ResearchNow

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Research Now is a quarterly feature of **Momentum**, produced by the Society's Research and Clinical Programs Department.

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MS and the mind: The latest research on cognitive function

by Sara Bernstein

It's one of the most sensitive topics among people with MS—we're talking about how MS affects your mind, about cognitive function. Researchers have made great strides in the last decade to understand how cognitive problems develop in people with MS, and to develop strategies to lessen their effects.

Cognitive changes are thought to affect about half of those who have MS. In most cases these changes remain relatively mild and do not have a significant impact on daily life. Five to 10% of people with MS, though, experience impairment severe enough to interfere with everyday activities.

Cognitive changes in MS are very different from those that appear in Alzheimer's. MS generally affects a few specific functions rather than globally impairing all intellectual abilities. These functions include memory; complex attention; speed of information processing; planning and prioritizing; visual perceptual abilities; and word-finding.

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"Watching" thinking with functional MRI

Because MS causes specific cognitive problems, investigators have attempted to correlate particular cognitive deficits with abnormalities in specific areas of the brain. The last decade has seen an explosion of such research, primarily using functional magnetic resonance imaging (fMRI), an imaging technology that measures the amount of oxygen used by different areas of the brain. Investigators administer fMRI scans while their subjects are performing certain tasks, to determine which areas of the brain are more or less active during the performance of each task.

In one study, a Society-funded team led by John DeLuca, PhD (Kessler Medical Rehabilitation Research and Education Corporation, West Orange, N.J.) examined brain activation patterns during a short-term memory task, known as "working memory" in six people with MS, compared to six people without MS. Both groups were able to perform the task, but different areas of the brain were activated during the task in people with MS. **Journal of Clinical and Experimental Neuropsychology** 2005;27:33–54

It's possible that this shift in the pattern of brain activation occurs because the brain actually is "reorganizing" itself, i.e., activating different areas to compensate for damaged circuits caused by MS. Caterina Mainero, MD, and colleagues (University of Rome) used fMRI during a task involving recall in 22 people with MS who had no or mild cognitive deficits. They found that brain activation changes occurred more often in those who performed better on the task. Also, they found that the sites of brain activation correlated with sites of tissue damage, indicating that the brain may be compensating for damaged areas by increasing the total area activated. **Neuroimage** 2004;21:858–67

> Better understanding and new treatment directions are beginning to emerge.

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Cognitive or mental fatigue can seriously interfere with functions of everyday life and work, but despite its importance, it has proved difficult to measure and evaluate because there are few objective measures of fatigue in general and cognitive fatigue in particular. Studies that have measured cognitive functions before and after patients are fatigued have generally found no difference in performance. However, when patients are made to engage in sustained mental effort, cognitive performance does seem to decline over time and this may capture the elusive concept of "cognitive fatigue."

A young investigator in Dr. DeLuca's team, Helen Genova, PhD, just got funded by the Society to use fMRI to investigate brain activity during mental tasks to investigate periods of cognitive fatigue. This project could help better define cognitive fatigue, how it affects people with MS, and how to evaluate whether therapies can improve cognitive fatigue.

Steps forward in cognitive rehabilitation and treatment

Some of the most important developments in research on cognitive function in MS are being made in cognitive rehabilitation programs, which help to evaluate and treat changes in a person's ability to think, reason, concentrate or remember.

Two promising strategies were developed by members of Dr. DeLuca's team with funding from the National MS Society. Joseph Ricker, PhD, studied whether the Story Method Technique (SMT) would improve memory in 28 people with MS. SMT involves organizing information in a story-like form, using visual imagery. People with moderate or severe impairments significantly improved memory

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Minding cognitive function in children with MS: Pediatric MS Centers of Excellence step up

Little is documented about how cognitive impairments may affect children with MS. The six Pediatric MS Centers of Excellence funded through the National MS Society's Promise: 2010 campaign are stepping up to fill this void, creating a standardized battery of cognitive tests to assess function; conducting research; and providing important resources for parents and children.

Lauren Krupp, MD, and colleagues at the National Pediatric MS Center at the State University of New York, Stony Brook, reported on the occurrence of cognitive deficits in those referred to the center between 2003 and 2008; 25 of 58 children or adolescents with MS had deficits. There was no association between cognitive symptoms and their scores on the EDSS, a scale that measures disease activity, meaning that, as is also true in adults, some individuals may not have physical impairments and yet show cognitive deficits. **Multiple Sclerosis** 2008;14:P785

The network of Centers have collaborated to understand and help children and parents deal with these issues, creating a neuropsychological battery of tests for children attending the centers. Joy Parrish, PhD, and colleagues at the Pediatric MS Center of the Jacobs Neurological Institute in Buffalo, New York, reported on use of the battery on 18 children and adolescents with MS, 10 with acute disseminated encephalomyelitis (ADEM, a related disorder), and 31 healthy controls. Kids with MS showed greater deficits in processing speed, reading skills and attention span, but overall IQ was not impacted. (Abstract #P02.130, American Academy of Neurology 2009)

Understanding how MS can affect children and adolescents is crucial to improving their experiences in school. Interventions might help

offset or improve possible cognitive impairments, for example:

- A child with attention deficits might benefit from sitting in the front of the classroom, thus minimizing distractions. This child also might benefit from a quiet environment—such as a resource room—when taking tests.
- Multiple-choice tests may be the best format for a child with memory deficits who has trouble retrieving information but can recognize it. Cognitive rehabilitation methods, such as repeating tasks or mnemonic strategies (memory tricks) may help these children as well.

The Society has developed two new handbooks, **Students with MS and the Academic Setting: A Handbook for School Personnel**, and **Managing School-related Issues: A Guide for Parents with a Child or Teen with MS**. These are available on our Web site at **nationalMSsociety.org/ped support** or by calling 1-866-543-7967.

A high-tech response to cognitive problems in MS

There's now a new, high-tech way for people living with MS to exercise their brain power: My-BrainGames, a free suite of online cognitive games for the MS community. MyBrainGames, available for free at **MyMSMyWay.com**, are the first online games designed specifically for people with MS under the direction of a team of leading health-care professionals specializing in MS and cognition, as well as by members of the MS community.

> There's a new wave in managing MS—playing games to help offset the effects of MS symptoms.

The games suite came out of the MS Technology Collaborative, formed by Bayer HealthCare Pharmaceuticals, Microsoft, and the National Multiple Sclerosis Society to better understand how people with MS use technology and to connect them to information and resources to help move their lives forward and manage their disease.

The Collaborative conducted a survey that included a representative sample of 2,390 Americans with MS—the most comprehensive examination ever of the role of technology among people with MS. Seventy percent of people surveyed said they are interested in keeping up with the latest technology, and nearly half agreed that "technology plays a vital role in helping me live with MS." Those with more severe types of MS, and those facing more pronounced visual, fatigue, cognitive, speech or dexterity challenges place even higher importance on technology in helping to move their lives forward and in staying connected.

MyBrainGames are a fun way to challenge the player's information processing speed, working memory, complex attention and task switching. Each game is available at varying levels of difficulty and players can even create customized levels to best suit their individual abilities. All scores can be saved, allowing users to track their performance over time.

Formal research on the possibilities of using technology to improve cognitive function is just beginning. Tony Gentry, PhD, OTR/L (Virginia Commonwealth University) reported on a small study of 20 people with MS and cognitive impairment who were trained to use PDAs (personal digital assistants) by occupational therapists. Nineteen were able to learn how to use the PDAs, and reported significant improvements in everyday activities that involve memory and attention. These results warrant confirmation and further study (the improvements occurred using subjective reports from patients, not objective scales), but they represent a new avenue for cognitive rehabilitation research. **American Journal of Occupational Therapy** 2008;62:18–27

compared to controls who completed traditional memory exercises. **Multiple Sclerosis** 2005;11:58–68 A larger study is now recruiting 200 people with MS (see **clinicaltrials.gov/ct2/show/NCT00166283)**.

Yael Goverover, PhD, studied the "self-generation" strategy, which suggests that individuals remember items or words that they "make up" better than the items or words that are provided to them. In a small study of 20 people with MS and mild cognitive impairment and 18 controls without MS, tasks learned by using self-generated words were recalled and performed better than those learned by recalling words provided to the subject. **Archives of Physical Medicine and Rehabilitation** 2008;89:1514–21 Now at New York University, she is funded by the Society to continue these studies in a larger group of people with MS.

The Society took a big step toward propelling research into cognitive rehabilitation when it awarded a five-year Mentor-Based Postdoctoral Fellowship in Rehabilitation Research to Dr. DeLuca, financing the establishment of a training program in cognitive rehabilitation research. Their first fellow, James F. Sumowski, PhD, has published fascinating results on how cognitive change that occurs in MS might be offset by an intellectually enriching lifestyle (e.g., higher education, greater acquired vocabulary, cognitive leisure activities), which have been shown to reduce cognitive impairments in other neurologic diseases.

Dr. Sumowski studied "cognitive reserves" in 58 people with MS and 43 controls without MS, and reported that intellectual enrichment (as determined through a vocabulary test) protected people with MS from reductions in processing speed and memory. **Journal of the International Neuropsychological Society** 2009;15:606–12 Dr. Sumowski is continuing these studies with funding from the National Institutes of Health.

Treating cognitive change

Can a drug treat cognitive problems in MS? The jury is still out, with several studies recently completed or underway:

L-amphetamine sulfate (a nervous system stimulant) did not significantly improve self-reported cognitive change or processing speed—the primary endpoints—in a study of 136 people with MS, but did improve secondary endpoints of some aspects of verbal and visual memory. These findings would have to be replicated in a study designed primarily to determine changes in learning and memory. **Journal of Neurology** 2009;256:1095–102

Two ongoing studies are looking at drugs used to treat Alzheimer's disease: a multicenter trial of memantine is recruiting 146 people with all types of MS, and a study of donepezil is recruiting 144 people with all types of MS. A recent study of memantine versus placebo in 126 people with MS and cognitive impairment demonstrated no benefit for those on active treatment. (Abstract #S11.002, American Academy of Neurology 2009)

Two studies are investigating alternative therapies. The Society is funding a study of ginseng to improve mental alertness and fatigue in 108 people with MS at Oregon Health & Science University, and two VA Medical Centers in Oregon and Washington are recruiting 158 people for a study of ginkgo biloba extract to improve cognitive function.

For information about ongoing studies, visit **nationalMS society.org/trialsrecruiting**.

Can exercise improve cognitive function? Barbara Giesser, MD, and colleagues at UCLA tested a robotic device that moves the legs while the person is suspended over a treadmill, in hopes that this technique will improve ambulation. Her team actually reported a beneficial effect on **cognitive** function in this Society-funded study (Abstract #P08.165, AAN 2009), and she now is funded by the Society to study the effects of aerobic exercise on cognitive performance.

As research expands our understanding of the underlying factors involved in cognitive changes in MS, we are moving closer to stopping these symptoms from affecting the lives of people with MS.

Investing in the future of MS research

by John R. Richert, MD

In these challenging economic times, the National MS Society has had to make some tough decisions about research funding. One of the programs that remains a priority is our postdoctoral research fellowship program. In the greater scheme of things, our discovery research projects by experienced investigators serve as the linchpin for research progress; our targeted initiatives push investigators into new research areas that are not getting the spontaneous attention that they deserve; and our fellowship programs bring in new blood and new ideas to energize MS research and ensure its future.

Former fellows make good

Just look at the accomplishments of some of our past fellows:

- Dennis Bourdette, MD (1981–1985) is now Chairman of, and the Roy and Eulalia Swank Family Research Professor in, the Oregon Health & Science University Department of Neurology, and Director of its MS Center. Dr. Bourdette's team has forged novel explorations of therapeutic strategies for MS, including alternative therapies such as alpha-lipoic acid and ginkgo biloba. He heads a Collaborative MS Research Center funded by the Society to understand the damage that leads to progressive disability in MS.

> Funds for training programs get results.

- Jorge R. Oksenberg, PhD (1988–1990) holds the G.A. Zimmermann Endowed Chair in Neurology at the University of California, San Francisco. Dr. Oksenberg has been a key force in the growth of MS genetics research. In particular, his team has spearheaded the collection of data from African American people with MS, to determine the reasons for important differences between their experiences and those of Caucasians with the disease. Dr. Oksenberg also is leading a Collaborative MS Research Center that is seeking to discover "markers" to predict MS progression.
- ▶ Tanuja Chitnis, MD (1998–2001) now is Director of the Partners Pediatric MS Center at the Massachusetts General Hospital, part of a nationwide network of Pediatric MS Centers of Excellence funded through the Society's Promise: 2010 campaign. Dr. Chitnis and her colleagues are bringing us new data on the demographics, disease course, and treatment possibilities for this previously underserved population within the MS community, as well as gleaning information that will help us better understand the causes of MS in adults.

The men and women who seek research fellowship training from the National MS Society are a varied group. Some are attracted to the field because of the complexity of this disease. Some have a personal connection, such as a parent with MS. Some want to devote all of their time to laboratory research, with a dream of finding one molecule that will turn the world of MS research on its ear. Some want to divide

Tanuja Chitnis, MD (right), and her patient Chris, at the Pediatric MS Center at Massachusetts General Hospital.

COURTESY OF MGH MEDIA RELATIONS

their time between the lab and the clinic, so that they can bring their research findings directly to people with the disease.

COURTESY OF CLEVELAND CLINIC FOUNDATION

Walid Jalabi, PhD (left), is continuing his studies in the lab of Bruce Trapp, PhD.

Launching careers devoted to MS

Let's take a look at some men and women who have just wrapped up their fellowship training:

▶ Walid Jalabi, PhD (Cleveland Clinic) trained in the laboratory of Bruce Trapp, PhD, exploring a possible mechanism by which resident immune cells in the brain may protect nerve cells. Using advanced genetics technology, his team has identified several genes that are activated in a "neuroprotective pathway." The team determined that this pathway, when activated, can rescue nerve cells from death. Dr. Jalabi is continuing these studies in Dr. Trapp's lab, to explore the possibility that this protective activity could be exploited as a therapeutic strategy in MS.

● Amy Waldman, MD (Hospital of the University of Pennsylvania) has completed a highly successful National MS Society-American Academy of Neurology MS Clinician-Scientist Development Award, which specifically trains physician scientists (scientists with MDs not PhDs). Working with mentor Laura Balcer, MD, MSCE, Dr. Waldman evaluated whether several tests that are used to track disease activity and treatment success in adults with MS could also be used in children. Armed with positive data about the usefulness of several tests, she is now collaborating with medical centers in Baltimore and Dallas to study a larger group of children. As we seek to improve the lives of children with MS, a tricky issue is testing medicine safely. Dr. Waldman's efforts to find the best ways of measuring success in this population are sorely needed. She is continuing her research at Penn as an instructor.

● Vinodh Pillai, MD, PhD, trained under mentor Nitin J. Karandikar, MD, PhD, at the University of Texas Southwestern Medical Center in Dallas. Dr. Pillai studied the immune attack in MS, specifically regulatory T cells (T regs)—a class of immune cells that can prevent damage but may be defective in people with MS. It has been difficult to separate these cells from attacking T cells. However, in samples isolated from people with MS, Dr. Pillai developed a new procedure that allows for such separation, which may eventually be used in MS diagnosis and in predicting treatment responses. Dr. Pillai is continuing his medical training with a residency in pathology at Harvard.

BILL STANTON

Commitment to MS research is the goal of the program, and it has been paying off for decades. The initial Society investment—currently about $150,000 for a three-year fellowship—has leveraged funding for former fellows for MS-related research (obtained through Society, federal agencies, private foundations, industry, universities, and other sources) of nearly $370 million.

Fellows are a vital force propelling MS research forward. Each young man or woman represents an opportunity for our cause—an opportunity to recruit an energetic and bright person who might one day find a therapeutic strategy, diagnostic technique or biologic mechanism that moves us closer to a world free of MS. ■