TESTIMONY

of

Marcus E. Raichle, M.D.
Washington University School of Medicine
St Louis, Missouri

to the

Committee on Science, Space, and Technology
Subcommittee on Research and Technology
U.S. House of Representatives
31 July 2013

Good morning Mr. Chairman and members of the subcommittee. Thank you for the opportunity to provide testimony on the frontiers and challenges of human brain research, including its potential and limitations in curing brain diseases. My name is Marcus Raichle. I am a neurologist and the director of the Neuroimaging Laboratories in the Mallinckrodt Institute of Radiology at Washington University in St Louis where I am Professor of Radiology, Neurology, Neurobiology, Psychology and Biomedical Engineering. I am a member of the National Academy of Sciences, the Institute of Medicine, the American Academy of Arts and Sciences and a Fellow of the American Association for the Advancement of Science.

Human brain research has advanced tremendously over the past 40 years beginning with the introduction of X-ray computed tomography or CT in 1973 by Godfrey Hounsfield, an English electrical engineer working at EMI, Ltd. CT obtains its information by passing X-ray beams through the brain at many different angles to measure its density. CT not only revolutionized the way we look at the brain by providing the first true 3D brain images in living subjects but also stimulated the development of two other imaging techniques that together have provided unprecedented images of the anatomy and function of the human brain in health and disease. The first of these was positron emission tomography or PET which allows us to measure brain function in terms of its chemistry, circulation (i.e., blood flow) and metabolism using unique, cyclotron-produced radioisotopes. The other technique, introduced shortly after PET, is magnetic resonance imaging or MRI which provides superb anatomical images of the brain as well as measurement of its ongoing function. MRI obtains its information by measuring the properties of atoms in a strong magnetic field. The technology behind each of these techniques is most remarkable and continues to evolve particularly in the case of PET and MRI.

While technological developments involving physicists, engineers, chemists and computer scientists have been critical to the development of PET and MRI for human brain research the success achieved in using these techniques to image the human brain in health and disease has required extremely important input from clinical and basic neuroscientists as well as behavioral scientists schooled in techniques required to quantitatively measure human behaviors. A prime example of the collaborative nature of this work was the first major study of language organization in the normal human brain obtained with PET in 1988. This was the culmination of

over 15 years of work by a multidisciplinary team of investigators whose talents ranged from computer science and image processing to linguistics and cognitive psychology.

Growth in functional imaging research of the human brain has been exceptional. Since its introduction in 1993, functional MRI or fMRI as it is best known has accounted for over 17,500 in the world's scientific literature along with an additional 14,000 papers using PET. The thirst for information about the brain, particularly the human brain, is universal and imaging for better or worse has been used by many as a medium for the discussion.

Functional brain imaging has followed a long tradition in neuroscience: studying neuronal responses to stimuli and during task performance. The resulting images, which now appear in thousands of scientific papers as well as in the popular press, routinely show areas of the brain which 'light up' as tasks are performed. These images represent the *difference* between performing a task and/or viewing a stimulus, and a control condition, which could be as simple as lying quietly in a scanner with your eyes closed. While the changes that are observed in these *difference images* have been immensely valuable in showing us the complex network of brain areas involved in particular tasks they obscure the fact that most of the activity of the human brain is ongoing at all times regardless of what one is doing. This has come to be known as the brain's intrinsic activity. How do we know this?

This discovery of the importance of the brain's intrinsic activity arose from a consideration of the cost of brain function. As adults we invest 20% of our body's energy budget in brain function, an organ that represents only 2% of our body weight. This means that the cost of brain function is 10 times that expected on the basis of its weight. When comparisons were made between this enormous ongoing cost of brain function and the additional cost of task performance it was realized that the latter was a trivial addition, usually just a few percent locally and not detectable when looking at the overall cost. From this work it became apparent that if we were to understand normal brain function in health and disease it will be critical to increase our understanding what the brain was really doing as represented by its intrinsic or ongoing activity.

fMRI has been invaluable in opening the door to an understanding of the brain's intrinsic activity. When one examines the brain with fMRI what is striking, but for a long time ignored, was the fact that the images contained a great deal of 'noise' (i.e., seemingly random signal changes). What scientists often do in the presence of noise in their data is to average across many data points thereby eliminating the noise. For many years this is exactly what was done with fMRI data until it was realized that this 'noise' contained a remarkable amount of information about the ongoing organization of the brain. In fact, this discovery has been so remarkable as to cause a paradigm shift in the way in which functional brain imaging is used to study the human brain. So-called 'resting state' studies where subjects simply lie quietly in an MRI scanner with their eyes closed have become a standard component of imaging research. It is not only important in revealing the large scale organization of the human brain but also a valuable tool in studying the effect of disease where task performance can sometimes be difficult if not impossible for patients.

Human brain imaging as it is now being performed with MRI and PET is providing an increasingly detailed understanding of the human brain: how its component parts are organized

into a functioning system, how they develop and change with age, how the brain is wired together, how the metabolism of the brain varies with the needs of its component parts and how all of these aspects of the organization and function of the brain are affected by disease. The pursuit of this broad agenda of research is exemplified by the recently initiated, NIH sponsored *Human Connectome Project*.

One of the great challenges for neuroscience is now making sense of this enormous influx of new data. Lurking beneath the surface of the fascinating new images of the human brain is the need to make sense of the brain signals that generate these images. How do changes in brain circulation and metabolism, the basis of our imaging signals, relate to changes in brain electrical activity? Traditionally, brain electrical activity, particularly the spiking activity of neurons, has been considered the primary signal of brain activity. It is now clear that the spiking activity alone is insufficient to understand brain function. Other electrical activity occurring in the membranes of brain cells, both neurons and supporting cells, contribute to brain function and brain imaging signals. Furthermore, the complex metabolic machinery within brain cells of all types is setting the stage for functional brain activity that is being programmed at very basic levels by the genes expressed within brain regions and with specific cells types and their processes. We must, therefore, invigorate a dialogue among scientists across levels of analysis from cell biology, genetics and neurophysiology to human brain imaging. This will challenge the comfort level of many but is necessary if we are to make progress. Schooling young investigators to think broadly and in new ways will be essential to progress. New tools will, of course, aid in this endeavor just as CT, PET and MRI created a revolution in the way we view the human brain. But tools alone, in my estimation are not sufficient if not accompanied by an integrated sense of how we should approach our understanding of brain function in health and disease.

Much of what I have said relates to how neuroscientists are thinking about brain function but what about the average American who has or worries about someone afflicted by a brain-related disease? In providing an answer to this question it is appropriate to say that anticipating brain disease is critical. No better example exists than in the case of Alzheimer's disease where biomarkers derived from imaging will play a critical role in understanding the disease years in advance of symptoms and evaluating therapies before symptoms appear and irrevocable damage has occurred. When damage has occurred, such as in stroke, understanding why some recover and other do not, an active area of imaging research, will lay a much better foundation for rational approaches to rehabilitation. Finally, in diseases such as depression and Parkinson's disease imaging has provided critical information about the circuits involved and has allowed neurosurgeons to place stimulating electrodes in the brain that greatly reduce otherwise intractable symptoms much as cardiac pacemakers aid in correcting abnormal heart function.

Finally, it must be said that fascination with how the brain works captures the imagination of scientists and lay persons alike and in so doing enriches discussions of how we behave has human beings.

Thank you for your attention.