Weightlifting for the Mind

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The brain is like a water clock, a system of carefully calibrated hydraulics.

The brain is like a telegraph machine, or rather, a phone, receiving calls from neurons and propagating the information to stimulate motor responses.

The brain is like a computer, performing complex calculations quickly, functioning as the central processer and establishing countless connections between various ideas.

Those metaphors and many others have taken hold throughout history as ways of describing how the brain operates. But the work of Dr. Yaakov Stern, a neuropsychologist at Columbia University, provided support for a new idea about how the brain works: The brain is like a muscle, growing stronger as people learn and work and solve problems. This idea is called cognitive reserve. With more exercise, the brain can help to fend off the devastating effects of age and disease. Like muscles, if you do not use and exercise your brain, you might lose it.

Shaking the scientific community's allegiance to its old metaphors for the brain was not easy. Those understandings of the brain are inseparable from religion, politics, and social status. Once a new idea was established, unseating it was heresy.

"This is how science works. Just people and ideas and evidence is amassed over time to support or refute them. If you wanted people to believe in it, you need to provide more evidence." Dr. Yaakov Stern explained. Stern is the Florence Irving Professor of Neuropsychology in the Departments of Neurology, Psychiatry, and Psychology, and the Taub Institute for the Research on Alzheimer's Disease and the Aging Brain at Columbia University.

Stern knows firsthand the challenges of introducing an uncomfortable new idea into the tightknit scientific community, specifically in the context of Alzheimer's disease.

Alzheimer's disease derives its name from Dr. Alois Alzheimer who noticed brain changes in a woman who died from a mysterious mental illness related to memory loss in 1906. He examined her brain after she died and found abnormal deposition and tangled fibers, which we now understand are called amyloid plaques and tau. These changes to the brain are central to our understanding of Alzheimer's disease along with loss of neural connections. Throughout the 20th century, researchers investigated every aspect of the disease, from the changes in the brain that could be seen on imaging to autopsy data after death to causes of cognitive decline. In the end of the 20th century, debates focused greatly on the causes of the disease and how it could be prevented, which is where Dr. Stern's research became focused.

Dr. Stern's involvement in research on Alzheimer's disease was both by chance and inevitable. Stern was raised in Nebraska, Ohio, and New York City. He grew up listening to his father tell stories about his father's father, Stern's grandfather, who was "senile." Stern recounts: "At that time they just called it senility. The term Alzheimer's disease was restricted to the familial form which occurs at early age." The family brought Stern's grandfather to a doctor who said "we will be able to cure it soon but not now." Stern described it as incredibly frustrating since "there

was nothing to do." Stern wished that in the future, discussions surrounding the disease would be more hopeful.

Stern studied psychology in college and then took a year off after college, as he tried to figure out what he wanted to do with his life. During this year, he and his future wife visited his brother-in-law who was studying philosophy at City University. His wife found the picturesque City University Graduate Center mesmerizing. "This is so beautiful, why don't you apply here," she suggested. It was too late to apply to most of the graduate programs, but there was a program called "experimental cognition" still accepting applications. He sent in his application, and they called him for an interview.

"Are you interested in animal studies," Stern's interviewer asked. Stern recalls, "Well I know they taught primates language and that is cool. They said, 'we do rats.' They said, 'and we do this thing called neuropsychology.'" Stern decided to join the 'rat lab' for a year and also became very interested in this new and exciting field of neuropsychology, which focused on the relationship between behavior, emotion, cognition, and brain function. Through his professors, he met Dr. Richard Mayeux who was working at Columbia University and began to work with him on research about Parkinson's disease and depression. He found the work interesting but not his passion. He was then pulled into Alzheimer's research, working on a study in the northern Manhattan community looking at elderly patients who did and did not have dementia. This was at the time that it became clear that Alzheimer's disease was common.

Around the same time that Stern was working with Mayeux on studying elderly patients with dementia, he started to hear that there might be differences in the risk of developing Alzheimer's as a function of education. It was the first hint of the ways in which the brain acted like a muscle, suggesting that the organ was not necessarily fated to decline steadily over time, but rather that people could exercise and fortify it in the same way they could a bicep.

Dr. Richard Katzman was first to write about the link between Alzheimer's and education. Katzman performed a prevalence study in China where he found that lower education was associated with higher rates of dementia. His research was preliminary and seen as unable to establish a firm association since he examined patients who already had Alzheimer's and worked backwards from there to find a connection to their education levels. Stern set out to find firmer evidence, using a different kind of study. Stern's group performed an incidence study, which examines the rates of dementia development in patients who started out without dementia. By using an incidence study, Stern could look at patients who were living in the same environments and had known education levels and watch to see if they developed Alzheimer's or not. "This was something we could really ask about in [the northern Manhattan] cohort. There were very few people who had done incidence studies where they started with people who were not demented and saw who became demented. At that point, there were maybe three or four incidence study. Two positive and two negative findings." Stern's team ultimately found that education served a protective function against dementia, which led to a groundbreaking publication and supported the idea that the brain needed to be exercised throughout one's life.

At first, this idea that education, a societally designed construct, could prevent cognitive decline, clashed with how other scientists looked at the brain. They put a lot of weight instead on the pathology of the brain, believing that the amyloid buildup central to Alzheimer's inevitably set in motion a series of changes that would result in memory loss.

"I gave a poster presentation at the Academy of Neurology and people would chuckle. The idea that education or life experience could fight the effect of a brain change like amyloid sounded crazy. It turned out that as time went on and many more studies were done, people realized that the negative studies didn't have the power to see effects. That was a very controversial idea," Stern explained. "As a neuropsychologist, the idea was very intriguing that people could have same level of amyloid but one person could be demented and another could not."

The idea behind Stern's research was this: if two people have the exact same disease markers and pathology in their brain from Alzheimer's disease, you would expect them to have the same decline in cognitive function and memory. However, this was not the case. If two people had the same level of disease in their brain in terms of amyloid, the people with higher levels of education could go longer before showing outward signs of the disease. Another way of thinking about it is that if you look at two people with the same amount of cognitive decline and you scan their brains, people with higher education have more severe disease markers/amyloid/brain changes, suggesting that people with higher education are better able to compensate for a diseased state.

This idea exhilarated Stern: "There was a question out there and I could say something about it. I was always very interested in individual differences!" When Stern published his first big paper on this topic in 1993, "a lot of people, even my colleagues at Columbia, did not believe it. It was not a well-accepted concept."

This was not the first time that Stern had to square up against the scientific masses. When he was doing research on Parkinson's disease, much of his research was also controversial. He focused on the cognitive changes in the disease and role of depression while most scientists claimed it was a purely motor disease. Similarly, he was undeterred by the unconventional themes in his research and was committed to producing more evidence to support his discoveries.

As time went on, Stern's ideas about Alzheimer's disease and the role of education became more widely accepted as more and more evidence and studies amassed supporting his ideas. In fact, Stern's papers on this concept are widely cited, earning thousands of citations. His big idea for the way in which learning could help fortify the brain against bad outcomes was named cognitive reserve. Over a lifespan, the brain functions as a reservoir, collecting the protective features of education, occupation, and skills rather than only pathology. These protective features mean that people are not powerless in their brain's battle with age-related decline, like previously believed, but rather, they are equipped with an arsenal, built from living their lives and going to school.

“Cognitive reserve is a very hopeful story,” Stern explains. “It doesn't matter if you have very bad pathology. There is a large portion of people who will never be demented as a function of reserve.” He sees this message as so hopeful because “there is a whole set of things to impart reserve. It’s hard to know if we can prevent pathology, but can we tolerate it? Yes. There have been a lot of interventional studies. Grandiose projects, larger studies that really enrich people's environments in ways that measurably impact age related cognitive change and dementia.” Stern sees the future of the field of Alzheimer’s research on cognitive reserve moving towards interventions to enhance reserve. Researchers are interested in meditation, diet, exercise, and cognitive training. They want to know how various aspects of lifestyle impact cognitive decline including socioeconomic status, occupation, genetics, and race. For example, it seems that workers in jobs that require more social engagement have greater cognitive reserve. It is not understood why. Researchers hope to use their results to address systemic inequalities that result in different rates of the disease and decline.

Changing the deeply embedded social inequalities that prevent people of lower socioeconomic status from reaping the benefits of the brain’s protective powers proves challenging. Unfortunately, the solution is not as easy as giving everyone a free gym membership to exercise their brain. Stern suggests that as a society, to build cognitive reserve in those who have been historically marginalized, there is a need for better schooling and generally improved access to education, starting at a young age with programs like daycare. He emphasizes that these benefits are amassed over a lifetime, so learning and engagement must be continual.

While there has been increased momentum to understand how cognitive reserve works and how it can be used to protect people, there have been many challenges in the research. “As the concept became more popular, there were lots of people talking past each other because they were not using the same terminology or operational definition,” Stern laments. Various international organizations have worked to establish task forces and focus groups to come up with agreed upon definitions since terms like “reserve,” “maintenance” and “resilience” had been used interchangeably despite having different meanings. Cognitive reserve was understood differently at different institutions, which resulted in different measures to quantify it. It has taken many years of workshops with dozens of prominent researchers who are experts in the field to define one concept (https://reserveandresilience.com/). Stern leads focus groups and organizations dedicated to defining cognitive reserve, which can be a difficult concept to grasp and operationalize.

Stern’s favorite part of research is “the path from having an idea to turning that into real research. That can take a very very long time. The process of nurturing that idea and figuring out how to make that work and transforming to a study and finding something new is very fun. In one paper, we said reserve may be implemented by flexibility. For example, when my daughter was learning math, 7+6 is like 7+3+3. That has been something I have really tried to figure out how to investigate. I finally worked with a graduate student who was a research assistant. We developed a task that directly tapped flexibility of solution strategy. This is now being incorporated into our research. The problem was nurtured 12-15 years.” Stern greatly

enjoys the collaborative nature of research, and credits many of his mentors for his discoveries. However, Stern hardly considers these scientific advancements inevitable.

If Stern's future wife had not been enchanted by the campus of City University, Stern may never had applied to their program and become involved in his research, which has resulted in countless world-renowned papers and scientific advancements in the field of Alzheimer's disease research. Throughout history, many scientific ideas have come about by chance and changed with the whim of politics or social circumstance. When first proposed, the idea that the brain was understandable as a machine and not merely a mysterious combination of substances completely controlled by God baffled the public and made prominent scientists laugh. Over time, as more and more evidence and scientists support an idea though, it becomes entrenched as it becomes incorporated into the current dogma. While it is frightening to think that so much of what we accept as scientific truth may have come about because of a trip to visit an in-law, it is also exhilarating to think of all the promise of the unknown and brave thinkers who "stepped out on a limb" and "swam against the current."

Without those courageous thinkers, willing to endure the laughter of their peers, we might not understand that the brain might be a clock, machine, or computer, but it is also a muscle. Stern helped us understand that with more exercise the brain becomes stronger and lasts longer. "Use it or lose it," Stern explains. "People get the idea that they should remain active and exercise and shouldn't sit around. More exercise means the longer [the brain] can go before degenerating." Stern and other researchers on Alzheimer's disease do not have all the answers about how to prevent cognitive degeneration, but they are committed to the continual questioning of their own and other's ideas that drives science forward.

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