BRIEFING PAPER SERIES / *Research & Scholarship*

Studying the Brain to Understand Ourselves

FEATURED FACULTY
Joseph W. Harding
James Krueger
Maureen Schmitter-Edgecombe
John "Jay" Wright

Neuroscience. Science of the brain. Somehow words don't convey the enormity of the endeavor: trying to understand our body's astonishing ability to grow, adapt, learn, remember and think. In the 21st century, humanity's common body of knowledge—of art, history, science, literature—is beyond what any single person could learn. But, equally awe-inspiring, especially to a neuroscientist, is the enormity of what our bodies "know" to do from the moment we are born. In an internal cosmos of almost unimaginable complexity, trillions of neural signals navigate the sea of protoplasm every moment of our lives to keep our heart beating, our blood pumping, our mind collecting, sorting, storing and organizing information that helps us realize our human potential more fully. It's a field where certainty is elusive and progress is painstaking, but every step brings us closer to understanding who we are as a species and how we work. Questions such as how do we sleep and why do we sleep? Why do brain injuries and disease affect some memories and not others? What can we do when a function that should be automatic, suddenly isn't? Working in their own labs and in collaboration with their colleagues, nationally-recognized faculty members in the Department of Veterinary and Comparative Anatomy, Pharmacology and Physiology and the Department of Psychology at Washington State University are tackling these fundamental questions and others. James Krueger, Maureen Schmitter-Edgecombe, John "Jay" Wright and Joseph W. Harding are among many scientists at WSU whose work is being supported by major grants from the National Institute of Health, the National Science Foundation, the National Institute on Aging and other federal agencies because it has the potential to change lives.

TO SLEEP PERCHANCE TO DREAM...OR IS THERE ANOTHER REASON?

Why do we sleep and how do we sleep? Philosophers as far back as Plato and Aristotle had their ideas, but Dr. James Krueger, professor of neurobiology, is as close as anyone has ever come to providing real answers.

Krueger, who first rose to the front ranks of sleep researchers when he was working at Harvard in the early 1980s, says figuring out the function of sleep is one of the most important problems in all of science because an understanding of why we sleep will be needed before we can hope to understand thought, perception and emotion. Thus, for example, Krueger is trying to answer the question, what does the brain need that sleep provides?

Krueger's theory is that sleep allows the brain to reorganize its "synaptic superstructure." Synapses are the connection between neurons, the kind of brain cells that carry information, and they are what allow the brain to talk to itself and other parts of the body. There are over a trillion synapses in the human brain. Synaptic connectivity patterns are constantly reconfigured every day as people learn and experience new things. These changes have to be superimposed on the synaptic structure already present.

Krueger believes that sleep allows the brain to incorporate new memories while maintaining much of the original synaptic pattern design so that the mind can, in effect, regroup and be ready for the next day's onslaught of stimulation and synaptic re-wiring. This process aided by sleep is called synaptic scaling.

Krueger and his associates have tested this "synaptic superstructure" theory at WSU with rats. Knowing that rats gather environmental information with their whiskers, researchers shaved the whiskers off one side of a rat's face. Within a few hours, researchers could detect changes in the opposite side of the brain in the somatosensory cortex, the area that contains neurons that register the whisker sense of touch. Krueger and his colleagues were then able to compare the differences in synaptic structure between rats that were allowed to sleep and those that were kept awake. Rats that had been allowed to sleep appeared to adapt more quickly to the change, adding support to the theory that sleep aids synaptic reorganization.

Krueger and his colleagues are continuing to investigate this relationship between sleep and synaptic reorganization, but a main focus of his research continues to be the biochemical regulation of sleep, as well as the relationship between sleep and infectious diseases. He has identified a variety of neurochemicals that affect sleep and is continuing to investigate how those neurochemicals function to create a biochemical cascade that results in sleep.

Kreuger, who has published more nearly 300 articles, joined WSU in 1997. That same year he was awarded the prestigious Javits Neuroscience Award, which came with a seven-year grant of nearly $2 million. His work has been supported by numerous other grants from NIH, The Office of Naval Research, and the US Army Research and Development Command.

LOSING MEMORY BUT NOT YOUR LIFE

Whether memory loss occurs over a long time, say 10 years or more, or in one traumatic moment, the consequences are utterly devastating. Maureen Schmitter-Edgecombe, an associate professor in the Department of Psychology at WSU, has seen the fear and hopelessness that accompany severe memory loss. But, her research gives her, and others, reason to hope. She doesn't suggest that memory loss can be "overcome," but she does believe many people can be helped to live independent, satisfying and productive lives, even while living with the challenge of impaired memory.

In her work as a cognitive and clinical neuropsychologist, Schmitter-Edgecombe has two distinct but related areas of research. One is working to identify and then assist those who have mild cognitive impairment, a condition that is often a precursor to Alzheimer's disease. Because of her promising research in this field, Schmitter-Edgecombe was one of 15 young scientists selected to participate this year in the highly competitive Sixth Annual Institute on Aging sponsored by the National Institute on Aging. This spring she was awarded a 4-year $500,000 grant from the National Institute of Stroke and Neurological Disorders to conduct a longitudinal study on age-related memory disease.

The other focus of her research is working with survivors of motor vehicle accidents or others who have suffered a traumatic head injury that put them in a coma for a period of time. In both cases she has advanced the field of cognitive neuropsychology by focusing attention not only on the abilities that were lost, but on what remains. More specifically, her goal is to figure out how the remaining capabilities can be used

most effectively so that a person suffering significant impairment can still live independently.

Not all memory is the same. Though the definitions sometimes overlap, there are many types of memory, including short term, long term, episodic, semantic, explicit and implicit, and different areas of the brain process different types of memory. In a healthy adult, information is recalled quickly and seamlessly from various domains. For instance, a man driving home from work might suddenly notice a 1956 Chevy which reminds him of his father, which reminds him he needs to buy a birthday card for him right away, which reminds him that he was supposed to buy groceries on the way home. He remembers that he forgot the list, but he's sure that bread and tomatoes were on it.

A person with early Alzheimer's disease or a traumatic brain injury would not be able to traverse the many layers of memory processing. While older memories, which have been consolidated in long-term memory, usually remain, information which was consciously learned and must be consciously recalled, such as the grocery list, would not. The challenge is to help people learn to work as efficiently and effectively as possible with the capabilities that remain.

According to Schmitter-Edgecombe's research, healthy adults suffer relatively minor memory lapses of any kind until they are well into their 70s or 80s. Unfortunately, nearly 400,000 Americans are diagnosed with Alzheimer's disease every year. She believes that early identification is important because it would allow people to learn new ways of learning and remembering. By building on memory processes that are unlikely to be significantly impaired, people can significantly prolong their independence and their involvement with the people and work that matters to them.

For example, a person suffering mild cognitive impairment might learn—more precisely, he or she might over-learn, or learn to the point of automaticity— to write down useful information in a memory notebook. Since remembering to write in a notebook is part of the challenge, one strategy Schmitter-Edgecombe has tested is asking people to use a watch alarm that goes off hourly to remind them to write in their notebook. The notebook then becomes an external memory aid and could prolong a person's independence by years.

Schmitter-Edgecombe has been at WSU since 1994. Her work has been supported by grants from the National Institute for Child Health Development among others. Her B.A. was from Bucknell University and her doctorate from the University of Memphis.

FINDING NEW WAYS TO BATTLE DEGENERATIVE MEMORY DISEASE

It's the kind of research usually associated with a large, metropolitan medical school, but it's happening right here at WSU. John "Jay" Wright and his colleague Joseph W. Harding, have not only identified a new type of brain receptor that appears to be crucial to understanding Alzheimer's disease, but they have synthesized a dozen drug compounds that can improve memory and perhaps significantly delay the onset of this devastating disease.

Animal trials in their lab at WSU have been promising, but the next step, toxicology tests and human trials, are so expensive that Wright and Harding have had to find a private company to take on the project. Once the one or two most promising drugs have been identified, CogState Ltd., an Australian company, will likely begin the testing necessary to determine the drug's safety and usefulness to humans.

Harding and Wright, both professors in the departments of Psychology and Veterinary and Comparative Anatomy, Pharmacology, and Physiology, began their collaboration 27 years ago when both were new to the university.

The art and science of what Wright, a behavioral physiologist, does, is create rodent models of a disease state— such as high blood pressure—which affects humans but doesn't naturally occur in animals. Once he has figured out how to impair the appropriate brain receptor, Harding, a medicinal chemist, works to create a chemical compound to repair the damage. Their work with memory actually began when they were looking for a receptor they thought affected blood pressure. The plan was to locate the receptor, impair it in such a way that the rat's blood pressure would rise and then create and test various drugs designed to lower blood pressure.

They found the receptor they were looking for, one that was previously unknown, but it didn't affect blood pressure. It affects memory.

Unexpected and initially disappointing, the discovery forced the two scientists to change the focus of their collaboration. As sometimes happens in research, what appeared at first to be a dead end has become an exciting and productive avenue of research. While other researchers have already identified brain receptors for blood pressure and have designed drug therapies that appear to be effective, Wright and Harding are on the cutting edge with their research on the AT4 receptor and it's link to degenerative memory disease such as Alzheimer's.

Wright and Harding have tested their theory by putting rats through a water maze that requires them to use visual clues to find a slightly submerged pedestal to rest on. The researchers first tracked the learning curve of normal rats and timed how quickly they could find the pedestal. Harding and researchers in his lab then impaired the AT4 receptor and again tracked the learning curve, documenting the extent of the memory loss or impairment. Finally, the impaired rats were given synthesized drugs and put through the maze again.

Results have been very encouraging. Rats treated with several of the drug compounds have shown significant improvement in their ability to remember how to use the visual clues to find the submerged pedestal. But, as veteran researchers, Wright and Harding know to temper their enthusiasm and just keep working.

In addition to this work, Wright's lab is currently testing theories about memory consolidation and the importance of sleep by manipulating the AT4 receptor in rats and tracking the differences in spatial learning and memory. Harding's lab continues its work to better understand the function and mechanism of neuropeptides, particularly the angiotensins, of which AT4 is one.

Their work has been supported by grants from the NIH, NSF, American Heart Association, Sleep Medicine Education Research Foundation, WSU Alcohol and Drug Abuse Program, Parkinson's Disease Foundation, and a contract from the Lilly pharmaceutical Company. Wright completed his B.A. and M.S. in psychology at Western Washington University and his Ph.D. in experimental psychology at Michigan State University. He joined the faculty at WSU in 1975. Harding earned his B.S. in chemistry at Allegheny College and his Ph.D. at the University of Delaware. He has been at WSU since 1976.