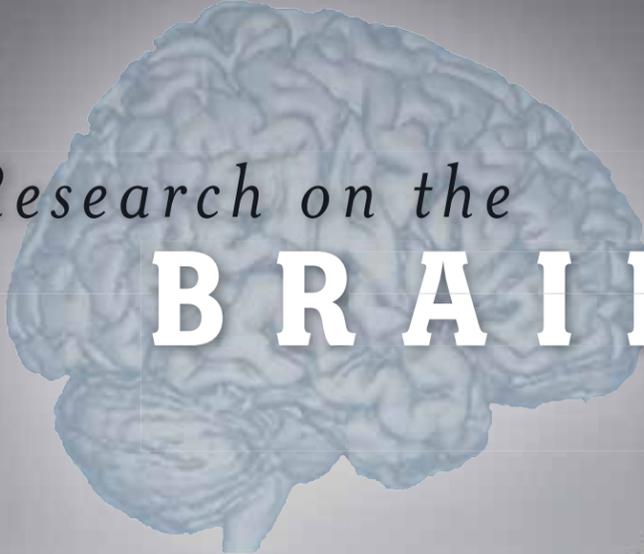


NEUROIMAGING ADVANCES AT UB ARE RESONATING WORLDWIDE



Research on the
BRAIN



FROM LEFT:
Jennifer Cox, PhD,
Robert Zivadinov, MD, PhD,
and Michael G. Dwyer

MAGNETIC resonance imaging provides a window into the brain, making possible striking technical advancements in understanding neurological disorders—advancements that seem almost like science fiction.

Quantitative magnetic resonance imaging (QMRI), for example, shows which brain structural morphologies are healthy and which are not. A second type, functional MRI (fMRI), identifies in real time the areas of the brain being recruited to accomplish a particular task: Tap a finger and the parts of the brain controlling that movement gleam on the computer screen.

One of the world's leading scientists in the growing field of MRI scanning is UB neurologist Robert Zivadinov, MD, PhD, associate professor in the university's Jacobs Neurological Institute (JNI) and director of the Buffalo Neuroimaging Analysis Center (BNAC). Zivadinov and his BNAC staff of 24 are harnessing the power of MRI to delve deeply into the brain to identify the causes of multiple sclerosis (MS), Parkinson's disease, Alzheimer's disease, lupus, stroke and other neurological illnesses, and to develop new drugs to treat them.

Zivadinov's reputation as an expert in MRI has been established by his work as principal author or coauthor on 76 studies published in refereed journals, and as an author on 15 additional papers currently in press. All of this has made him a sought-after lecturer throughout Europe and the U.S., which keeps him traveling 150 days a year.

One of those invitations in 2007 came from the European Committee for Treatment and Research in Multiple Sclerosis, orECTRIMS, which sponsors the most prestigious international conference dedicated to MS research. He was asked to be principal lecturer on MRI and remyelination at the organization's annual meeting held last October in Prague. In addition, his BNAC colleagues presented 16 abstracts at the event, considered a substantial number for a single institution.

STORY BY LOIS BAKER | PHOTO BY DOUGLAS LEVERE

SETTING THE PACE

ZIVADINOV is a native of Rijeka, a seaside city on Croatia's Adriatic coast, which he describes fondly as "beautiful, beautiful, beautiful." The region was spared deprivation and devastation during the Balkan wars, and his parents and brother live there still. Zivadinov himself was not so fortunate, eventually landing in the midst of the conflict when, as a new graduate of the University of Rijeka's Faculty of Medicine, he was called upon to serve a nine-month term as a war-zone physician in 1991-92.

In the subsequent nine years he completed a four-year neurology residency at the University of Trieste, Italy, (his mother is an Italian citizen) and obtained master's and PhD degrees in neuroscience from the University of Rijeka. While completing his degrees, he treated MS patients, conducted research and published consistently in respected journals.

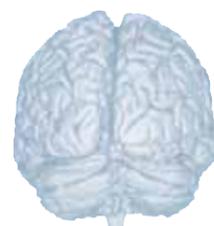
Working with patients, some as young as 18 years old, motivated him to organize the Center for the Analysis of Magnetic Resonance Imaging in Trieste, the first laboratory to conduct computerized imaging of MS in that part of Italy. During those years, he and center colleagues published a series of important MS studies.

Among those impressed with Zivadinov's work was Frederick Munschauer, MD, chair of the UB Department of Neurology and chief of the JNI, who had heard Zivadinov present at professional meetings on the findings of two landmark studies on which he was principal investigator.

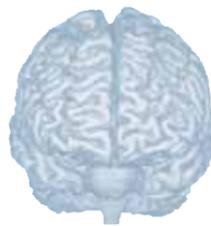
One paper, titled "Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS," published in the October 2001 issue of *Neurology*, showed that prolonged treatment with pulsed methylprednisolone delayed brain atrophy and progression of disability in this most prevalent type of MS. The study altered the direction of research into drugs that treat relapsing-remitting MS and launched more than 15 clinical trials by pharmaceutical companies to test the effect of adding methylprednisolone to their existing MS drugs.

A second study, published that same year in the *Journal of Neurology, Neurosurgery and Psychiatry*, showed for the first

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Posterior



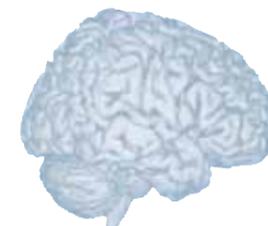
Anterior



Inferior



Superior



Right Lateral



Left Lateral

time that brain atrophy can predict future cognitive deterioration in the brains of patients with early relapsing-remitting MS*.

RENOVATION AND EXPANSION

Munschauer recruited Zivadinov to UB and the JNI in March 2003 to serve as the BNAC's associate director. Zivadinov assumed leadership of the BNAC when Rohit Bakshi, MD '91, associate professor of neurology and BNAC's founding director, left for Harvard Medical School the following October.

Since Zivadinov became director, the BNAC has generated more than \$10 million in outside funding. Through initial grants from Buffalo's John R. Oishei Foundation,

funding from pharmaceutical companies to conduct MRI drug studies, and grants from the National Multiple Sclerosis Foundation, he has transformed the center into a major force in neuroimaging research, education and clinical diagnosis locally, nationally and internationally.

He has overseen a \$10 million physical renovation and expansion of the center in Buffalo General Hospital, financed primarily by Kaleida Health, and has built a four-part infrastructure that supports patient diagnosis, clinical trials, research and education.

Clinical research is one of the center's most profitable enterprises. BNAC specialists read and analyze the findings of MRIs for multicenter clinical research trials sent from nearly 100 centers around the world. They also conduct analysis and research in collaboration with major pharmaceutical companies, which is an important funding source for the center.

The BNAC also houses a technical imaging unit and a clinical imaging unit. The technical imaging unit develops new algorithms and software programs that are applied in

research projects and clinical diagnoses. The clinical unit tracks patients' disease progression with a variety of newer conventional and nonconventional QMRI techniques and generates a rich database for the JNI's own research.

Zivadinov and colleagues follow approximately 3,000 MS patients with MRI at the Baird MS Center—a part of JNI that is headed by Bianca Weinstock-Guttman, MD—in addition to processing nearly 10,000 high-quality scans per year for patients with a variety of neurological diseases.

The experimental scanning unit concentrates entirely on developing cutting-edge MRI sequences and scanning protocols that can be patented and eventually applied to patient diagnosis, monitoring and research. Finally, the administrative unit holds it all together and carries out the center's educational activities.

IMPENDING PATHOLOGIES

One of the center's major accomplishments has been the development of a color-coded system for analyzing MRI brain scans of MS patients, called a lesion-classifier analysis. Using this program, MRI scans automatically are labeled to distinguish stable lesions (yellow), from new lesions (red), from lesions that have resolved (green) or those that have become atrophic (pink). (See *Figure 1* on inside back cover.)

The classifier-analysis system is among the new tools for analysis that the BNAC intends to patent. "This is a very useful program for clinical and research purposes that can be applied to many diseases," says Zivadinov. "In brain tumors, as in MS, you want to understand the dynamics of lesion changes over time. It is important to distinguish between old lesions, new ones and those that are stable or atrophied."

All MS patients treated at the JNI undergo a classifier analysis at every clinical visit, providing essential information to the physician while generating a vast database of images that serve as a rich research resource.

Zivadinov is convinced that the most exciting aspect of such new nonconventional techniques is their potential to

uncover and monitor impending brain pathologies before they become clinically manifest: to make the "invisible visible."

"This is one of our most important contributions to the field of imaging," he says.

APAPER HE AUTHORED in the May 29, 2007, issue of the journal *Neurology* revealed that, aside from lesions in the white substance and between the white and gray matter of the brain, many existing smaller lesions are not visible on scans using conventional MRI. The existence of these developing lesions can be proven indirectly by new methods of MRI, such as magnetization transfer imaging, diffusion tensor imaging and spectroscopy, advanced techniques that are used in BNAC. "The future of the modern QMRI lies in underlining and uncovering invisible pathology," says Michael G. Dwyer, BNAC technical imaging director. "This can be applied not just to MS, but to many other neurological diseases."

BNAC recently developed voxel-wise magnetization transfer imaging software capable of uncovering areas of pathologic demyelination long before the visible lesions are delineated using standard 1.5 Tesla conventional MRI (see *Figure 2* on inside back cover).

No Uncertain Terms

Given the number of terms and abbreviations introduced in this article, we thought our readers would appreciate the following quick-reference guide.

BNAC—BUFFALO NEUROIMAGING ANALYSIS CENTER
fMRI—FUNCTIONAL MAGNETIC RESONANCE IMAGING
JNI—JACOBS NEUROLOGICAL INSTITUTE
MRI—MAGNETIC RESONANCE IMAGING
MS—MULTIPLE SCLEROSIS
QMRI—QUANTITATIVE MAGNETIC RESONANCE IMAGING

* SINCE COMING TO BUFFALO, ZIVADINOV HAS PUBLISHED SEVERAL PAPERS ON COGNITION AND A VARIETY OF MRI TECHNIQUES IN COLLABORATION WITH RALPH BENEDICT, PhD, UB PROFESSOR OF NEUROLOGY AND HEAD OF THE JNI'S NEUROPSYCHOLOGICAL DIVISION.

TREAT NOW, DON'T WAIT

“WHILE THERE MAY NOT be a cure for most neurological diseases, the benefit of very early detection is that drugs that can modify symptoms or slow progression could be used much earlier than was possible in the past,” notes Zivadinov.

“Fifteen years ago there were young people with MS who were wheelchair bound by 35,” he continues. “We don’t see this devastation any more. Drugs have changed the natural history of the disease. It’s the same with Parkinson’s, and it may be for Alzheimer’s. The key is to diagnose these diseases as early as possible. You don’t have to wait for a person to develop Alzheimer’s before attempting treatment. There are subtle regional changes in the hippocampus many years before a patient develops the clinically advanced disease. So if we could use these quantification techniques to predict who is going to develop Alzheimer’s—at least in patients who show some mild cognitive impairment—maybe drugs that are not effective in the final stages will work earlier.”

So the prevailing question Zivadinov poses to the neurological field is this: Do we treat the present symptoms or the future disease?

“Should I treat the changes that are invisible but detectable on QMRI several years before the disease becomes clinically manifest or progressed, or should I wait to begin treating the patient when it is already too late? If you treat the patient when the disease has already progressed, you will be several years too late. If we can see brain atrophy occurring in patients during early stages of the disease,

If you treat the patient when the disease has already progressed, you will be several years too late. If we can see brain atrophy occurring in patients during early stages of the disease, should we let it go, or should we intervene, even though they may not present advanced clinical symptoms?

should we let it go, or should we intervene, even though they may not present advanced clinical symptoms?”

For Zivadinov there is no question. The catch, however, is that insurance companies are willing to pay for neurological treatment but not prevention—a mistake, in Zivadinov’s opinion, and one that he continually lobbies to correct.

EXPANDING THE SCIENCE

While the power of MRI devices in standard use today is 1.5 Tesla, improvements have been made, and 3 Tesla-strength devices are becoming available that can reveal significantly more pathology in the brain.

A 3 Tesla—one of the first in the country—is already housed at the BNAC. Currently, Zivadinov and his team are comparing a number of 1.5 Tesla and 3 Tesla imaging techniques with other immunological and genetic biomarkers in MS and other neurological diseases in collaboration with Murali Ramanathan, PhD, associate professor of pharmaceutical sciences.

The potential of fMRI to expand the science of neurology is equally promising, according to Zivadinov. Unlike a QMRI, taken while the patient is quiet and passive, fMRI is acquired while the patient is participating actively in a task. The BNAC currently is using fMRI in collaboration with several UB researchers.

Jennifer L. Cox, PhD, assistant professor of neurology and director of BNAC’s Experimental Scanning Program, heads the fMRI subunit. The BNAC plans to increase involvement in this type of brain imaging because it can be applied in “a million different projects,” including those that are not disease based, says Zivadinov. “We are very interested in using fMRI to test normal people,” he says. “For instance, does a singer use the same areas of the brain as a non-

singer, or do specific areas in a singer’s brain change activation patterns over time? There have been studies of taxi drivers in the UK showing certain areas of the brain are more developed than others. The intriguing question is, ‘Did these subjects choose to become taxi drivers because they have a special capacity [for complex navigation], or did that capacity develop through structural-functional adaptation?’ These types of studies would be extremely interesting.”

DEEPER INTO THE BRAIN

Evidence of the high regard in which the BNAC is viewed is its research affiliation with the General Electric Company, a major manufacturer of MRI scanners. The agreement provides access to GE’s massive computing power at its medical systems headquarters outside Milwaukee, Wisconsin. BNAC physicists use this access to develop increasingly powerful and sophisticated novel scans (sequences) for MRI exams. No other facility in Western New York has similar access.

Zivadinov describes the value of the GE affiliation this way: “You buy a top-of-the-line SUV—with GPS, leather seats, all those fancy things—but you still can do only certain things with it. But if you buy a Ferrari, which is about 10 times more expensive, it has options that a luxury SUV does not have. So our 1.5 Tesla and 3 Tesla scanners here at Kaleida Health’s Buffalo Niagara MRI Center are Ferraris. Why? Because they operate in ‘research mode.’ We can adopt and develop new sequences for GE that are not yet commercially available, but are already being applied in the BNAC at clinical and research levels. That’s why we created our experimental scanning unit—so we can develop new sequences that allow us to see deeper and deeper into the brain. Can you tweak a Ferrari? You have to go to a special place to tweak the Ferrari. That’s what we are doing here. BNAC is able to tweak a Ferrari.”

NO LESS THAN “NUMBER ONE”

Aside from directing research and clinical activities, Zivadinov and the BNAC staff maintain a full schedule of educational activities to train physicians on MRI imaging. Symposia on using MRI for MS, for which attendees receive continuing medical education (CME) credit through UB, were held in six cities throughout the U.S. in 2006 and 2007.

Parkinson’s disease will be the theme of the 2008 symposia. Monthly MRI seminars on MS have been held at the BNAC since 2004. More than 300 neurologists from across the U.S. have participated to date. In addition, UB-accredited, web-based CME courses on 10 clinical subjects are available through the joint collaboration between BNAC and JNI’s Kenneth Alford Medical Education Center.

The BNAC also supports a select number of MRI international scholars and fellows annually through the Dr. Lawrence D. Jacobs Fellowship Program. Jacobs chaired the UB Department of Neurology, founded the JNI, and was known worldwide for his pioneering work in MS and MRI.

Zivadinov’s plans for the BNAC are impressive. His ultimate goal is no less than making it the “number one” MRI institute in the world.

Meanwhile, he is promoting the use of MRI imaging at multiple levels throughout UB. “Imagine if we could create more collaboration in fMRI, in structural imaging, in different diseases and normal conditions,” he says. “I see the BNAC as an engine for imaging research in Buffalo.”

He also wants to become more involved in clinical trials and in NIH-funded research.

“Hopefully,” he says, “all this will come.” **BP**



A Point of Convergence

STUDY COLLABORATIONS USING ADVANCED MRI ANALYSIS

The availability of advanced MRI analysis at Buffalo Neuroimaging Analysis Center has led to research collaborations with UB researchers conducting studies in a variety of areas, including:

JANET SHUCARD, PHD, a neurologist, to image cognitive deficits in lupus patients;

JOHN VIOLANTI, PHD, an epidemiologist, to study post-traumatic stress disorder in policemen;

KERRY GROHMAN, PHD, in the Research Institute on Addictions, to study imaging aspects of neurocognitive rehabilitation in alcohol treatment;

RICHARD SALVI, PHD, in the Center for Hearing and Deafness, to identify the regions of the brain and biochemical changes that give rise to the phantom sound of tinnitus;

PETER Q. PFORDRESHER, PHD, in the Department of Psychology, to study manipulations of auditory feedback during the production of musical sequences;

HANI ABDEL-NABI, MD, PHD, in the Department of Nuclear Medicine, to study the impact of regional cerebral metabolic assessment in patients undergoing evaluation for mild cognitive problems;

JOHN BAKER, PHD, in the Department of Nuclear Medicine, to study computer-assisted SPECT diagnosis of vascular dementia.