Traumatic brain injuries are a major cause of disability and death in adults and children, and the leading cause of death and long-term disability in childhood. An estimated 1.5 million Americans, including one million children, sustain a traumatic brain injury each year, most frequently from car crashes, falls, sports, and abuse or assault. The short- and long-term effects can include physical, cognitive and psychosocial-behavioral-emotional impairments.

Traumatic brain injury is also a major risk factor for development of epilepsy. Seizures may occur immediately after the injury, but there may be a delay of months or even years before seizures commence. Post-traumatic epilepsy compounds the original brain injury, producing secondary brain damage and further cognitive impairment. Chronic seizures are often poorly controlled by the drug treatments currently available.

“Only about 70 percent of all epileptic patients can be rendered seizure-free by currently available antiepileptic drugs, and none of the drugs used to date can prevent the initial onset of epilepsy after traumatic brain injury,” said Raimondo D’Ambrosio, Ph.D., research assistant professor of neurological surgery at the University of Washington and a research affiliate at the Center on Human Development and Disability. “There is presently nothing we can do to decrease the likelihood of later seizures.”

In an effort to remedy that situation, D’Ambrosio and colleagues have produced an animal model of spontaneous chronic recurrent seizures, the hallmark of epilepsy, using fluid percussion injuries to laboratory rats. They reported their findings in the February 2004 issue of the journal Brain, noting that “the lack of an adequate (animal) model of post-traumatic epilepsy in which, similarly to the human condition, chronic spontaneous focal seizures follow a single episode of traumatic injury, has hampered the identification of clinically relevant epileptogenic mechanisms and the development of effective therapies.”

Until now, the method of producing brain injury in the animal model has involved implantation of iron chloride in the cortex, which leads to focal (localized) seizures. “The problem is that no human being becomes epileptic through this mechanism,” said D’Ambrosio. “The injury, and therefore the epileptogenic mechanisms, are different.” Other animal models of epilepsy involved injection of neurotoxins or electrical stimulation, both quite unlike the human condition. Earlier attempts at inducing epilepsy with head injury models similar to human cases of head injury have failed.

In the D’Ambrosio lab, the degree of injury to the juvenile rat (administered painlessly by a process of fluid percussion while the animal is anesthetized) is equivalent to a human’s severe closed head injury, such as might be inflicted with a hammer or bat or baseball. D’Ambrosio notes that, for this research, his lab utilizes juvenile animals equivalent in development to human teenagers, the most likely victims of traumatic brain injury.

Like the brain-injured human, the...
Project ACCESS: Technology tools may assist people who have cognitive disabilities

In our high-tech society, devices that once were relegated to the realm of science fiction are becoming commonplace and affordable. We talk on mobile phones that do double or triple duty as digital cameras and keepers of our calendars and address books. We drive cars that monitor how our vehicle is performing and call for assistance if we’re in trouble. We hike in the mountains and navigate on the water with global positioning system (GPS) devices that use satellite signals to help keep us on track and off the rocks.

Researchers are now beginning to adapt and enhance these everyday labor- and sometimes life-saving devices, with the goal of allowing some people with significant cognitive disabilities to live with increased independence, as well as relieve their caregivers and family members of some of the burdens of care.

At the University of Washington, investigators from the Center for Technology and Disability Studies (CTDS), a component of the Center on Human Development and Disability and the Department of Rehabilitation Medicine, are collaborating on a research project with scientists from the Department of Computer Science and Engineering (CSE), who have prototype devices already under development. Project ACCESS (Assisted Cognition in Community, Employment and Support Settings) was recently funded by the National Institute on Disability and Rehabilitation Research.

“We’re very excited about this as an interdisciplinary project,” said principal investigator Kurt Johnson, Ph.D., associate professor of rehabilitation medicine and director of CTDS. “We have been talking about assisted cognition for people with developmental disabilities and brain injuries for some time. As the field of artificial intelligence has matured, there is increasing potential that ‘intelligent’ devices might be created that could provide assisted cognition without the direct supervision of a caregiver or personal assistant.”

Investigators from CSE include co-principal investigator Henry Kautz, Ph.D., and Gaetano Borriello, Ph.D. Investigators from CTDS are Mark Harniss, Ph.D., Pat Brown, Ed.D., and Brian Dudgeon, Ph.D.

CSE investigators are working on two devices. The Activity Compass, which exists as a proof-of-concept prototype, meshes several technologies: a Palm Pilot, a GPS receiver and a wireless modem. Over time, it will learn a user’s typical daily routines and monitor for variations, and then decide whether a prompt is needed if the routine is unexpectedly changed.

Henry Kautz watches as a graduate student programs the prototype Activity Compass with data on Metro bus routes.

UW photo by Mary Levin
The ADL Prompter, which currently exists as a concept and set of supporting designs and algorithms, will monitor data collected by sensors embedded in a living or work environment and use artificial intelligence to interpret data from the sensors and make decisions based on the user's needs.

The CSE investigators' initial focus was on patients with Alzheimer's disease. However, using Alzheimer's patients as research participants can be difficult, since their cognitive function is constantly changing. The idea of collaborating on a grant came when Harniss began attending Kautz's seminars, and realized CSE's prototype devices could be of value to clients with intellectual disabilities who are served by CHDD's Employment Training Program, while the ETP clients could participate productively in the research. "They tend to have very stable and consistent cognitive function, and will make good research participants as we develop and refine prototypes," said Harniss.

In subsequent years, the researchers will utilize two additional groups in developing the devices: people with multiple sclerosis and people with traumatic brain injury. "In the first part of our research, we're gathering information about potential devices and what would best aid our clients," said Brown, who heads the Employment Training program. "We think a device that would help with navigation, that would make it easier to travel by bus to and from work and community activities, would make sense."

For example, said Harniss, a device like the Activity Compass, combining GPS and cellular telephone technology, could assist individuals with moving around in the community and could communicate with the public bus system. "Every Metro bus in Seattle/King County has a GPS connection. The device might tell the user, 'The #72 bus is coming. You should get on it to get to your job.' The device would prompt the individual and, ideally, contact the caregiver if there were problems. It would also have the capacity to gather information about the person's location and direction of travel and, based on that information, give a different set of prompts. It would potentially be able to learn the individual's common navigation patterns but allow for some flexibility: it should be able to support the user who goes to novel places as well."

Such technology might enable the individual to take a regular bus to work, rather than relying on a special bus or van service, said Brown. "With such a device, caregivers could feel confident that the people they care for are okay. It has the potential to foster more independence and allow people to experience the community without always needing someone to accompany them."

Another device might provide memory prompts. "This is definitely an issue for many people with intellectual disabilities and traumatic brain injury," said Brown. "The idea would be a device that provides social cueing without being obtrusive. For example at work, the prompt might say 'it's time to take a break with everyone else,' or 'you've been on break for 15 minutes'—the same reminders that coworkers or a job coach might give, but less obtrusively, and promoting independence."

The ADL Prompter could involve placing sensors throughout the home to monitor and help someone live safely and independently, said Harniss. "Did the individual get up? Did he open the cupboard and get his breakfast cereal? Is the stove on or off? Did she take her medication or at least open the pill bottle? There are many daily-living prompts that would be useful for a range of people."

Such devices would provide more independence, said Harniss, at the same time maintaining some security and protection, while reducing the efforts of caregivers. "That's a big concern. Families end up doing a lot of the work, and there is a lot of burnout. However, there are also privacy issues for the individual with disabilities, because you're monitoring someone who may not want to be monitored, or even understand it. There must be controls and safeguards to ensure people's right to privacy, which in a sense is being taken away by technology intended to provide more independence."

As Computer Science and Engineering researchers move forward on developing devices involving artificial intelligence and ubiquitous computing, Harniss and Brown will interview selected ETP clients and caregivers about their current transportation patterns and needs. "We'll start with people who use Metro's ACCESS buses or other transportation, analyze their responses, and provide this information to the computer science people who will use it in development of tools," said Harniss.

"At the same time, we'll be thinking about how to design a device that provides adequate information and yet is simple to use. It will have to involve universal design, since many individuals have sensory or mobility disabilities in addition to cognitive disabilities. It should also work for a broad range of individuals in addition to people who are cognitively impaired—for example, people who are blind or visually impaired."

See 'ACCESS' on page 8
Mention Tourette syndrome, and what probably comes to mind is someone who exhibits uncontrollable vocal outbursts of cursing and obscenities. In fact, statistics from the Tourette Syndrome Association indicate that fewer than 15 percent of people diagnosed with Tourette syndrome, or TS, have such obvious vocal tics. "Socially unacceptable or socially unusual tics are an infrequent manifestation of Tourette syndrome," said Samuel H. Zinner, M.D., a developmental-behavioral pediatrician at the Center on Human Development and Disability (CHDD) at the University of Washington, who has made TS a special focus both professionally and personally. "It is a much more complicated and diverse neurological disorder that, in some respects, we are only beginning to understand." A member of the medical advisory board of the national Tourette Syndrome Association, Zinner has run local support and social skills development groups for children with TS.

TS was first identified in the late 1800s by French neurologist Georges Gilles de la Tourette, but was considered an extremely rare disorder until about 20 years ago, said Zinner. "Originally it was thought to have a prevalence of about one in 10,000. The working prevalence that we now use—although we know it's still grossly underestimated—is about one in 1,000 who meet very strict definitional criteria. When we broaden the definition to include people who don't have vocal tics but who do have motor tics with some of the other neurological co-morbid conditions, there are at least 10 times that many. Some recent research studies have found a prevalence of TS as high as one in 30."

Zinner sees several patients with TS each month in his neurodevelopmental clinics at CHDD and Children's Hospital and Regional Medical Center in Seattle, and he is investigating the possibility of establishing a TS specialty clinic at CHDD, which would be a referral site for patients throughout the Northwest. "There is clearly a need," he said. "The nearest TS specialty clinic is in San Francisco, and there are an estimated 5,000 youngsters under age 18 with TS in the greater Seattle area alone."

Zinner's hope is for an interdisciplinary clinic whose purpose would be diagnosis, short-term and long-term management, and provision of a patient population for research studies. Disciplines involved would include developmental behavioral pediatrics, neurology, psychiatry, neuropsychology and education. The age range of patients would be from toddlers through young adults.

TS can be considered a genetic disorder of disinhibition, said Zinner. "What is inherited is a predisposition to a wide range of manifestations, which may not necessarily include tics. A child with a tic disorder is more likely to have a parent with a tic disorder or with obsessive-compulsive disorder (OCD). We think that TS is caused by an autosomal dominant gene or genes, but that additional factors contribute to determine how the disorder is expressed."

While the neurological basis of Tourette's is not precisely known, there seems to be a failure in the filtering of some information to the brain. More precisely, the basal ganglia at the center of the brain inadequately screen incoming information from other brain regions, so that unwanted information leaks through. This unfiltered information manifests in a number of ways, which may result in tics, compulsions or impulsive activity.

"With OCD, obsessions are not filtered appropriately," said Zinner. "Attention deficit hyperactivity disorder (ADHD) is another disorder of disinhibition. There is a host of other developmental-behavioral disorders that we regularly see with TS, including learning disabilities, sleep disorders, mood disorders, anxiety disorders and elimination disorders such as bedwetting."

In children with TS, motor tics usually first appear around age 6 or 7. Another subset of children first presents with tics at about age 11 or 12. Eye blinking may be the first sign, and tics may progress to throat clearing, sniffing, arm thrusting, kicking, shoulder shrugging, jumping or countless other manifestations. Males are affected three to four times more often than females. At least half the time, symptoms of attention deficit hyperactivity disorder—ADHD—precede the onset of tics.

As part of his research into establishment of a Tourette's clinic at CHDD, Zinner is contacting practitioners across the United States and Canada who have specialty clinics or see numerous patients with TS, to survey their administrative and clinical management patterns. "There is no consistent management approach," he said. "Many practitioners focus on medication management. But we have to approach TS from many di-
significant self-injury. There are people in their child has no tics. At the other end of the spectrum, some people's tics cause significant self-injury. There are people who stare at the sun, damaging their retinas; others bang their heads and damage their cervical spine, or bite themselves. They don't want to do it, but the relief from the urge is accomplished only when they feel the pain.

If tics are problematic enough that they require treatment, Zinner suggests beginning with a non-medication approach. One strategy, habit reversal, can be effective with highly motivated people, usually older than age 10. "Children must be able to articulate this very significant tension they feel before having a tic, and then teach themselves a competing movement, so the tics are not so visible. As an alternative, the child can learn to slow the tic down, or can learn a 'parakineti tic' that disguises it to make it seem purposeful, such as brushing the hair out of the face while at the same time jerking the head. People with TS may be able to replace obvious tics with less obvious ones, like squeezing the toes tightly while in public, and waiting until they get home to let the more obvious tics out. This strategy may alleviate the urge without letting out the observable tics."

Other options include clonidine (used to treat blood pressure), benzodiazepine, and the tricyclic antidepressants. Botulinum toxin (Botox) works effectively in many people with tics by paralyzing the muscle or muscles that tic, but because the tics often move from one group of muscles to another, it may have limited utility. An advantage of Botox is that it appears to also diminish the urge to have tics in the muscles that are injected. Some people self-medicate with tobacco or marijuana. While effective for some, said Zinner, obvious ethical and legal issues preclude the prescribed use of these agents, except in experimental conditions.

Beyond treatment of symptoms, there is a significant amount of research focusing on which neurotransmitters and brain substrates are involved. "Until recently, we were pretty certain we had pinpointed the genes involved," said Zinner. "We now know this is not the case. ADHD itself is problematic enough that medication is usually of significant benefit. The message needs to be circulated that, with few exceptions, it's okay to give psychostimulants to people with TS. Tics naturally wax and wane, and doctors may erroneously attribute worsening tics to the medication."

Dr. Sam Zinner

"We have to approach Tourette syndrome from many directions. The first goal is in education: keeping the family, teachers and classmates informed that TS is a neurological disorder. These are not willfully disobedient children, and they often really suffer."

"...keeping the family, teachers and classmates informed that TS is a neurological disorder. These are not willfully disobedient children, and they often really suffer."
Functional MRI may help correlate brain damage and functioning in individuals with FAS and FAE

Fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE) are lifelong developmental disabilities caused by prenatal exposure to alcohol. While characteristic facial features give outward clues to the brain damage in individuals with FAS, it is more difficult to delineate the varying types of brain dysfunction in people damaged by alcohol before birth who do not exhibit facial or other physical anomalies.

Paul Connor, Ph.D., is an acting assistant professor of psychiatry and behavioral sciences in the UW’s Fetal Alcohol and Drug Unit and a research affiliate of the Center on Human Development and Disability. With FADU director Ann Streissguth, Ph.D., and colleagues, he is an investigator on a number of research studies into the effects of prenatal exposure to alcohol.

“Although patients with FAS have more physical deformities, such as heart malformations and facial anomalies,” said Connor, “the brain dysfunctions of people with FAE are often as severe as—if not worse than—brain dysfunctions in patients with FAS. Past studies have shown the disruptive effects of prenatal alcohol exposure on individual brain structures, including the hippocampus, the cerebellum, the corpus callosum, glial cells and myelin, basal ganglia, neural crest, receptors and cortical neurons. Drinking early in pregnancy may lead to many of the facial anomalies seen in children with FAS, whereas the deleterious effects of alcohol on the brain can occur at any time during pregnancy.

“A binge pattern of drinking—five drinks on a weekend, for example—tends to be more damaging to the fetus than a drink a day for five days,” said Connor. “But we caution that any amount of alcohol during pregnancy is problematic. All the dose-response studies show there are subtle changes in the brain even at low doses. We don’t know a safe amount. Many people have assumed that FAS is worse than FAE, but we don’t find this to be the case. Alcohol exposure at any time during fetal development can lead to cognitive and structural deficit.”

In individuals with FAS, said Connor, facial features frequently normalize at puberty because of hormonal and muscular changes. “You’re left with the long-term effects on cognition and behavior.” We’ve been finding this in our research for a number of years, and other investigators confirm it as well. We’ve taken to calling the whole range of damage ‘fetal alcohol spectrum disorders,’ taking a page from the nomenclature of autism, emphasizing that there is a whole range of effects.”

Connor is principal investigator on a study using the relatively new technology of functional magnetic resonance imaging (fMRI) to identify the varying patterns of brain dysfunction in young adults with FAS and FAE. Functional M RI gives researchers a non-invasive means of pinpointing areas of neural activation in the brain as an individual performs assigned mental tasks while lying in the scanner. The images produced are based on the magnetic properties of oxygenated versus deoxygenated blood within the brain; regions being activated require more oxygenated blood.

“To our knowledge, this is one of the first studies using fMRI to identify functional deficits within the brains of patients with FAS and FAE,” said Connor. “It offers an advance over structural M RI in its ability to assess the metabolic activity of the brain rather than static cerebral damage.”

For the fMRI study, 48 young people aged 18 to 30 were selected: 16 with FAS, 16 with FAE, and 16 controls with no history of prenatal alcohol exposure. Each group is evenly divided by gender. To create homogenous groups, selection of subjects was based on arithmetic skills exhibited in an earlier structural MRI study, since arithmetic is an important and relatively common area of deficit in people with FAS and FAE. The goal is to use fMRI to identify differences among the three groups in the pattern and amount of neural activation in various parts of the brain, as each participant engages in a series of five neuropsychological tasks that test different brain functions.

Earlier studies by Fetal Alcohol and Drug Unit researchers have shown varying patterns of neurobehavioral performance based on the shape of the corpus callosum, the white-matter pathway that connects the brain’s two hemispheres and facilitates communication between various regions of the brain. “In subjects with FAS or FAE, the callosi are too thin or...
Connor and his colleagues hope to shed light on the subtypes of fetal alcohol damage. "In the future, the techniques used in this study could aid in early identification and diagnosis of fetal alcohol brain damage," said Connor. "Information gained from fMRI could assist clinicians in choosing the appropriate services and interventions for people damaged by prenatal alcohol exposure, by identifying their specific areas of strength and weakness."

While fetal alcohol exposure results in permanent organic brain damage that will not go away, there are probably ways to ameliorate its effects. The ultimate goal of our studies is to move toward new treatment approaches to help improve the lives of these individuals. Functional MRI may be able to measure changes in the actual functioning of the brain and determine the effectiveness of specific treatment interventions.

Not only did we find this variation in the shape of the callosum, we saw patterns of neuropsychological functioning that meshed with the shape. Subjects with the thin callosum performed poorly on motor function, but their executive functions were not too impaired. Those with the thick callosum tended to have poor executive function, but relatively normal motor function."

After training in test-taking and becoming accustomed to the confinement of the scanner, each participant performs the mental tasks in the scanner, during a day-long session with rest breaks. The tasks have been shown to be sensitive to prenatal alcohol effects in previous lab exams and do not require a vocal response, which would confound the results. They include an arithmetic test; a test of auditory attention in which subjects press a button when they hear a tone; a working-memory test in which the subject presses a button when a letter being presented is identical to that presented two times ago; a Stroop color word test that requires naming the color of a word printed in a color different from the color it actually names; and a test of motor coordination that requires a sequence of finger tapping. The scans will show which parts of the brain are activated during each test. By combining the results of earlier structural MRI studies and neuropsychological testing of the same individuals with the forthcoming results of the fMRI study, Connor and his colleagues hope to shed light on the subtypes of fetal alcohol damage.

"In the future, the techniques used in this study could aid in early identification and diagnosis of fetal alcohol brain damage," said Connor. "Information gained from fMRI could assist clinicians in choosing the appropriate services and interventions for people damaged by prenatal alcohol exposure, by identifying their specific areas of strength and weakness."

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Post-traumatic epilepsy . . . from page 1

Like the brain-injured human, the animals recover from the acute injury. "There is a silent period during which they seem to recover," said D'Ambrosio. "Then epileptic activity begins to appear. After the silent period, 60 percent develop abnormal brain activity. It increases over time and becomes very obvious.

"The question has been, what happens in the brain in the period between the injury and the appearance of epileptic activity? Up to now, there has been no animal model of epilepsy that closely resembled the human posttraumatic condition. There has been no model available to investigators trying to determine how to modify the progression of pathology and prevent the onset of epilepsy."

The animal model produced in his lab is remarkably similar to the human condition, said D'Ambrosio, for a number of reasons:

- the epilepsy follows a single event of severe fluid percussion injury, a clinically relevant model of head injury
- the loss of neurons and the glial reactivity are similar to the situation found in human epilepsy
- there is a latent or silent period before the onset of seizures
- the seizures begin spontaneously following the latent period
- they begin as partial or focal seizures that may or may not spread
- the seizures evolve, becoming longer and spreading throughout the brain
- they are resistant to at least one classic antiepileptic drug, phenytoin (brand name Dilantin).

D'Ambrosio has developed the animal model, D'Ambrosio plans to use it to study the mechanisms involved in the delayed onset of seizures in acquired epilepsy. In addition, his lab will initiate a drug-screening project, using the rat models to test existing and new drugs to see which might be effective in preventing the onset of posttraumatic epilepsy after brain injury.

"We have a battery of drugs that we would like to test. There may be some epileptogenic mechanisms that are not targeted by existing drugs," he said. "We have the real hope that we will find drugs that will prevent the onset of posttraumatic epilepsy, as well as control seizures once they occur."
individuals to use them,” said Harniss. “It is likely that within 10 years, assisted cognition systems will enable individuals with significant cognitive disabilities to experience greater independence in employment and community activities, without sacrificing personal safety or appropriate levels of support.” More information on Project ACCESS is on the web at cognitivetech.washington.edu.

New research affiliates join CHDD

Jeffrey Ojemann, M.D., received his medical degree from Washington University in St. Louis in 1992. He completed a seven-year residency in neurosurgery at Barnes-Jewish Hospital in St. Louis, a fellowship in pediatric neurosurgery at St. Louis Children’s Hospital and a fellowship in epilepsy surgery at the University of Washington. He is an associate professor in the UW Department of Neurological Surgery and an attending neurosurgeon at Seattle’s Children’s Hospital & Regional Medical Center and Harborview Medical Center. His research focuses on the effects of neurosurgical procedures on memory and cognition in children and adults, including an NIH-funded study examining memory fMRI changes with epilepsy surgery and studies looking at the role of flumazenil PET in the pre-surgical evaluation of seizures.

Leo J. Pallanck, Ph.D., holds a doctoral degree from the Albert Einstein College of Medicine and completed post-doctoral research in genetics at the University of Wisconsin-Madison. An assistant professor of genome sciences, he joined the University of Washington faculty in 1997. Pallanck’s laboratory uses genetic and molecular approaches to elucidate mechanisms of synapse formation and function, and to identify genetic pathways leading to pathology in heritable forms of neurodegenerative disorders. His laboratory’s neurodegenerative disease studies involve fly and insect cell culture models of Parkinson’s disease, Niemann-Pick type C disease, and spinocerebellar ataxia type 2. The long-term goals are to test specific models of disease pathogenesis and identify genetic pathways responsible for pathology in these disorders.

Visit the CHDD website at http://depts.washington.edu/chdd