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The Next Generation

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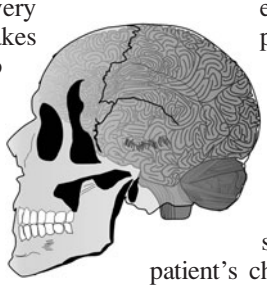
IT IS TRULY AMAZING HOW FAR our scientific endeavors have taken us. We have explored outer space, mapping our unique address in the cosmos. We have explored inner space, identifying subatomic particles and characterizing their roles in weaving the fabric of matter and reality itself. We have sequenced the human genome, providing us with countless biological insights ranging from the origin of our species, to the etiology of many diseases. But when it comes to the science of the brain, neuroscience, we are woefully ignorant. Considering that the brain is the organ we use to consider, this is something of a paradox. Nonetheless, brain science is the least explored of all our sciences.

As we have discussed before in our perspective pieces, the brain is just another organ. Like the heart, liver, lungs, and kidneys, the brain can be healthy and it can be unhealthy. Unlike the other organs, however, the brain is very difficult to study. Being housed inside the skull makes it far less accessible than the other organs. It is also not easy to identify or assess brain functions based on its structure—it is not a ''what you see is what you get'' (WYSIWYG) organ. In the real world, Mary Shelly's Dr. Frankenstein cannot, as yet, take the brain out of one animal and replace it in another. Finally, the brain is quite complex with many distinct functional areas that act in concert and in mind-bogglingly elaborate networks as the body's central processor, coordinating all of our physiological functions, thoughts, behaviors, memories, and personality. It is important to keep in mind the difference between complexity, which is inherent to an object or system based on the number of independent or connected parts, and complicated, which is the subjective perception or experience of a system. While the brain is clearly complex, it does not necessarily have to be complicated. The vast gap in our understanding of the brain's complexities, however, has only served to differentiate the brain from our other organs and to place it upon a tenuous pedestal, shrouded in darkness and mystery.



It is human nature to fear the unknown. The invisible and mysterious nature of brain function leads to an exponentially greater amount of fear and trepidation when it comes to brain disease and dysfunction. In fact, the brain is the only organ for which diseases are entirely diagnosed based upon symptoms and syndromes. Diagnosis of peripheral diseases such as hypertension, heart disease, diabetes, infection, or cancer is based on measured, quantitative biomarkers. These biomarkers can take the form of things like temperature, blood pressure, blood biochemistry (e.g., triglycerides, LDL and HDL cholesterol, and HbA1C, CRP), genetics (e.g., *Apo-E4*, *HPA2-met*, and *BRCA1/2*), images (e.g., positron emission tomography, functional magnetic resonance imaging, and X-ray), urinary metabolites (e.g., KIM-1), and antibody prevalence (anti-viral or anti-citrullinated protein/peptide antibodies). These biomarkers essentially serve as a fingerprint allowing for a very specific disease diagnoses based on pathologies, or the underlying root causes of disease.

When we go to the doctor feeling unwell, we want to hear that there is hope for a helpful treatment. We have learned that this particular type of hope is given to a patient in three ways: (1) by providing him or her with information, often expressed as results from tests that determine if a particular bodily function is operating out of the normal range; (2) by providing an appropriate therapy based on the test results; and (3) returning the tested values to a healthy range. The less we know about a disease, the less hope for an effective treatment can be offered to a patient and consequently the more fear, trepidation, and stigma is placed on that disease. Often times the patient's character (or that of the patient's parent) is questioned or a topic of discussion in lieu of the underlying dysfunctional brain circuit or biochemical pathology. This is what we face when it comes to mental health and illness, and consequently mental health has many deterring barriers of fear, trepidation, and stigma.

We have, in previous perspective pieces, compared brain disease to cancer. Now we are going to make a comparison between brain illness and heart disease. Not long ago, heart disease was shrouded in the same dark mystery as the brain is now. Heart disease was something that happened to Uncle Bob when, after years of being overweight, not exercising, eating poorly, smoking, working too hard, and generally being stressed about his challenging life, dropped to the floor gripping his chest in the throes of a heart attack. Initially, of course, there was little to do for Uncle Bob. The 1950s began the age of cardiovascular health enlightenment. In 1956, cardiopulmonary resuscitation (CPR) was developed. Importantly, during this time the Framingham heart study began the many decades of discovering correlative biomarkers linked to cardiovascular health. These included blood lipid

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levels, the ECG, obesity, and blood pressure. Then, in the 1960s, direct current defibrillation (i.e., ''the paddles'') was introduced into clinical practice. This mechanical technology that saved so many lives was followed in the 1970s by the development of the class of drugs known as the statins—a lipid-correcting pharmacological intervention that has further saved countless lives. Since the 1970s, scientists have used these tools and biomarkers to more deeply understand heart disease. These insights included the development of novel imaging modalities, refinement of blood chemistry diagnostics (biomarkers), and genetic and epigenetic screening.

The landscape of therapies that have been developed can now be tailored to an individual in an affordable, accessible, reproducible, and accurate manner. Treatment begins with lifestyle modification—eating healthy, exercising regularly, not smoking, drinking alcohol only in moderation, and active weight and stress management. If lifestyle modification is not sufficient to bring biomarkers into a healthy target range, then personally tailored pharmacologic intervention can be extremely effective. If lifestyle modification and pharmacologic intervention are not sufficient, we still have further recourse of invasive medical intervention, which include percutaneous coronary intervention (PCI or angioplasty), bypass surgery, stenting, and other open-heart surgeries.

Our understanding of heart disease has come so far that most people, at least in the Western cultures, are familiar with the risk factors and understand the lifestyle modifications that can prevent or stave off disease progression. When a person visits his or her physician, it is part of a standard health checkup to not only ask the patient about his or her lifestyle habits and practices, but to measure heart disease biomarkers and follow this up with potential lifestyle and pharmacological interventions. With the visible and understood nature of heart disease and the therapies available to treat it, we are not embarrassed by the presence of a risk factor or a diagnosis of hyperlipidemia, high blood pressure, or atherosclerosis. We do not feel labeled or stigmatized and certainly do not feel that there is a fault in our character. We have this comfort despite the fact that heart disease remains the number one killer of adults in the Western world.

If cardiovascular health has experienced an age of enlightenment, brain health is wallowing in the dark ages. We have yet to design and administrate clinical brain disease longitudinal studies analogous to the Framingham heart studies. Consequently, we fall short of identifying the risk factors and biomarkers associated with most brain health diseases. As expected, therefore, the invisible nature of mental illnesses creates a negative public perception that leads to labeling, character judgment, fear, and trepidation. The barriers to hope and healthy brains unfortunately don't stop with the public perception of mental illness. It is not unlikely to diagnose two individuals having similar symptoms with the same mental illness, for example, depression. Due to the complex nature of the brain, however, it is possible that these two individuals suffer from completely divergent pathologies. This can become a dangerous problem when pharmacologic interventions are administered. For example, when treated with a serotonin-specific reuptake inhibitor (SSRI), one of the patients may experience a complete reversal of symptoms, while the other spirals further into despair and experiences suicidal ideation.

When it comes to violence, this is intimately relevant. Violence is a jigsaw puzzle made up of lots of different brain health pieces, both social and biological (behavioral and biochemical—''tell me about your mother'' and ''pee in this cup''). We need to piece them together to understand and prevent future violence, to learn how the social pieces interact with the biological pieces to shape violent behaviors. We need to research how the pieces fit together and identify the risk factors and the signs and symptoms leading to violent behaviors and understand how they correlate with measurable biomarkers. Once we understand, we can then offer meaningful lifestyle modifications and create effective interventions and therapies to help overcome the causes of violent behavior. Until we have these visible answers, we will be unable to create effective and individually tailored paradigms of lifestyle modification, pharmacological intervention, or other medical interventions.

Building a detailed, next-generation understanding of neuroscience is needed to transition to the next generation of brain health understanding. Key to this next step is a brave willingness to approach the complexities of the brain, to innovate, and to imagine. Creative, out-of-the-box-thinking scientists who are willing to ask difficult questions and take on the challenges that come with neuroscience and the study of the brain are of paramount importance. Further, commitment to designing innovative technologies capable of monitoring the changing complexities of brain function in real time and in great detail is needed. This drives a need for bright engineers to bring these designs to life and to build them such that they function in an affordable, accessible, accurate, and reproducible fashion. Finally, mathematically minded visionaries who can make sense of the incredibly complex, nonlinear, noisy, and often incomplete nature of brain data will make sense of the complexities found therein. In essence, we need to support science, technology, engineering, and math, or STEM, education. Perhaps most importantly, we need to educate the everyday citizen in all aspects of brain health to dispel fears and myths around mental illnesses and to empower self-care and advocacy for others.

A disease cannot be cured, or even appropriately treated, until it is understood. Every day, new technologies and innovations can be developed to understand the brain a bit more. The ability to study the brain and determine why it may not work properly is becoming more accessible every day. As we learn more and expand our ability to understand the brain, we can develop medicine and therapies to treat, and even cure, brain health problems. The next generation of brain health will be championed by our youth. To nurture a curiosity and desire in our nation's youth, focused on the brain, is of utmost importance. To do so, it is up to us to not only pave the way for them but also make this path a prestigious and lucrative one. Community engagement in brain health discussions and stressing the importance of how to take care of one's own brain, much like we do now for our cardiovascular health, can create an empowered generation to advocate for their own health. Finally, it is necessary to embrace this next generation of neuroscientists as we move away from the invisible realm of mental illness and into the visible science of brain health.

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