn.

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People with disabilities. For example, lack of text descriptions for graphics, charts, navigation buttons, etc. on a website is a common barrier that affects individuals with vision impairments who rely on screen readers to access web content.

"An accessible website is attractive, easy to navigate and available to all users: students, faculty, staff and members of the public who have disabilities and may use assistive technology such as screen readers," said Johnson. "A web site that is inaccessible to people with disabilities not only limits access to campus information and library resources, it is likely to prevent students at both the college level and the K-12 level from fully accessing coursework. Some 70 percent of undergraduate courses at the University of Washington have an on-line component, ranging from discussion sections to exams. Younger students also routinely and increasingly have assignments that require use of the web."

Not only is there a legal requirement based on federal law, but web accessibility makes good economic sense, helps fulfill an institution's commitment as a member of the community, and works better for all visitors, whether or not they have disabilities.

"An estimated 30 million people in the U.S. have disabilities or functional limitations due to injury, illness or aging," he said. "To be accessible to the community at large, websites and other technological means of disseminating information must meet the needs of an increasing number of individuals with disabilities."
Down syndrome ... from Page 3

During the scan, Pinter or a parent stays in the room with the young person, chatting between tasks. The virtual reality goggles help to lessen the sense of enclosure as well. Pinter has not found it necessary to end any session prematurely because of claustrophobia. For the next round of testing, Pinter hopes to use a new MRI simulator available to CHDD research affiliates to better train and familiarize young subjects with the scanner.

To gain an understanding of the language deficits in DS, the first task involves object-naming. The participants are shown pictures of familiar objects, which they silently name. As a control test of visual activation, abstract, unnamable images are also shown.

In the young people with DS, the scans show activation in the right frontal lobe, exactly the opposite of the vast majority of the general population.

"This is a very compelling result," said Pinter. "The Down syndrome subjects show a mirror image in their brain activation. In more than 90 percent of right-handed people, the left frontal lobe activates when they perform this task. Even in left-handed people, fewer than half have right-brain activation. And all of these subjects were right-handed." Ongoing studies will control for handedness and involve about twice as many subjects.

Pinter says the challenge is to design tasks that address DS deficits, when the deficits themselves might prevent accurate interpretation. "In several tasks, there was bilateral activation. This may be 'frustration' activation; you tend to use a lot of areas of the brain when you're attempting something that's hard. With fMRI it is often not easy to differentiate between recruitment of additional areas of the brain and 'noise' in the signal. More subjects will help tease out what parts of the brain are important for such tasks."

Pinter points out that it may be unfair to compare DS subjects with young people of normal intelligence, because the same tasks are much more difficult. "We might be comparing apples and oranges. Perhaps we should use young people with non-syndromic mental retardation and fairly equivalent IQs as controls. If that's not feasible, we could grade the difficulty of the task; for example, making it possible for each group to get the right answer 80 percent of the time.

"However, for the question of which side of the brain one uses to produce expressive language, I don't think IQ is an issue. The important thing is to find the answers to some of the big questions, and then figure out which results are specific to Down syndrome and which are related to IQ."

To further analyze brain function in DS, Pinter and Aylward are developing additional tasks, including one that will present auditory stimuli to study receptive language.

"I'm interested in these kids during their educational years," said Pinter, "in part because it's important to understand what's different about their brains, to establish a baseline for what areas activate when they perform cognitive tasks. In many respects, parents of children with DS have been on their own, trying different nutriceuticals and drugs designed for Alzheimer's and other diseases. fMRI has the potential for use in evaluating different educational strategies as well as the efficacy of drug therapies."

An important goal of the research is to provide a yardstick by which to rationally judge potential therapies. "Doing fMRI experiments in children with developmental disabilities involves a lot of work and time, so up until now very little has been done in the DS population," said Pinter. "There is enormous potential here, because we have a consistent genetic problem and well-delineated deficits that are consistently noted across a whole group of people.

"At this point, we still know very little about the brain bases for the cognitive deficits in DS. We know there is an extra chromosome, so now we're down to 225 genes of interest. Within the next five years, this kind of baseline study will provide a foundation for functional neuroimaging of gene expression, and those studies may then help us dissect the genetic bases for the development of normal brain function. I think these are the humble beginnings of something important."

Dr. Pinter moves to a position in pediatric neurology at the University of California at Davis later this year, but plans to continue to collaborate with Dr. Aylward and others at CHDD on the Down syndrome functional brain imaging project.