BRAIN TEASER

Even as a youngster in her hometown of Palermo, Italy, **Caterina Rosano** had a fascination with the mysterious powers of the brain. Now, as a physician and epidemiologist, she is still immersed in understanding how the brain works—and what the aging brain may reveal about the secrets of longevity.

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Physician Caterina Rosano walks toward Fifth and Bellefield avenues on her way to work. As she approaches the corner, the pedestrian walk-light is blinking "go," yet she observes an elderly woman hesitating to cross. It's raining, and the woman juggles an umbrella in one hand and her purse in the other. Rosano is hardly inconspicuous as she nears the corner. She's dressed in a stylish black leather jacket, black slacks, not-exactly-practical boots, and a red scarf. Still, she emits a quiet, observant presence. What she sees is a woman, probably in her late 70s, calculating risk versus reward: Is there enough time remaining to cross the four-lane boulevard before oncoming traffic springs ahead? On another level, what she sees is someone striving to maintain independence in the face of increasing limitations—someone facing the realities of aging. For Rosano, it's a reminder of the essence of her scientific work, which explores the riddles of aging.

"There's something mysterious about older adults," she says. "Why do some adults live longer and better, surviving against all odds"?

Rosano—an accomplished researcher in the University of Pittsburgh's Center for Aging and Population Health—defines healthy aging as the ability to function independently. Her work suggests that it's not an absence of health obstacles that matters, but rather an ability to compensate for them.

Rosano doesn't have much of a view from her campus office in the Bellefield Professional Building. That's why she has panoramic photos of her native Italy taped to the walls. The pictures give her a semblance of sunlight, even on gray days. Usually, though, her focus is not on the weather or the view. Instead, images and articles about the brain dot the wall above her desk. Much of the time, Caterina Rosano has the human brain on her mind.

Now, Rosano is extending and broadening such studies, breaking new ground in the field of neuroepidemiology. By understanding the relationship between the brain and physical functions, she aims to identify predictors of successful aging. The goal is nothing less than to unriddle the mysteries of aging.

That's really nothing new. From her youngest days, she was eager to improve her own brainpower. During her childhood, she had a hearing impairment that has since been corrected, but the initial ailment pushed her to compensate for her less-than-perfect hearing. She wanted to be smart, then smarter, which launched her odyssey to learn and keep learning.

She found a ready ally in her father, who had a roomful of books, many about improving brainpower and boosting IQ. Together, they spent hours in his library, playing games, solving puzzles, and challenging each other to be better, faster, smarter. Sometimes she did well on a quiz and sometimes not. She wondered: Why was that? What accounted for her learning well, or not? What, exactly, was going on in her brain?

"I know," she admits now, "it sounds very dorky." But that's where her passion for the brain—her passion for *improving* the brain—started. And never stopped.

Her youthful curiosity and her eagerness to learn ultimately led to medical school at the University of Palermo in Italy. There, she began to delve into biological models of how the brain learns. When she graduated in 1995, she accepted a postdoctoral fellowship in neuroscience at Jackson Memorial Hospital in Miami. At the time, her research focused on the brain's ability to regenerate tissue.

In those early days of her career, Rosano's drive to understand the brain was confined to the laboratory, working with animal models. As a "bench" researcher, she spent her time examining cells and molecules in the brains of rats. She examined the effects of stress on brain chemistry, on cell survival, and on learning. She also looked at factors that protected cells from the potential damage of stress. The research was intriguing, but it would take years, perhaps decades, to yield benefits for humans.

So, her quest to learn more and to help people more directly led her to Pitt's Center for Neuroscience, which she joined as a research associate in neurobehavioral studies in 1999. The center is a premier site for brain-function studies, versed in the latest brain-imaging technologies. A key tool in those endeavors was magnetic resonance imaging (MRI), a scanning technique that reveals remarkable anatomic and physiologic details. Rosano began to use the technology to explore human brain performance in both young and old adults. It offered an entirely new realm of possibilities for unraveling the enigma of the brain.

As so often happens at the University of Pittsburgh, she soon learned about other intriguing research opportunities. She also began to pursue a master's degree in epidemiology—the study of the causes, transmission, patterns, and prevention of diseases in populations. In 2001, she was awarded a National Institute on Aging (NIA) fellowship to pursue studies on the epidemiology of age-related brain-function impairment, and she conducted research in Pitt's Department of Epidemiology within the Graduate School of Public Health (GSPH), which ranks third in the nation in attracting federal funds for research enterprise.

During this time, Rosano contributed by bringing her brain-imaging skills into studies of gait and balance. Slowdowns in gait and disorders of balance can be disabling, create falls, and may limit independence. She worked closely with epidemiologist and Pitt researcher Anne Newman. At GSPH, Rosano—who earned a master's degree in public health in 2003—was able to combine MRI technology with a treasure trove of existing data on elderly populations.

In 2005, she became a scholar in the Pittsburgh Claude D. Pepper Older Americans Independence Center, a program in Geriatric Medicine funded by the NIA that partners with the Center for Aging and Population Health in GSPH. Along the way, she received grants and more intensive training through the center, where she was working with a range of Pitt experts on aging and the brain, especially Stephanie Studenski, a Pitt professor of medicine and the Pepper Center's director, and Howard Aizenstein, a professor of psychiatry and bioengineering, as well as director of Pitt's Geriatric Psychiatry Neuroimaging Lab.

With the help of Newman and other epidemiology colleagues, Rosano began to delve into the department's huge database of longitudinal studies—studies conducted in populations over long spans of time to acquire scientific insights about health through the years.

For example, back in the mid-'90s, Newman launched the Health, Aging, and Body Composition Study, involving more than 3,000 adults, to identify risk factors important for maintaining mobility. In 2005, Rosano recruited 300 local residents from this study and took MRI scans along with sophisticated gait measurements. Now with approximately 250 of the original volunteers still living and still participating, Rosano is able to conduct comparative follow-up studies.

She intensified her search for evidence of age-related brain changes that affect cognitive and physical functions. Her research, using advanced software on brain images acquired in the Cardiovascular Health Study, for instance, identified vascular brain abnormalities that seemed to affect gait. Elders with slower gaits and balance difficulties also had less gray matter in particular regions of the brain. A smaller prefrontal lobe, even in the absence of cerebral vascular disease, appeared to be related to slower gait.

But her work also began to reveal more hopeful evidence. Last spring, *The New York Times* and other national media reported on Rosano's research with a group of elders, all more than 70 years old. One group committed to physical activity—walking at least 150 minutes a week—the other half remained sedentary. She found intriguing differences in the brains of the two groups. Even up to two years after the end of the year-long study, those who walked regularly were faster at test-taking and made fewer errors compared to the others. Rosano's

brain imaging scans showed that more parts of the brain were activated in the walkers versus those who were sedentary. In the *Times* May 2010 story, Rosano concluded: "Some level of physical activity, even started later in life, can potentially impact the brain."

Now, Rosano is extending and broadening such studies, breaking new ground in the field of neuroepidemiology. By understanding the relationship between the brain and physical functions, she aims to identify predictors of successful aging. The goal is nothing less than to unriddle the mysteries of aging.

"A mystery," she says, "makes me want to know what's behind it, don't you think? That's the essence of someone who does research—the investigator, the detective. That's how I see researchers, as detectives trying to put togther all the clues and the pieces of the puzzle."

She's getting help from various Pitt research collaborators, many of whom are increasingly interested in the exception rather than the rule. Among them is Newman, who today is chair of Pitt's Department of Epidemiology, director of the Center for Aging and Population Health, and a professor of epidemiology and medicine. Aging is tough, says Newman, and there's a lot to be learned from the people managing to do it well.

"One of the first times I met Anne," Rosano recalls, "she told me we should study the cream of the crop, and it really stuck with me because, at first, I didn't know what that meant. What's the crop? What's the cream?"

Although the expression did not initially translate well, Rosano soon understood the sentiment: Focus on those who age better than the rest of us, who rise above the inevitable maladies of a long life.

Examining health data from older adults gathered over the course of decades, Rosano found something she expected—a segment of elders who managed to stay relatively healthy despite the onset of aging. In research parlance, these are the "outliers," people who fall outside the normal ranges of their group. These are the cream of the crop for her research pursuits. But there was a deeper mystery, something even more elusive than the health of the cream of the crop: Another group of elders defied every expectation.

Rosano

In a separate subset of about 6,000 aging adults, Rosano and her research team examined data from MRI brain scans and pen-and-pencil tests that gauged cognitive function. About 20 percent of the test group scored poorly in terms of the physical condition of the brain in MRI images, yet these same individuals scored extremely well on the cognitive tests. She retested, looking at additional data. Again, about 22 percent had the resilience factor—bad brain MRIs but good test scores.

"One-fifth of the people we look at completely escape any sort of prediction," she says, "and this is what is fantastic to me. These people function and move around very well, but their brain MRIs don't look good, and we don't understand why."

The members of the one-fifth club apparently have a secret that enables them to live longer and live longer free of dementia than the other four-fifths of the test population. So, she asks: What's the mystery? What's so different in the pasts of these people to account for their resilience?

Among the possibilities, spikes in blood pressure appear to be more detrimental to the brain than a measured rise in pressure over time. Perhaps a slower progression in pressure gives the brain time to adjust, without causing harm, Rosano speculates. In another of her studies, she is beginning to see that the brains of those with diabetes appear older than usual—could high glucose be a factor in causing the brain to age more quickly?

Rosano's research offers tantalizing clues about the aging brain. Maybe it's a greater ability to problem solve, along with the ability to rewire new connections in the brain. Scientific revelations during the past decade have shown that the brain has a lifelong ability to rewire neural pathways, to compensate for damage. It's a burgeoning field of study called brain plasticity. Could some elders have a better capacity for neural rewiring; if so, why?

"We are beginning to see that we have to look at the brain in much greater detail," she says. "It's not enough to look at how big it is, not enough to look at how much blood goes through it. We have to look at neural activity and microstructural changes combined. We have to look at how fast and where specifically these changes occur."

So, Rosano and her research team are using more advanced, cutting-edge brain MRI scans to see greater details. And they're creating new ways to examine these elusive details. As usual, Rosano wants in on the secrets of brain power, and she's committed to understanding it.

"We have learned a lot already," she says. "If we continue to search, we'll get more pieces of the puzzle."