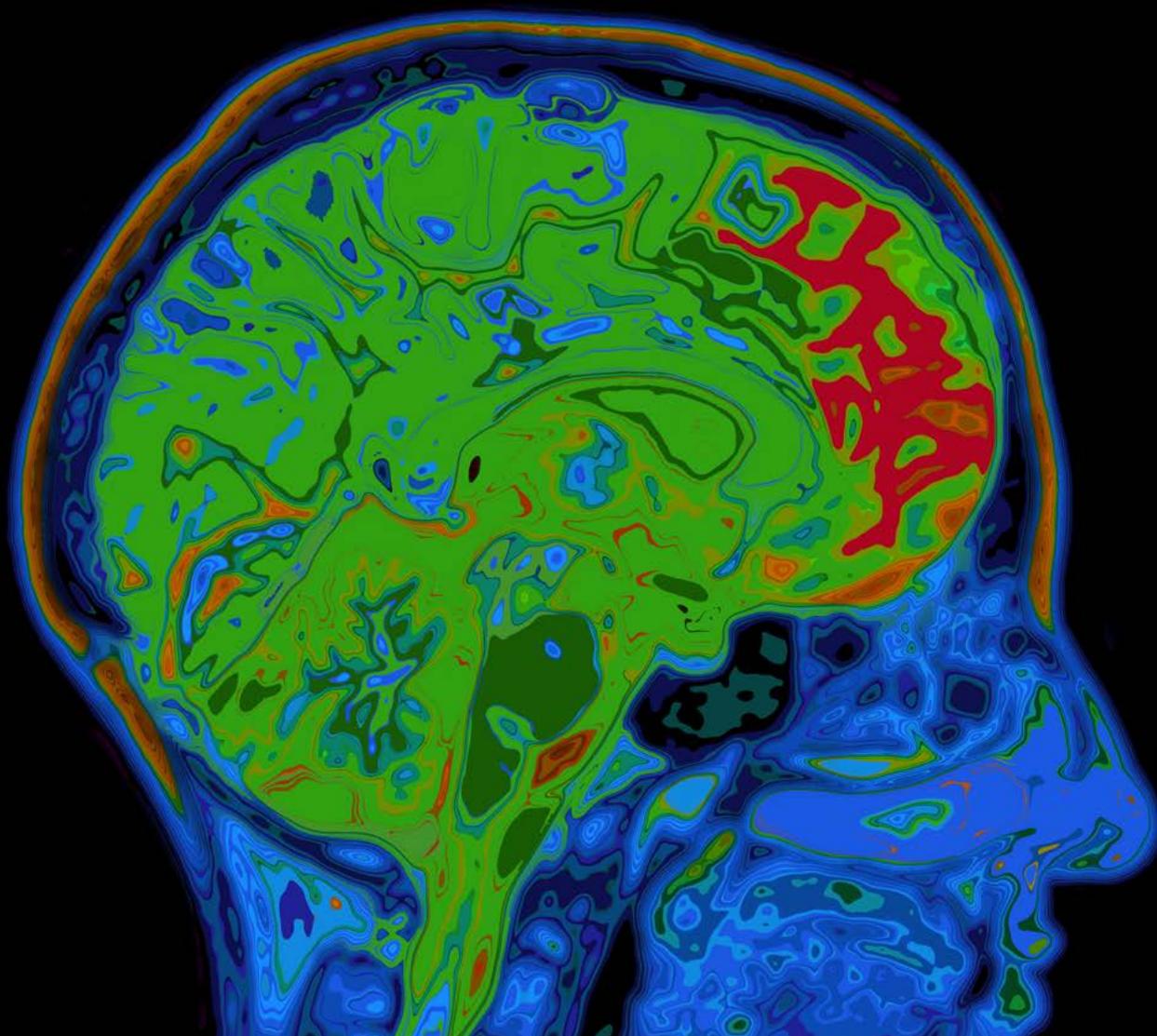


SEEING ISN'T ALWAYS BELIEVING

THE REALITIES OF IMAGING TECHNOLOGY AND NEUROSCIENCE



SYMPOSIUM REPORT
July 23, 2015

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For further information about this symposium series or reports, please contact the Director of the Center for Neurotechnology Studies, Jennifer Buss, Ph.D. at: jbuss@potomac institute.org.

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Potomac Institute for Policy Studies
901 N. Stuart St, Suite 1200
Arlington, VA, 22203
www.potomac institute.org
Telephone: 703.525.0770; Fax: 703.525.0299
Email: webmaster@potomac institute.org

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SYMPOSIUM AGENDA: JULY 23, 2015

2:30 pm – 2:35 pm	Welcome and Opening Remarks Jennifer Buss, Ph.D. <i>Research Fellow, Director of Center for Neurotechnology Studies at the Potomac Institute for Policy Studies</i>
2:35 pm	Speaker Presentations
2:35 pm – 3:00 pm	Marvin Chun, Ph.D. <i>Richard M. Colgate Professor of Psychology; Master Berkeley College; Professor of Neurobiology at Yale University</i>
3:00 pm – 3:30 pm	Paul Vaska, Ph.D. <i>Brookhaven National Laboratory; Professor, Department of Biomedical Engineering, Stony Brook University</i>
3:30 pm – 3:50 pm	Panel Discussion and Q&A
3:50 pm – 4:00 pm	Closing Comments Jennifer Buss, Ph.D. <i>Research Fellow, Director of Center for Neurotechnology Studies at the Potomac Institute for Policy Studies</i>

EXECUTIVE SUMMARY

On July 23rd, 2015, the Potomac Institute for Policy Studies hosted a seminar to address the various ways in which neuroimaging technology has advanced, and how these new developments can be used to achieve the goals of the President's BRAIN Initiative. The BRAIN Initiative has spearheaded an effort to map and understand the human brain, and novel neuroimaging technologies need to be developed in order to accomplish this goal. Neuroimaging encompasses the set of techniques that researchers use to create a structural and/or functional map of the nervous system. There have been many laudable achievements in developing neurotechnologies over the years, especially in the area of imaging and observing the brain, but technology development has become more difficult over recent years. Because of the growth of capabilities in other fields, from microelectronics and supercomputing to artificial intelligence, there is a renewed opportunity for collaboration that can result in even more significant improvements to the neurotechnology imaging tools available to researchers.

Dr. Marvin Chun of Yale University spoke about the progression of neuroimaging in the last 25 years. He primarily uses fMRI (functional Magnetic Resonance Imaging) to build the capacity to predict attention-related behavior. Imaging research has encountered three phases: mapping (1990s), decoding (2000s), and predicting (present). Mapping provides an overview of the structures and functions of different parts of the brain. Decoding combines math and neuroscience to create computational models that can be used to visually recreate what people are thinking. Prediction is then the ability to analyze and quantify individual differences in behavior. Dr. Chun emphasized that using brain imaging for prediction is now feasible and could have huge implications, introducing the capability to diagnose disease and predict characteristics like intelligence, attention, academic aptitude, etc. In addition, Dr. Chun identified imaging as a way to detect brain activity in patients suffering from a persistent vegetative state. While these people have normal sleep-wake cycles, there is no physical indication that higher mental function is occurring. Using fMRI, scientists can now detect brain activity by asking these patients to think of specific actions; the fMRI has been shown to pick up this activity, indicating that higher brain function is occurring. While rare, this can play an important factor in making decisions about the fate of such patients, which also raises ethical concerns. This application of fMRI indicates its potential to serve as a diagnostic tool for neurological diseases. Currently, the BRAIN Initiative places significant emphasis on mapping. Dr. Chun stated that while mapping is an important part of understanding the brain, it is not enough, and additional focus on decoding and prediction is imperative to ensure that neuroimaging capabilities can be applied to the population.

Dr. Vaska discussed new approaches in multi-dimensional neuroimaging, detailing both the benefits of combining temporal and spatial imaging techniques, but emphasized the extreme difficulty and financial cost associated with such projects. By combining structural imaging techniques,

such as CT or MRI, with functional techniques such as PET, fMRI, SPECT, and EEG, researchers can measure multiple functions at once, thereby achieving a greater understanding of the biology of human behavior. Much of Dr. Vaska's work revolves around Positron Emission Tomography (PET) scans, which he described as non-invasive, translatable from animal to human subjects, and quantitative, meaning that they can acquire physiological parameters such as metabolic rate, or receptor availability. Using PET, researchers can target numerous neurotransmitter systems via the injection of radiotracers. Dr. Vaska stated that the scarcity of combinatory imaging techniques results from technological difficulties, in that current imaging technologies are severely limited. Dr. Vaska explained these limitations, asserting that present techniques offer poor resolution, are inconvenient for subjects (who must remain absolutely still in claustrophobic scanners), and limit the types of stimuli that can be presented. According to Dr. Vaska, animal subjects are even more complicated because it is difficult to control animals in the scanner and their brains are smaller. Therefore, the majority of animal imaging studies are accomplished on anesthetized subjects. Dr. Vaska has worked with a combination of PET and CT imaging techniques to achieve both spatial and temporal resolution amongst his subjects. His focus on associating physical brain characteristics with behavior, and his attempts at such behavioral neuroimaging led to a novel technology called the RatCap. RatCap is a brain scanner that attaches to a rat's head, removing the need for anesthetization, and allowing for functional images to be related to behavioral changes. The project took a total of 10 years to develop, and required an extreme re-working of existing imaging techniques. In the future, Dr. Vaska hopes to bring such wearable brain scanners to human subjects, which would allow researchers to examine spontaneous behavioral events such as concussions, or other traumatic brain injuries. Dr. Vaska anticipates future technologies that will eventually permit the combination of all current imaging techniques. As the field of neurotechnology holds such great promise, it warrants the development of policy options that will make brain mapping with new neuroimaging technology a reality.

Following the speakers' remarks, the panel discussed how to identify when imaging technologies are ready for application, the accuracy and precision of current imaging technologies, and the need for more funding to allow current research projects to reach their full potential. The Potomac Institute for Policy Studies has completed an analysis from the speaker's remarks and the subsequent discussion. Because new developments in neurotechnology allow for the quantification of neurological data, there is a great opportunity for the field to push toward a better understanding of human behavior and cognition. Federal investment needs to target both science and technology in order to complete the goals of the BRAIN Initiative. Federal investment and coordination of neurotechnology development needs to ensure that the right entities converge and that there is a focus on interdisciplinary engineering to enable new developments in imaging modalities, neurotechnology, and data sharing. Developing new neuroimaging capabilities, among other neurotechnology solution sets, requires significant coordination and strategic planning.

FINDINGS, CONCLUSIONS, AND RECOMMENDATIONS

THEME #1: QUANTITATIVE BEHAVIORAL AND COGNITIVE NEUROTECHNOLOGY APPLICATIONS

FINDINGS:

- **Neurotechnology research is elucidating the biological bases of behavior and cognition in the brain.**

Psychology has long been the study of the behavior of people, and sociology the study of the behavior of societies. New developments in biology and neuroscience have provided a hard science to the biological basis of human (and model organism) behavior. The advances in the last 10 years are monumental compared to the progress achieved during the decade of the brain (the 1990s). Imaging technologies have increased in capability and resolution, which has allowed designation of brain architecture to actions, thoughts, and emotions. As we continue to invest in brain mapping technologies, we will continue to make neuroscience the primary field for understanding and adjusting human behavior.

- **Neurotechnology applications reach beyond brain mapping allowing us to quantify and predict human behavior and individual differences.**

We can use brain imaging to analyze, quantify, and even predict behavior and individual differences in behavior. Researchers are using neuroimaging techniques to predict many different types of behavior. Neuroimaging-based depictions of differences in neural activity within certain brain regions allow for the determination and prediction of outcomes for attentiveness, ease of educational intervention, intelligence, developmental disorders, and other performance-related traits. Research in whole-brain activity networks is fueling the creation of models for diagnosing attention deficit-hyperactivity disorder and other cognitive states.

CONCLUSIONS:

- **Neurotechnology research is entering a new phase for diagnoses, treatments, and enhancements.**

The application of neuroimaging in quantifying and predicting behavior is an essential component of how neurotechnology will benefit society. By characterizing individual differences, we can start diagnosing neurological diseases and disorders. Advances in neurotechnology have provided alternative treatment procedures and insights into enhancing human cognitive performance. This type of work will address considerable serious implications of brain impact and trauma, Alzheimer's disease, autism, depression, and much more.

- **We can use neurotechnology to characterize and understand behavioral and cognitive traits.**

We can identify neuromarkers and begin diagnosing the precursors of autism for early intervention, predict who is going to suffer from major depression when experiencing stress, and predict who is going to respond better to psychotherapy versus drugs. These cognitive traits can be used as the basis for advanced neurotechnologies (e.g., enhancing our intelligence, our interactions with machines, or aspects of our environment).

- **Current brain mapping imaging techniques are available to assist in the BRAIN Initiative.**

The BRAIN Initiative can and should take advantage of current developments in imaging to map the brain and develop further advancements. The primary goals of the BRAIN Initiative are to provide new technologies to further understand the brain and to create a map of the brain to understand and better diagnose and treat human diseases. The techniques needed to map the brain can be funded by the BRAIN Initiative and can build upon existing technologies. Multimodal imaging techniques and adjustments to current capabilities, such as a miniature PET for scanning model organisms, are critical to build upon our understanding of the brain.

RECOMMENDATIONS:

- **We should target and invest in the new technology in neuroscience, not just the established paradigms of brain mapping.**

Neuroscience funding has received a significant boost with the BRAIN Initiative, but substantial BRAIN Initiative funds have been focused on the mapping of brain circuits. Again, this endeavor is very important basic, and fundamental research. We need (and can do) much more than mapping. Brain mapping must be accompanied with neural decoding and prediction, and neuroimaging technologies like fMRI enable the linkage of brain and behavior for both health and disease, for both basic scientific questions and applied situations. The BRAIN Initiative needs to ensure that it is investing heavily in all of neuroscience's research areas, rather than exploring connectivity alone. A singular focus on brain mapping will lead to failure to achieve the goals of this initiative.

- **We need to apply available neurotechnologies to understanding human behavior.**

We are ultimately interested in neuroscience because of the insights it provides into the inner mechanisms of human behavior. It is essential to make strong connections between the technology used in neuroscience research and measured and observed behavior. Without good measurements of behaviors, well-defined behaviors, and clear ideas of what behaviors we want to study, many of these neurotechnologies are not very useful. It is the relation of neurotechnology research to the measurement of behavior that matters most – Neuroscience imaging research is most impactful when incorporated into behavioral and social situations. For example, looking at the harmonious activity of multiple brain regions, analyzing networks, and understanding how brain areas communicate with each other are all valid research directions, but when

they are applied to improving special education and treatment plans for children with attention or learning disorders, we achieve the true value of the research.

- **The BRAIN Initiative's goals need to be clearly defined.**

The BRAIN Initiative needs to reflect the interdisciplinary nature of neuroscience research by funding research in all of the domains of the field. Research in all aspects of neuroscience, from the micro to the macro, is necessary to improve our understanding of the brain. Developing an understanding of neural systems requires measurement and data collection in conjunction with advanced computing, modeling, and simulation. Neuroscience research should include methodological development of technologies that incorporate the dynamics of neural systems from multiple research perspectives. These efforts need to be explicit and the BRAIN Initiative needs to expand its program scope and range of activities to successfully reach its goals. The BRAIN Initiative should not define its goals solely in terms of brain mapping, but rather it should set goals to bolster research in all aspects of neuroscience. Mapping the brain is not a sufficient end state for a national neurotechnology initiative, so the BRAIN Initiative's goals should be more far-reaching and focused on the multifaceted approach that is necessary to understand neural systems through measurement and data collection in conjunction with advanced computing, modeling, and simulation.

THEME #2: NEUROTECHNOLOGY TRENDS FOR INCREASING IMAGING CAPABILITIES

FINDINGS

- **Researchers are combining imaging modalities, computational methods, and neurotechnology techniques.**

Neuroimaging techniques can be combined together in multimodal methods to provide additional information about an individual. For example, positron emission tomography (PET) is often paired with computed tomography (CT) to provide useful anatomical information and functional information simultaneously. PET and magnetic resonance imaging (MRI) are also frequent pairing targets, delivering complementary information with the strengths of each technique. These combinations pose technological challenges because an MRI scanner is a very harsh environment for inserting any electronics (found in PET systems). Beyond the combination of neuroimaging modalities, researchers are also implementing multi-dimensional approaches that combine behavior and imaging, but this poses its own set of difficulties. There are other options to turn to for brain stimulation, from neuromodulation and optogenetics to transcranial magnetic stimulation. Powerful neuroimaging methods are available; they are being incrementally improved all of the time, and synergistic methods are being developed. As we move forward, simultaneous imaging of the living brain with various functional methods is extremely powerful. We rely on machine learning methods to build mathematical models of how the brain responds to stimuli, which can be observed through multimodal imaging capabilities.

- **The progression of imaging technology development has stalled.**

While researchers are adept at making the most of their available imaging technology and combining multiple neuroimaging modalities together to obtain novel results, the development of new imaging technology options has not been very active. Methods developed 20 years ago or more are still the most common technologies in use. While strong advances in neurostimulation techniques like optogenetics and transcranial magnetic stimulation have spurred new research, the development of new neuroimaging technology with increased resolution and utility has not followed suit.

CONCLUSIONS:

- **Advances will come from multimodal, multi-dimensional, and cross-disciplinary paradigms.**

Neuroscientists are making progress by combining multiple complementary imaging methods and including behavior recordings and modulation in their research. We should be trying to obtain as much information as possible at once, so that we know that we are imaging the same areas over the course of behavior and changes to mental state. Additionally, leveraging expertise from disparate fields like microelectronics, physics, and computer science can assist in advancing the field. A lot of the success in the development of the miniaturized PET scanner can be attributed to Brookhaven National Laboratory's expertise in building small, powerful application-specific integrated circuits that combine analog circuits with digital ones. This novel technology depended on the combination of expertise between neuroscientists, engineers, and physicists. This system allows researchers to incorporate PET imaging with investigation of animal behavior, social interaction, neuromodulation, and optical imaging.

- **Neuroscientists know what research they want to perform, but they are lacking capabilities without the development of new forms of imaging.**

Neuroscientists have demonstrated their resolve in answering research questions about the brain with the limited toolset that is available to them, but they are constrained by the lack of technology that will provide better image resolution. In addition to the additional value that can be gained from collaboration between researchers in different fields, progress in our understanding of the brain will be augmented and accelerated by the development of new neuroimaging technology.

RECOMMENDATIONS:

- **Federal investment and coordination needs to ensure that the right entities are brought together to create novel neurotechnology.**

It is very difficult to successfully combine imaging and behavioral modalities. Each of these modalities is rather complicated by themselves, and when you try to combine them, you run into all sorts of limitations. There has been recent legislative activity that addresses the National Laboratories and the Department of Energy (DOE) in

an attempt to confront this difficulty. The National Laboratories and the DOE can leverage their expertise in supercomputing, modeling, and simulation capabilities to assist in medical and neurotechnology research efforts. Because the National Laboratories tend to be mission-focused, the best course of action is to ensure that their mission includes this development of crosscutting neurotechnology. They have unique resources that are very difficult to find in universities, certainly in terms of detection electronics, but also large, precise facilities. Brookhaven Laboratory has a wide range of resources, electronics, and detectors that can be applied to neurotechnology development. There are huge resources to be put into them, and if it becomes a priority, then they can do a lot. It is just a question of federal investment.

- **It is necessary to focus on interdisciplinary engineering to enable new developments in imaging modalities, neurotechnology, and data sharing.**

In addition to a large-scale National Laboratory focus on neurotechnology, there are a lot of opportunities for interaction and teamwork between many populations of researchers. This includes collaborations between physical scientists who work with modalities like positron emission tomography and those who work with magnetic resonance imaging. New technology that comes out of one subfield can overhaul other researchers' capabilities. Collaborations can also be initiated between scientists who collect physical data from PET imaging and other imaging techniques and scientists who collect behavioral data through their research. Being able to meaningfully interpret physical data in a behavioral context, and vice versa, allows researchers to more effectively answer their research questions. One of the issues with pooling a lot of data is that PET studies, fMRI studies, and others are all performed in complicated, different ways. This makes comparisons between data from different areas of interest and different laboratories more difficult. There is a large opportunity for leadership in the area of standardization that would help to make these data sets more comparable among different studies.

- **Federal investment needs to target both science and technology in order to complete the goals of the BRAIN Initiative.**

We need to follow a coordinated road map that goes with tracking science to create the technology that can add to the scientific field afterwards. We need to coordinate all of our research together with federal and private funding. It is necessary to build up both the fundamental science and the technological applications of neuroscience. Fundamental neuroscience research will lead to greater understanding of neural structure and function, a theory of brain and cognition, and the architecture of these complex systems. This will enable success in brain-computer interface technologies, brain injury prevention and repair, neuroenhancement, cognitive computing, and artificial intelligence. The Potomac Institute for Policy Studies' *Neurotechnology Futures Report* delves further into the roadmap for success in neuroscience research. The roadmap has two tracks. The first track involves understanding the fundamental science, or scientific discovery and understanding of the brain and cognition. The second track involves the development of technology and applications, which will feed back into scientific discovery and into the development of products and applications

for medicine, the military, and the public. A successful neurotechnology initiative will cooperatively develop research and technology, in both public and private institutions, to further our ability to understand the brain and create useful tools and technologies for society.

EVENT TRANSCRIPT

JENNIFER BUSS

Introduction

I would like to welcome everybody here today. We are going to be talking about neurotechnology developments in imaging capabilities. We have been using images to detect neurological conditions for just over a century, and we have seen specific advances in the past to improve the fidelity and quality of our images. The expansion of our methods came with advances in computers in the 1970s. In the beginning of the 20th century, we were using x-rays to see soft tissue in the brain, and injecting air into the brain to attempt to contrast gray matter from white matter. We now have MRIs and CT scans for functional and structural imaging and can see areas of blood flow in the brain. While it sounds like we've come very far, it's taken 150 years to make this kind of progress. In the last 40 years we haven't made significant advances, just incremental improvements to existing techniques. We are beginning to be able to use these instruments for applications in brain computer interfaces, diagnosing disease, inserting technology into the brain, and changing people's brains (as well as tracking these changes over time). We can look at images of a person's brain from a year ago and today and see how their neural connections and processes have changed. But we still do not have enough information in order fully identify reasons for disease or really even map the brain. The BRAIN Initiative is really about mapping the brain and technology advances to get us to that point. This is why we are here today: to discuss how we can start to use imaging to advance the Brain Initiative. Today, we have Dr. Paul Vaska from Brookhaven National Labs and Dr. Marvin Chung from Yale to talk about how they have been using images and how they can see this working with the BRAIN Initiative. I am going to turn this over to the speakers who know a lot more about this than me.

Right now, we have images but do not really understand the background behind it. You can see some brain images and they're not telling you the whole truth, which is how we arrived at the title of the seminar, "Seeing is Not Believing." Dr. Chun has been researching this since 1994 when he was working on his PhD at MIT. This is definitely a topic he can speak to. I heard him speak on this a few months ago utilizing many different examples of where we need to see advances in imaging to know what we are really doing. So I'm going to have Dr. Chun come up and speak about imaging and cognition.

Linking Brain and Behavior with Functional Brain Imaging

Thank you so much for having me. I am grateful to the Potomac Institute, Dr. Buss, the Congressman, and everyone here in this room for your interest and support of neuroscience research because it is so vital, and more importantly, so exciting. This is a tremendously exciting time to be a neuroscientist or a consumer of research from the neurosciences. We are literally in the midst of a revolution. Just as our telescopes have opened the skies, microscopes have opened up the whole world that is unseen to the naked eye. We have many tools now in the neurosciences, especially in the human neurosciences, to probe the mind and how it controls behavior. I work with functional magnetic resonance imaging (fMRI) and this is an example of one of those machines. In my mind, fMRI is my telescope and my microscope. What is really phenomenal is that while we have had those other devices for hundreds of years, fMRI has only been actively used for about twenty-five years. I would say that 1990 is around when people really started to see and utilize the potential of fMRI. I will be going over some of the amazing progress that has been made in the past twenty-five years. In the first ten years, what I'll call the first decade of fMRI, the 1990s, the whole field was rightfully focused on brain mapping. Researchers were trying to figure out where functions were happening in the brain, if they could be localized. As a quick example, you can imagine putting someone in the scanner, showing them a set of scenes that are important for navigating around the environment, or showing them a set of faces that are important for social interactions. These are very basic, fundamental visual capacities that we all have, and if you look at what the brain does differently when you are seeing scenes versus when you are looking at faces, you can reveal or map out different areas that are specialized for each of these functions. You can use fMRI to identify where the brain is active when you are looking at places, scenes, and navigational tasks. Likewise, you can find other areas of the brain that are active when you are looking at or thinking about human faces. So these are the kinds of efforts that people spent their time on in the 1990s, including myself. I was fortunate to start working in functional imaging during this decade.



Image Courtesy: Dr. Marvin Chung.

This is not all that we want or can do with neuroimaging. I would say that with a couple of seminal papers in the years from 2001 to 2005 (which we will call the second decade of fMRI, the first decade of the twenty-first century), fMRI has become very useful for decoding the contents of the mind, decoding what people are thinking or feeling. Just as one example from my own lab, we can show people images of faces and based on their functional neuroimaging responses alone, we can decode or guess what faces people were looking at by reconstructing the face. This is a form of mind reading if you may, because this image is strictly based on what our computer

models are reading out from the fMRI signals. This is a brief overview of what the second decade of fMRI research has brought us, and I will go into more detail of course, but now we are actually approaching a third decade.

I would argue that this one is the most exciting phase of neuroscience research, of neuroimaging research, where we can now use brain imaging to analyze, quantify, and even predict behavior and individual differences in behavior. This is where neuroimaging is going to reach its full potential for benefitting society. Because now, by characterizing individual differences, we can start diagnosing disease. We can characterize traits that allow for better performance, and we can use this as the basis for advanced neurotechnologies. For instance, we can enhance intelligence or enhance our interactions with machines and with other entities in the environment. We are fortunate that over the past three decades of fMRI, the NSF, by the NIH and other government agencies, have generously funded our research. This funding has received some boost with the BRAIN Initiative. However, at least described, and especially as initially formulated, a lot of the BRAIN Initiative funds were focused on the mapping of brain circuits. Again, this endeavor is very important basic and fundamental research. What I would like to portray today is that we need more than mapping and we can do much more than mapping. Hopefully I will be able to convince you of that.

Fortunately, the Potomac Institute and Dr. Buss played a fantastic central role in this concept, highlighting this point that mapping is not enough. In fact, I will just pull out the conclusions from one of their seminars from last year, which made me very excited to participate today, because I think they really nailed it. The first conclusion is that brain mapping alone does not improve our understanding of the brain. It is essential, but it is only a first basic step. A second conclusion is that the BRAIN Initiative has mismatched goals and implementation. Again, the BRAIN initiative is important but it needs to be broader. A third conclusion is that neuroscience is converging with other revolutions in technological fields. I have to share this analogy from the report. Looking at a technology like Google Maps, maps are important for figuring out where you are and where you need to go. That is the first basic step but you also want to navigate and find out what is happening in those maps. For example, Google maps can put up traffic overlays and other useful information to augment the base map.

In the third decade of fMRI, we have to link the technology to behavior because ultimately this is why we are interested in neuroscience. We are interested in the inner world and the inner mind of our behaviors. I think that we are at that stage and I think we can continue to push forward.

Let me return to some of the advances of recent years by starting with decoding. I think one of the most important early studies on decoding is this one: participants in the scanner were asked to do nothing. They were asked to close their eyes while they were being scanned and asked to run the faces of all the acquaintances they had seen during the day through their mind. They were also asked to recall the various places that they had to go through to get from their home to where they were. The question is, can we read out what they were thinking? Face imagery matches face perception and scene imagery matches image perception to the extent that you can look at these activations alone and guess whether these people were doing face imagery or scene imagery. At this point, I should note that a lot of these studies I am showing are from

around the field, but I will also share work from my own lab. The next few studies will be more readily understood with some audience demos. First, I am going to test your memory by showing you a set of words on the computer screen. These words will go by quickly and I want you to memorize them because I am going to test you five minutes later. To prevent you from rehearsing those words to aid in memorization, I am now going to show you a video as a distraction task. This is a famous video where your job is to count how many times the team in white passes the ball to each other. Now that you have all watched the video, raise your hand if you saw the dancing bear. For those of you who missed it, the bear walked in and waved his arms and then moonwalked out. It looks like half of you completely missed the bear. I showed this to you for two reasons: one of course to keep you from rehearsing that list of words, but the other reason is to motivate my next slide.

See the “Test Your Awareness” video:
<https://www.youtube.com/watch?v=Ahg6qcgoay4>

There are many instances where you are unaware of what is around you. That is just the limitation of attention. The question is, is there any way to access that information of which were you not conscious? For those of you who missed the dancing bear, the question is, is the dancing bear represented somewhere in your head? And can we use these tools to access something in your mind that you are not even able to report? These questions motivate one of the most important studies in neuroimaging research that was conducted over at the University of Cambridge. They tested a patient who was in a persistent vegetative state, which, as you know, is someone who is completely out of communication with their physicians or with any loved ones. They are completely unresponsive to any verbal or physical prompting. It is like they are locked in but you do not even know if they are conscious or not. And in many cases, physicians do not expect that they have consciousness, that they may be mentally dead even though they are otherwise physically alive. What makes it trickier than a coma or any other kind of brain damage states is that, as we know from a famous case called Terri Shiavo, is that they actually have very normal wake and sleep cycles. Their brains have a basic physical function but it is not as clear whether they have mental function. You can imagine how this becomes so difficult when deciding whether to withdraw life support or not, especially if the patient is bedridden (in this case, for 15 years). This situation was made famous because of the state and federal court cases. Many people debate whether this was the right thing to do because there really was not much tissue left after 15 years of being in this state. The reason why I raise this as motivation is because many patients are not in this state long enough to expect that level of deterioration and the question is, if they are unresponsive to the doctors and their family members, at what point can one properly infer whether they have consciousness or not? And again, you cannot use language or any other tools to figure that out.

A study published by Adrian Owen and colleagues posited that we could answer this question with fMRI because of the mental imagery study we just showed you. Take controls who can follow instructions, put them in the scanner, and have them close their eyes. In one condition, you have them think about playing tennis. In another condition, you have them walking through their house. These distinct patterns for tennis imagery and navigation imagery can be detected through fMRI. And once you see these patterns, you can make a fairly accurate inference that they are

engaging in the task and following your directions. But importantly, you can ascertain that they are purposely following your directions, which for many people means a state of consciousness. They found a patient who fulfilled all of the criteria. In her case, she was only in the state for about a year so her brain structures were intact. The question is, how does she respond in this task in this scanner? When she thought about tennis or walking around the house, the fMRI results from the targeted areas in her brain were similar to those of controls. She was reliably able to engage in the task as designed. This allowed researchers to use fMRI to suggest that this patient had retained conscious thought when previously there was no way to interact or probe what she is thinking. This raises a lot of questions about neurolaw: what is the diagnosis and at what point does mental life end? I should make it clear that most patients do not show this effect. What do these findings mean, do they mean that the patients do not have consciousness? These are ethical questions. What is the prognosis? These are questions under study right now.

What you can do with this system is communication. If you can think about tennis and think about certain spatial imagery, then you can attach the word "Yes" to one and "No" to the other. So if I ask you if your father's name is Tom and the answer is yes, you would think about tennis and if the answer is no, you would think about spatial navigation. Control subjects can do this yes/no 20 Questions game using fMRI. It is a very expensive, intensive way to do it, but as proof of concept it is starting to lead to ways to interact with such patients.

I do want to emphasize that there is a burst of new exciting discoveries being made. Up to now, we have really relied on very basic mapping of the brain: we have identified a face area, a spatial navigation area, a motor area, etc. But there is no shoe area, there is no cat area. You would not be able to pick those two items apart based on methods I have shown you so far. And so around 2005, scientists started to collaborate with engineers, computer scientists and machine-learning artificial intelligence researchers to develop fancy methods to decode activity in the brain so that you can know whether someone is looking at a shoe or a cat.

This led to a paper in 2011 at UC Berkeley where researchers showed people videos and recorded their brain activity. The researchers built models about how people's brains responded to the videos that they watched and they created reconstructions of these images. By recording a person's brain activity while they watch a scene, the computer model could interpret and recreate the image they were seeing. The recreations were crude and noisy, but were unmistakably capturing the essence of the images that the person was viewing. If you think about how this is a 20-year-old technology, it is pretty amazing that you can reconstruct what videos people were viewing using fMRI signals and scanning alone. I had an undergraduate student at Yale who was excited by findings like this. He wanted to do something even more refined than this. He did not like all the blurriness of these images. Alan Cowen, who is now at UC Berkeley, my post-doc Brice Kuhl, who is a professor at the University of Oregon, and I collaborated to show people faces to build up models of how the brain responds to faces, and then make guesses as to which faces people were looking at. For instance, if you show subjects a set of these faces in the scanner, we were able to reconstruct faces with about 60-65% accuracy. These images were less blurry than some of the videos you saw earlier and serves as a sort of a proof of concept that you can really take fMRI signals and use computational methods to decode them in such a precise way. I have been a professor for 20 years but it was this undergraduate research project that got me more press than

anything else I have done in my career. For the field as a whole, I was very excited to see that there was a strong public interest in this kind of work. We got coverage from the *Wall Street Journal*, CNN, *USA Today*, NPR, *Wired*, and so on.

There are very important practical implications. Let's consider pain. How do you measure pain? How do you describe pain? How do you share the magnitude of your pain with your physician? Pain is a subjective state. You can write down a number out of 10, but it is very subjective. Wouldn't it be

False Memory Paradigm (Deese, 1959; Roediger & McDermott, 1995)		
THREAD		BED
PIN		REST
EYE	1. SEWING	AWAKE
SEWING		TIRED
SHARP	2. DOOR	DREAM
POINT		WAKE
PRICK	3. NEEDLE	SNOOZE
THIMBLE		BLANKET
HAYSTACK	4. SLEEP	DOZE
THORN		SLUMBER
HURT	5. CANDY	SNORE
INJECTION		NAP
SYRINGE	6. AWAKE	PEACE
CLOTH		YAWN
KNITTING		DROWSY

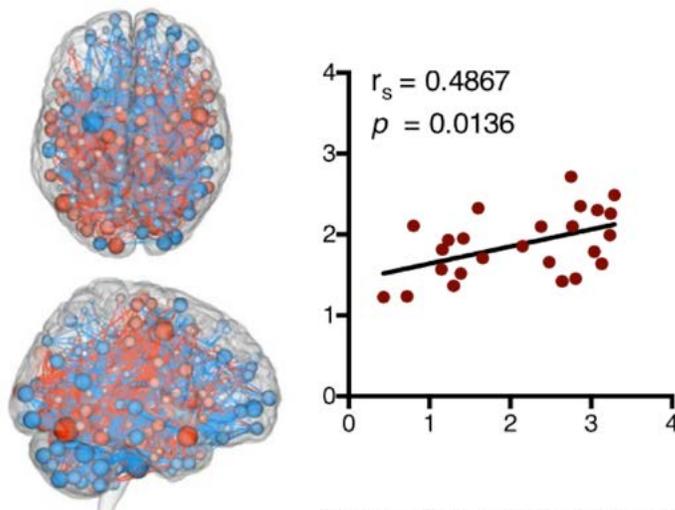
Image Courtesy: Dr. Marvin Chung.

wonderful if we had a neuromarker, a neural measure of pain? That is exactly what researchers, in this case Tor Wager, published in the *New England Journal of Medicine*. They showed that using these fancy decoding methods you can decode pain in these individuals – in normal subjects like us. All of this work raises mental privacy issues. If we can read out and decode the mind, can we do something that existing measures do not allow us to do? Can we detect lies better than existing methods? This is where I will return to our memory test from before. I am now going to show you a set of words, one word at a time, and if you remember seeing that word from one of the two earlier lists, just clap your hands. If you did not see one of these words before, just hold back. Now that I have shown this new list, it is clear that you have all generated false memories. I never showed the words needle and sleep to you in the first list, and yet when you saw them here, you acted as if you had seen those words only 10 minutes ago. All of the words I showed relate to “needle” but I never actually showed you the word needle. I tricked your brain into thinking that you saw the word needle and you acted as if you had seen it. This is called a false memory and we did the same thing for the word sleep. It is a very common component of how human memory works. The question is: how can we distinguish reality from the psychology? Brain imaging research is starting to devote time to these questions as well. There seem to be some brain areas that can tell the difference between things you truly saw versus things you falsely thought you saw, but ongoing work continues to suggest that our ability to do so is still limited. Let's imagine that you are trying to identify a perpetrator in an eyewitness lineup and they all look similar to each other, you might incorrectly identify the wrong person because of these similarities. Learning has planted the knowledge structures in your brain that allow these demonstrations to work and cause the false memory.

Finally, I will discuss prediction very quickly. Can we scan people and predict how they will behave? In one study, we asked people how they would judge racial discrimination cases. A 19-year-old African American with experience and qualifications was not given the job because he did not fit the company's look. If you were to award damages to Rodney, how much would you award?

We can predict with brain imaging based on response to black and white faces how much award these subjects would give in these hypothetical legal cases. This has joined the potential of using fMRI to predict behavior. The research that started to appear between 2011 and 2013 is what I mean by the 3rd decade of fMRI. You can look at activity differences in certain brain regions and predict how well they will respond to reading programs and you can predict their reading gains when diagnosed with dyslexia. You can predict how effective math tutoring will be in these students even before they start the tutoring based on how they respond in certain brain regions. Myself, I am interested in attention deficits as you saw from the dancing bear example. Attention deficits are characteristics of poor performance in work and school, but they are also a very common symptom of most mental illnesses and many other physical diseases. If I were to ask you how much inattentiveness are you experiencing or if you can say your child is suffering from inattention, you cannot put a number on it, it is a psychological state. A lot of the measures we saw earlier are not able to show that. However, wouldn't it be wonderful if, like measuring a fever with a thermometer, you had a metric to measure how much inattention someone is experiencing or how focused someone is using brain imaging? My students Monica Rosenberg, Emily Finn, and many other colleagues at Yale, are working with this idea that the brain operates like an orchestra. We should look at how harmonious the different parts are working together by looking and analyzing networks and how brain areas communicate with each other. We have collected our findings into a paper that is currently under review. Global networks (overall harmony of brain activity) can predict how attentive people are: we can predict behavior. Moreover, we can take our same models, apply them to patients who have received ADHD diagnoses or tests, and we can diagnose ADHD with our models of whole brain functional connectivity. We can predict intelligence, we can scan people while they are resting and predict what their scores will be on tests of what we call fluid intelligence (e.g., mental puzzle-solving tasks).

Global Networks Can Predict Attentiveness



Rosenberg, ..., Chun (unpublished); networks illustrative **Yale**
Image Courtesy: Dr. Marvin Chung.

One of my dreams is to be able to measure concussions. Concussions are a very subjective state too, something athletes suffer from all too frequently. My son once suffered a concussion and I took him to the hospital, as very frantic parent, and they basically responded saying how do you know he has a concussion? I almost lost it because of course I know that my son has a concussion. He ultimately was diagnosed with a concussion but that was the first response I got from the hospital. If you put him in a scanner, I will show you exactly why he has a concussion. Of course, this type of work will address a lot of serious implications of brain impact and mild brain

trauma. Can we diagnose who is likely to develop Alzheimer's? I think we can do that with fMRI and certainly people are working on it. Can we develop neuromarkers for autism, especially in children where behavioral symptoms are not yet apparent? Can we diagnose precursors of autism that may allow for early intervention, predict who is going to suffer from major depression when experiencing stress, or predict who is going to respond better to psychotherapy versus drugs? People are working on ways to use fMRI for these applications.

Can we predict who is going to perform better with training? An application that I am particularly excited about is predicting who will succeed in academic settings when they are in environments where they had suffered disadvantages and their full intellectual potential has not been realized. Can we use brain imaging to help identify individuals who will benefit from proper and better educational opportunities? You are basically opening up new ways of life for people who have not received the same kind of privileges that many of us here in this room have. My colleague John Gabrieli, who is over at MIT, says that that brain imaging prediction is a humanitarian and pragmatic contribution that cognitive neuroscience can make right now. Again, we are grateful for funding and everyone's support for the BRAIN initiative but we really have to go beyond brain mapping into decoding and prediction because fMRI provides that link brain and behavior for both health and disease, for both basic scientific questions and applied situations. Just to close with a final analogy, if this is a soccer game, and we are the US Women's World Cup Champions, we are at the penalty box, we are right at the goal. Let's not lose our momentum just when we have this opportunity to put that ball into the net.

JENNIFER BUSS

Dr. Chun talked about many things that we at the Institute have been talking about in terms of ethics and our responsibility if we do know the brain state of someone who has been in the hospital. What do we do about that? The Institute published a report on the impacts of neurotechnology and published it in 2013, it's the Neurotechnology Futures Study that refers to ethics. It's something that we have been talking about in terms of policy because there are policy decisions that somebody has to make – whether it's a doctor or a researcher – about what is ethical to do on Capitol Hill as a policymaker. We believe we should base policy decisions on science, not morals or ethics. While we can research and understand some of the ethical implications of advances in technology, we should create our policies from what is best for the people based on the available data. Knowing the trends in science and technology help us to create the right investment strategies, as well. What technology should we be investing in either as a government or from the commercial world? We need to consider where are our boundaries and how far we can push them. The more we know about the brain, more we can help raise our baseline education, human health and performance, as well as help our defense and intelligence communities. Specifically, we need better imaging techniques to make policies about advancing human behavior. This is Dr. Vaska, he's from Brookhaven National Lab at Stony Brook University, and he's been focusing on developing technologies to advance brain imaging.

New Approaches in Multi-dimensional Neuroimaging

Thanks very much for the invite. My talk has many parallels to the one you just heard. I am a technology person so I am going to be talking from the perspective of developing new technology. My primary technology is positron emission tomography (PET) imaging, which is in many ways complementary to fMRI. First, I will go over the various imaging modalities that exist. You can break them into two different categories. There are structural imaging modalities such as computed tomography and magnetic resonance imaging (MRI). They are very good at giving high detail, high spatial resolution structure. There is another class that you can call the functional imaging techniques. The first one is PET, which is my area of specialty. Others include single photon emission computed tomography and the functional mode of magnetic resonance imaging (fMRI) that Dr. Chun spoke at length about. There are others: electroencephalography, magnetoencephalography, and a variety of optical techniques. I will be talking about the functional imaging modalities because I think those are more interesting for brain function.

I do want to tell you a little bit more about PET because it is generally something that people are a little bit less familiar with. One of the defining characteristics of PET is that it is non-invasive and translational, which means that you can perform studies in animals and then translate them to humans. It is a three-dimensional technique just like the other ones. Where it starts to become different is that it is a functional technique so that it can tell you what the function of the tissue is as opposed to just its physical characteristics. Another thing that sets it apart is that it is a quantitative technique. You can get numbers on an absolute scale about quantitative, physiological parameters such as the percent of available dopamine receptors in a part of the brain, or the absolute metabolic rate of the different regions of the brain in units of millimoles per 100 grams of tissue. To give you an example of what a whole-body PET scan looks like, it is mostly used

What is PET?

Defining Characteristics of PET

- Non-invasive, translational
- 3D
- Functional
- Quantitative

Procedure

- Prepare and inject radiotracer (short half-life)
- Tracer binds to target
- Measure quantitative distribution of tracer over time



in the clinic to image cancer. A radioactive form of glucose is used as a tracer that is taken up by the brain, the heart, the bladder, and the cancer in this specific case.

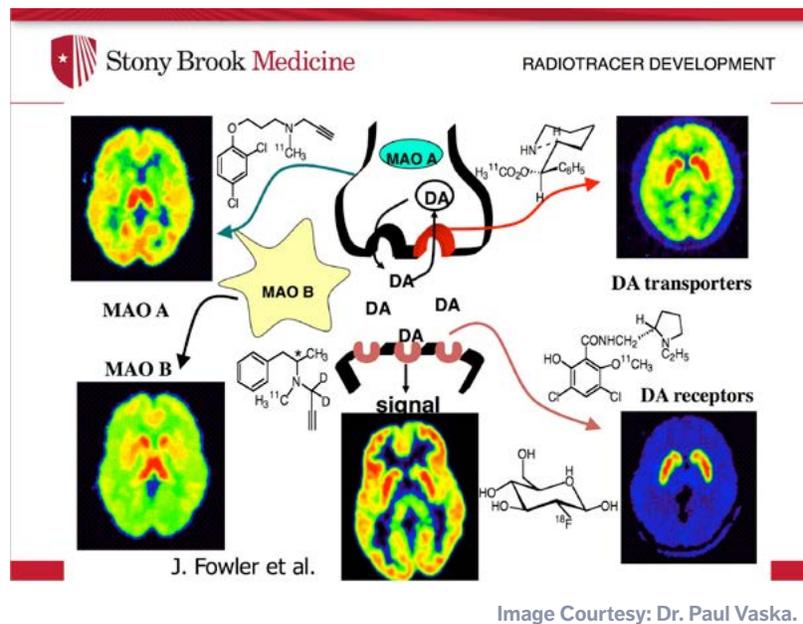
The basic procedure for performing PET imaging is to prepare this radiotracer because it has a short half-life. It gives off radiation so you do not want to receive too high of a dose. You inject it into the bloodstream and it goes through your body and binds to the target that you want it to and not to anything else, and then you measure the quantitative distribution of this tracer. This can be performed over a set period of time. When you inject the radioactive tracer, it distributes through the body. The tracer has gamma ray

Image Credit- Flickr. dion gillard "pet-scan-2008-06-04"

emissions that are detected by the ring of gamma-ray detectors and you can then reconstruct the image that you want.

One of the key aspects of PET is the different set of radiotracers that you can use. You can target all sorts of different neurotransmitter systems, enzymes, and proteins using PET. A lot of the tracers that we use will work on the dopamine system. If you see that the neural activity moves through the neuron, it releases dopamine, which binds to the dopamine receptor on the other side, and the signal continues to propagate. This cycle is repeatable, as the dopamine is retrieved by molecular transporters and can be used again. When a person takes cocaine, it blocks the dopamine transporters, and dopamine builds up in the synapse. This is responsible for the rewarding effect of cocaine. If you want to study the dopamine system, you can administer a tracer that binds to the dopamine transporter, and you get an image like this. There are a lot of receptors in the striatal regions here, and again, since this is a quantitative image, we can obtain a numerical number for the density of the amount of bound dopamine. You can inject a different tracer, which binds to the other side of the terminal. We do not have the spatial resolution (about a millimeter at best) to distinguish these two spots from each other, but based on the chemical specificity we know that this tracer binds to a specific receptor. The glucose scan tells you about metabolic rate, and quantitatively you can look at enzymes and other structures. These examples are just to show you that there are many different types of radiotracers out there and new ones are constantly being developed, and this variety in radiotracer choice makes PET a robust choice for imaging a lot of biological processes.

Like I said, there are lots of different neuroimaging methods. You saw CT, MRI, PET, etc. What are the different characteristics that they have? First, there is the meaning of the data. Depending on the radiotracer you are using, PET tells you different things. fMRI tells you mainly about blood oxygenation to estimate brain activity and CT focuses on x-ray scanning of regions of the body. Different methods have different spatial resolution. Each technique can image at the micron scale for optical imaging all the way up to the millimeter-centimeter scale for EEG. Temporal resolution varies greatly, the field of view varies greatly: you can image the whole brain or just a tiny part, with varying resolution with different methods. Other factors include the invasiveness, the radiation dose, whether you have to implant it surgically, and the freedom of movement (what the person/animal is actually doing). Because of all these differences they are actually highly complementary. For example, you can combine

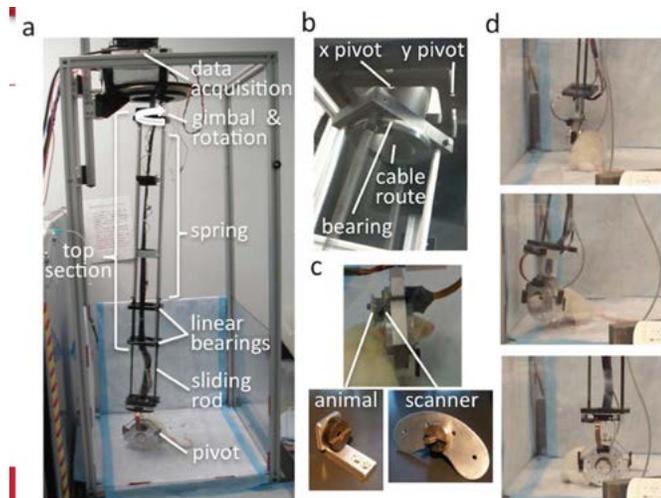


PET with CT. If you buy a clinical PET scanner, it has a CT scanner attached to it. The reason for that is because they are so complementary; CT gives you great anatomical information and PET provides functional information. You can overlay the two, and you know exactly where in the brain you are seeing activity associated with behavior. More recently, people have been combining PET and MRI together, and my group has done some work pioneering with that. It is very technologically challenging because an MRI scanner is a very harsh environment to insert any electronics. It has huge magnetic fields and radio frequency fields. We have been able to build these dual machines for animal imaging. You can actually buy commercial PET/MRI systems now.

I would like to talk a little about what I call multi-dimensional approaches. Everybody knows that the brain is extremely complex, with 100 billion neurons and many more synapses. There are all of these different methods for imaging, each with their different strengths and limitations. They are complementary and some are being combined now in multimodal approaches, like dual PET and MRI, PET and CT. You can go beyond imaging techniques and start to include behavioral techniques, which I call multi-dimensional approaches. Imaging the brain, especially in animal models, is very challenging. Imaging the brain while the animal is behaving is even harder. Behavior is the output of the action of what is going on in the brain, so it is an important parameter to know. And if there is no behavior going on, then it is a more limited data set. There are other options to turn to for brain stimulation, from neuromodulation and optogenetics to transcranial magnetic stimulation. One question that arises is, why are there so few of these modalities? So few modalities have been combined. The answer is that it is technologically very hard. Each of these modalities is pretty complicated by themselves, and when you try to combine them, you run into all sorts of limitations.

I will now go over some of the limitations in human neuroimaging. The subject lies on their back in the scanner in a supine position to avoid significant movement. The image gets blurry with movement and you no longer know what region you are imaging. Motion is a problem, resolution is not always as good as you would hope, and the process is uncomfortable which causes undesirable responses such as stress. When you are measuring the brain, you do not want to image a stressed brain, you want a normal brain. MRI causes noise and all of the systems tend to be claustrophobic. It is a very contrived environment. There are very limited stimuli and behaviors that you can present. You can use audio and visual paradigms using goggles and simple hand motions, but there are quite a lot of limitations. If you look at animal models, they can be even worse. Even though scanners have very high resolution, the rodent brain is so much smaller than the human brain that you are actually sort of losing out on clarity even though you are using a high-resolution scanner. On a relative scale, things look a little bit worse in rodents, especially in PET. Motion can be a problem as well, so you typically give the rodents general anesthesia. Since you are attempting to image the brain, giving the animal general anesthesia limits what you can do in terms of stimuli. I have been a proponent of behavioral neuroimaging, where the idea is to correlate physical brain characteristics with behavior in general. You can look at it from two sides: one, using physical data from a PET researcher like me, which is more meaningfully interpreted in a behavioral context, or two, from the behavioral side where the data is just the behavior, and if they can add mechanistic data about what is going on in the brain at the same time, they get very interested. It is a good combination, and you can define it broadly

as methods for correlating behavioral data with neuroimaging data, such as PET studies of dopamine systems and addictive behaviors, or correlations of brain region size and behavioral properties. What I am talking about is trying to image the functional changes relating behaviors over short time scales. What are the changes going on in the brain as an animal or human is behaving? To answer that question, you need simultaneous measurement capabilities, which is another technological challenge. You need to be able to measure what is going on in the brain while the behavior is occurring.

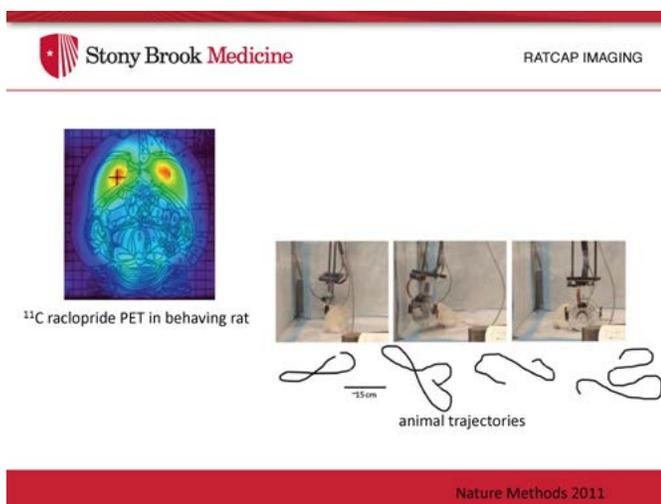


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Slide Courtesy: Dr. Paul Vaska.

I am a technological person, I have training in experimental physics, and I work at Brookhaven National Laboratory, which is a great physics lab. Brookhaven has all sorts of resources, electronics, and detectors. One of the problems we tackled in our PET group was that as animal PET imaging became more popular, more researchers wanted to perform imaging with an awake, non-anesthetized animal. Our approach was to build the Rat Conscious Animal PET (RatCAP), which miniaturizes the PET system and actually put it on the rat's head. This allows for imaging while the rat is awake and moving around. This removed the need for anesthesia and allowed for testing behavioral paradigms. The challenges were really substantial. We had to reduce the size. You saw the picture earlier of the PET scanner; it is about the size of a refrigerator. We had to reduce the size and weight, maintain the imaging performance, and somehow integrate behavioral data.

I will show you some of what goes inside of it: this is the standard PET detector. It is several centimeters long and very heavy. We had to replace all of the components in there with some very small solid-state components. Usually, a lot of wires come out of this part and that is why all the space is necessary. We put all of the electronics on a microchip. Brookhaven is very good at designing these application-specific integrated circuits (ASIC's) that combine analog and digital circuits, have a lot of power, and are very small. The system we built also has a flexible circuit board where we plug 12 detector blocks in and put



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Slide Courtesy: Dr. Paul Vaska.

them around in a circle. The system weighs about 200 grams, which is a bit much for rats so we had to build a support system. It has very nice spatial resolution and does cover the whole brain. We had to complete everything else that goes along with building a PET system, which includes getting the data off the scanner, reconstructing images, and putting all the corrections in there. It was funded by the DOE, and took almost 10 years. The components of the system move up and down easily so the rat can rear up on its hind legs, and pivots are placed throughout the device to allow even more freedom of movement. The animal can move around 15 cm while wearing this device.

We were able to inject a radiotracer that binds to the dopamine receptors in the brain and get a whole brain image while the animal is behaving. We were able to clearly image processes like dopamine activity in the striatum, which is an area that is heavily involved in the dopamine system in the brain. We published our findings in *Nature*, and got some lay-press as well. It is not a perfect system. One of the things that we were worried about was that the animal is somewhat constrained. We looked at stress hormones, and when the animal first puts on the device, the stress hormones go up. Stress levels will go up no matter what, even if the animal is just moving from one room to another, so it is a little bit worse than the baseline, but it seems to normalize after a while.

To show you some data from this, we compared the awake animal to the anesthetized state, and we observed the dopamine activity in the striatal region with the same tracer I was talking about before. There really are quite large differences between the awake animals and the anesthetized ones in terms of dopamine activity. We saw a big difference in the uptake of this tracer, between awake and anesthetized animals, which tells you right away that it is pretty important to be able to image animal models while they are awake. We also established that the scanner was sensitive to pretty dramatic changes in dopamine receptor occupancy. We would inject the tracer, and then we would inject an unlabeled tracer, which blocks a lot of the dopamine receptors, such that the specific binding drops off. We are looking at a cumulative measure of behavior before and after injecting a blocking agent. Taking the PET data, you can see the animal behaving, and then when we give it the injection, it stops and calms down a lot. This is a baseline measurement to show that things are working properly. The more interesting thing is that for the first time, we were able to show this result in a single measurement. Normally, when you perform a PET scan measurement, you image for an hour and get one number, and that is the receptor occupancy that is averaged over the hour. Here we are looking at minute-to-minute changes in behavior and minute-to-minute changes in the tracer binding and we saw a correlation. This is the first one that has been shown, that during one scan, we have shown the changes in tracer binding correlated with changes in activity. This shows how, with new technology and new methods, we can actually do quite a bit more than what has been done so far with PET imaging by incorporating behavior.

New directions for this particular system include integrating new behavioral tasks, social interactions, introducing other animals while doing imaging, and probing different neurotransmitter systems with different radiotracers. We have been thinking about including some neuromodulation and optical imaging as well. We can get PET for the whole brain, optical images in super high resolution for a particular part of the brain, and behavior all at the same time.

So going forward and thinking about the human brain, what could we do there? What could we do if we could miniaturize the scanner for humans? Essentially, you could reverse the typical process and instead bring the scanner to the subject. This is inspired by a device that was built in the '60s at Brookhaven, a little before my time. This was arguably the first PET scanner that was ever built. They actually did not know how to create images from it. They just put PET detectors around the head. The idea is to bring the scanner to the subject and maybe even enable the subject to wear the scanner. If you could do that, you would open up new types of studies. You could image all sorts of behaviors that you cannot do

now. You could look at spontaneous and transient events such as concussions, which is actually one of the things I am starting to look at. Different environments, different subject populations, such as homebound patients, or people who cannot go to the scanner for whatever reason. But the challenge is huge. It requires reducing the size and weight tremendously. I think our technology can get us pretty close to what we used for the rat imaging. It could actually be a completely wireless system because it does not take that much power. The possibilities are very open.

Portable scanners would be very useful for investigating concussions. The scanner, if not a wearable device, would be useful if it could develop images very quickly. In animal models, this is called the neurometabolic cascade. There are rapid metabolic changes that occur after a concussion, on the scale of minutes. Glucose metabolism will typically double within five minutes, and then come back down to baseline. So there is this really strong signal that comes up briefly and then it is gone, and you never have a chance to see it if you do not have a scanner ready and on hand. It just so happens that glucose metabolism is exactly what PET is extremely good at imaging. With the most common radiotracer, you can order it cheaply. I am actually working with a football team to get players consented and ready so they can use the scanner if there is a suspected concussion. We can try to capture the signal in humans and see whether it is a useful diagnostic tool, again because it is a subjective process right now, and we really need to be able to put numbers on things.



Mosaic of slices of patient's head, as seen in the PET Keosys software interface. By Mco44 at en.wikipedia [Public domain], via Wikimedia Commons.

Finally, I would like to talk about combining PET and MRI because we have done some of that work. MRI has replaced CT and you can actually buy a whole-body system now from Siemens for around 6 million dollars. This is kind of expensive, but the nice thing about MRI is that there is no additional radiation dose because CT uses x-rays. MRI has better soft tissue contrast in comparison. So there are technical imaging reasons to use MRI, but there are also really important synergies for brain science. Again, you are looking at transient phenomena in the brain, and ideally you want to use multiple functional imaging methods at the same time because you are measuring different aspects of these changes. If you measure them separately, you do not know that the brain function is the same. Ideally, you would be measuring them at the same time, and there is a lot of real potential here. For example, you could image neurotransmitter binding while assessing blood flow, or imaging the flow of cerebrospinal fluid in Alzheimer's disease, which is another area we are starting to go into. This is just an example of our system that we built for small animals. There is the simultaneously acquired MRI and PET, the tracer, and then a couple of different views. We have also imaged a mouse heart, which is interesting. This is one of the first small animal systems out there. They are not commercially available yet. As another quick example, this is a mouse where we used a dual-labeled tracer (copper-64 as a PET agent and then a super paramagnetic iron oxide particle, which is observable in MRI). This was looking for a cancer application with imaging of lymph nodes. They injected this mouse in the footpad and wanted to image over time seeing where this tracer went. If you just look at the PET, you just see a bunch of blobs and it is really not clear whether the process has worked. When we finally co-registered the MRI, the injected tracers in the footpad and the presence of the cancer became very apparent. Again, this is an example of how merging these imaging technologies can be really powerful.

To conclude, there are many powerful neuroimaging methods out there, they are being incrementally improved all of the time, and new methods are being developed. But as we go forward, simultaneous imaging with different functional methods in the living brain is extremely powerful and is more or less here now because of combined PET and MRI. There are other methods that are available now, but in the future, I think the best way forward would be to use multiple complementary imaging methods and include behavior recordings and modulation. We should be trying to obtain as much information as possible at once, so that we know that we are imaging the same areas over the course of behavior and changes to mental state.

I would like to thank my collaborators, especially those at Brookhaven. I would like to thank Daniela Schulz, a behavioral neuroscientist, David Schlyer and Craig Woody from multiple departments, students from Stony Brook, and the Department of Energy for our funding. Thanks very much.

PANEL DISCUSSION AND Q&A

MODERATED BY JENNIFER BUSS

Jennifer Buss

We'll take questions all at the same time. I want to thank both of you for coming and speaking. You both touched on a lot of the same topics that we've been talking about and I'm glad the audience here had an opportunity to hear some of the real research experience on it, rather than just hear me talk at them about the whole topic. I'm going to start with a question for Dr. Chun about decoding. So, if we have this – and you say we are capable of this right now – where do we draw the line of when we are going to be able to use this in making policy decisions? How reliable does it need to be? How accurate does it need to be? Can we do it for certain patients and not others? When will the tech be ready for primetime?

Marvin Chun

That's a great question and I think it's very context dependent. My general criterion is that it is ready for primetime if it's better than anything you've got right now. So, in the case of the persistent vegetative state patients, which of course is a really difficult situation, if I saw a patient show those signals, then that would affect any decision that I would make in such cases. And likewise for lie detection – right now there are methods that are not very good, but if they exceed, for instance a polygraph, because we have ways of assessing that if they exceed a polygraph, or if your eyewitness testimony or line up identification through some imaging enhancement is shown in the lab to be better than what we have now, then I think that's time for the scientists to come forward to the public for evaluation.

Jennifer Buss

I have one more question for Dr. Vaska and then I'll take questions from the audience. So you are creating all of these technologies and they are focusing on better accuracy, so where are the next technology steps that we need to get to that point of accuracy that things will actually be ready for the public to accept them as good technology?

Paul Vaska

I think the accuracy is something that tends to incrementally improve, and really if you look at PET images from the '90s, the 2000s, etc. you see dramatic improvements. They tend not to be in huge steps, so the technology is always being refined to be better and better. Cost is a big issue there, you can make them more accurate, but they become very expensive. For example, our technology is pretty expensive, so a whole body scanner for humans would be cost prohibitive. People wouldn't buy it even though its better performance. Unless you show that the performance is really buying you something and that's sort of ongoing.

Jennifer Buss

Are there certain technologies that would help that, better microelectronics, or better technologies on the other side that could help that advance better?

Paul Vaska

Right, so there is a lot of synergy between physics development that's going on in nuclear physics, at least in PET, MRI is a little different. So yes, there is new technology that came out of nuclear physics that actually not so recently sort of made our technology obsolete. We started ten years ago, and in ten years they have replaced photo sensors – technology has already gotten a lot better. So there is a lot of synergy in things, but it takes 10 years of technology development to really make a big step forward. That's why I think using some of this integration, technology that we already have and combining them is something that is also hard, but it is maybe a little bit more potential for big steps forward than these incremental improvements in spatial resolution, which are very useful.

Audience Member

I find it a little bit shocking that you would use lie detection methods for use now, rather than just for experimenting. They might be better than PET and they might be better than just judging, but they are so not good, that to use it, to actually make any decisions about somebody, I think is not appropriate. People could fool them for example, there's a lot of variation when you draw individual graphs or lines. So I'm surprised that you say you think they are ready for use...

Marvin Chun

No, no, I'm glad you asked that question because I thought I was saying the opposite. That one may want to use these methods for such applications, but that's one of the domain where we are very far from application for all of the reasons that you mentioned. In fact, for all of the progress we are making in other domains of decoding, lie detection is actually the area where we're not making any progress. I don't see the ability to use it in practical settings coming out within five to ten years. For all of the reasons you mentioned, but thank you for clarifying because I would want that point to be clarified.

Audience Member

I'm interested in the way you reconstruct faces. How would you do that, would you do it through decoding?

Marvin Chun

If I can explain it in 10 seconds, and I'm happy to share the paper with you, but long story short, we are relying on machine learning methods. So we are building mathematical models of how the brain responds to these face stimuli. So we learn that mapping, which is a mathematical function, and then that way when you present a new face and get a response, you can reverse that and apply it to make these guesses. If I were to throw one technical term out there because it sounds like you would be interested, we are relying on principal component analysis, and we are fortunate that there are a lot of good face-computer models that allow you to describe faces mathematically. So we're not describing pixels, we're describing faces mathematically and that's because of all of the advances that have been made in computer science. So we're relying a lot on those other methods.

Audience Member

Yes, it has to do with the technology and the subjects in these studies. Going back to the 1960s, where people talked about learning and there is an example of that here. From childhood, people are learning, and they are having positive or negative reinforcements. As they get older, they learn and develop their personalities. So you get personalities of people who have had positive experiences who are gregarious, and people who have had negative experiences, who have more loner types of personalities. That learning for positive personalities gives people, especially with faces, a lot more exposure to other people, a lot more interactions versus the loners who have a lot fewer interactions. With more interactions in positive personalities, you have a stimulus queue density, versus for the "loner" group, a stimulus queue scarcity. And that shows up in tasks such as threshold recognition of faces. One personality has a lot lower recognition threshold of faces than the loner. It also shows up in resolving complex figures. If you have a human figure embedded with an inanimate object, and you give it to both groups using a thetistiscope. The group that has had stimulus queue density resolves that much sooner and easier because there is a human there, and in other groups, there is no difference for inanimate objects but they have a higher threshold for humans. I'm wondering if we use this technology in the brain, you're finding out how mechanisms work, but how much are you learning about how to apply it to different types of people in getting subjects in databases? Is there a way that you can say, for instance, that somebody with a certain personality would have more of this kind of result showing up in a high tech instrument than other groups? Or is that still something for the future? It looks like you can reach back into the past and be able to apply it using some of the old kinds of knowledge bases.

Marvin Chun

So those are great insights. As one example, autistic children have much fewer social interactions than normally developing children, and when you scan their brains you can make the prediction that their face area will be less responsive. That has been shown. So yes, already, brain imaging can help distinguish individual differences and populations differences for something as extreme as responses to faces in autistic versus normally developing populations. Whether that can be expanded to differentiating different personalities for most normal persons is yet to be determined, and certainly people are working on it. I personally believe that it is feasible, that it's technically feasible to do so with refined methods. I think that's what is going to make this field so exciting. One may argue that this is just a product of their upbringing or their environment, but that is why I really am excited about prediction. Maybe there are intrinsic differences between people that will show how they will respond to a different environment. That is why I like to show the dyslexia study and things like that. I think that's where you can start using these applications for very positive domains.

Jennifer Buss

That reminds me of something that we've talked about recently. Kind of like going to the doctor, there is a normal blood pressure range that people have, but for you as an individual, your blood pressure range could be vastly different than the general public's blood pressure range. So if we can apply that then to what we are seeing in these brain images, yes. I'm sure there are some individual differences that we could say from day 1 through day 10 that defines your baseline. And then when you have an event happen, say a concussion, now you know what is different

from your individual baseline. But it takes us getting to the point of having the vast amount of technology around that we all know about each other.

Member

If you don't know what differences are in groups, how to differentiate groups, based on abilities or anxieties or other kinds of traits, what happens is you get a regression to the mean for all the data that comes in and you can lose something there.

Marvin Chun

I really love that point because fundamentally, I think we are both trying to conclude, without good measurements of behaviors and well defined behaviors, having clear ideas of what behaviors you want to study, a lot of these technologies are not very useful. It's their relation to these behaviors, so you are only as good as the behaviors you are trying to measure. So that's why this link is absolutely a very important priority for this whole enterprise.

Audience Member

Are there neurological or biological or biochemical arguments as to why ultimately you do not need a single neuron or single synapse, special or temporal resolution, like 10 microns would be enough, rather than when you get to 1 micron?

Paul Vaska

There are great debates about that. Obviously we would love to have single cell resolution throughout the brain. And the BRAIN Initiative is trying to go there. But when I go to meetings where they talk about, it is pie in the sky at this point. In the living brain, it's really just a question of realism and where exactly we create the cutoff. Better resolution always tells you more, and it tends to be incremental, but it's hard. We have had big discussions about what is the next level and we could not agree on it.

Audience Member

Recent advancements suggest that just because something showed up in one place, it doesn't mean it's different from something showing up some place else.

Jennifer Buss

One way I've heard it described is that just like we do population surveys, we will take a sample population, so if you can have a sampling of a certain area, you do not need to know every individual cell. I'm not sure if I buy into it, but that is one of the other sides of the argument that has been thrown around.

Charles Mueller

On that note, regarding resolution – should there be a data problem? Have we run into that, and do you experience a problem with data storage already by not being able to process all of the data? At a single cell level, do you have too much to do anything with it?

Paul Vaska

It's starting to become an issue, especially with multimodal data sets and things; it's pushing the limits of computing power. So yes, that has to come along with it. When technology is getting better, the computing has to get better too.

Charles Mueller

I want to ask a question for the two of you. First off, I really appreciate listening to everything you guys talked about today. It was incredibly insightful and well communicated. Given where you all are and what you're doing, what do you need going forward? What is the biggest thing that could help you? Would it be money, would it be time, is there some breakthrough in the underlying science that needs to happen? What do you need to really push your field forward?

Marvin Chun

I hate to give such a plain answer, but money is probably the biggest, most direct help, because I do feel that the ideas are there, but funding is very tight right now. Funding will buy time because funding helps hire the people who get the work done. So it does kind of come down to money. We always welcome advances, but there is already so much to do now with what we have and our existing computational resources. There is still so much to do right now. So unfortunately the answer is simple from my end.

Paul Vaska

Yes, it's the same thing. The ideas are there. There are a lot of cool ideas, and we need the money to implement them.

Audience Member

Another avenue of progress in neuroscience rights now is the big studies, where they are getting these huge data sets and they are trying to find out what we were saying before, about the normal distribution. Are we able to use it in a clinical or policy setting to actually say something about an individual? I am wondering if you think we just need better technology, if you think we also need bigger studies? Do you think the bigger studies in resting states might hold some of the answers at least by figuring out what a normal distribution of an attention network might look like? Maybe we could extrapolate that to individuals.

Marvin Chun

So we are very fortunate that these big studies are being conducted. The Human Connectome Project, in my field, has certainly been very useful. A lot of researchers around the world are learning a lot of those data sets. So personally I am very supportive of these big data efforts.

I just hope that they are not done while sacrificing the smaller labs that are studying the more specific questions because then you will have a Walmart scenario. I just worry about mom and pop shops like my own. If those types of small operations get crowded out because of the priorities on the bigger initiatives, then I think it's going to pose a problem. Again, boring answer, but I want both.

Paul Vaska

One of the issues with pooling a lot of data sets is there are PET studies and fMRI being done all over the place. I can mainly speak for PET but they are done in slightly different ways and they are very complicated studies. Some people inject more isotope or less, so they are hard to compare. For a specific study in a specific institute, you can have controls and you can have an experimental group and you can have a decent comparison, but once you start to go into different labs it becomes difficult. There is a lot of standardization that could probably happen as well to help make these data sets more comparable among different studies.

Audience Member

So there are a couple of bills right now moving in the House and the Senate that are dealing with the National Labs and the Department of Energy trying to get them more focused on various different things including super computing, modeling, and simulation capability. A lot of people do not know that the DOE and especially the National Labs can really help brain research and medical research. Dr. Vaska, you spent time at Brookhaven, so can you tell us how the National Labs can contribute, and how they can be forced to do so?

Paul Vaska

I think they will be willing to do so if it becomes part of the mission. They tend to be mission focused, so if the mission decides to be focused, they can turn and they will have to hire some different experts. I think they have a lot to contribute. The Labs have amazing resources that are very difficult to find in universities, certainly in terms of detection electronics, but also big facilities like light sources and things they can do like structural biology. There are huge resources to be put at it, and if it becomes a priority, then they can do a lot. It is just a question of, again, money, but also making it a priority.

CLOSING REMARKS

JENNIFER BUSS

There are a couple of things that I was thinking about as I was preparing for today. We talk about a picture being worth a thousand words, and right now, at least some of those words that we know from the pictures we are seeing are relevant, but which ones? Do we need more words to make that relevant? Where do we stand on that? I think we are missing some of the details to fully interpret some of the images that we are seeing. We are missing some context behind it. We don't have all of the data about the subjects that we are researching. So we have an incomplete picture. You heard today about pain and how doctors cannot really identify pain based on an image. There was a study done a few years ago that doctors were provided about a thousand MRI scans for headaches and back pain and they were asked to predict which subjects or patients had pain. They were unable to do so. They did it at a 50% rate. At a 50% rate, they might as well have been guessing. It didn't matter that they had an image in front of them. I could have gone around the room and said "You're in pain", "you're in pain", "you're not", and I probably could have done it better based on what I see on your facial expression than from an image of your back or your brain. So it's a problem, right? It's a problem for our patients because we can't tell them anything. We can't help them. And nobody wants to hear that from their doctor. It's a problem for our clinicians and our researchers because we can't study it. We don't have the right equipment and we can't make models based on what we get from these images. And it's a problem for policymakers because we can't make decisions based on what we're told from the scientists and the researchers. So it's a really big problem all around, and if we can have better resolutions in these images, or know more about what we're looking for from the metadata that's associated with these images, we can all make better decisions.

We are actually at that crux of the biological basis of behavior, mixing together psychology and neuroscience so that we can actually make a quantitative versus the qualitative assessment as we have seen in psychology for so many years. Psychology is changing to be a more "what is cognition?" philosophy style versus a hard science which we will begin to call neuroscience instead of psychology. One of the things that we talked about today was mapping the brain and Dr. Chung put up a great image of Google maps and then he overlaid traffic on top of it. I don't know how many of you noticed at the bottom of that image, it said what time we are looking at traffic. That would be awesome to have in these images when we are looking at the map of the brain that we're creating. It's not just creating the map and defining it however we want to define mapping: what resolution we want, how deep we want to go into this, do we want to look at every single cell? Can we look at just a sampling? But what information can be gathered from the map that we have? We want traffic information. We want to be able to click on a location and see the name of it or say "What time is my train coming at this metro station?", or "What time does the store open at this location?". So all of those overlays of data

on top of just the map of the terrain would be the most useful way to have these maps. It's not just creating it from the images, because that would be like what we can basically do now with the resolution that we have. But where do we take it from here, and how useful will this be in the future?

It's not just the idea of how useful it's going to be but it is technology that is going to bring us there. Researchers may eventually reach the goals with the technology that they have right now, but advancing the technology is what we are going to need. It's the technology that is being focused on in the BRAIN Initiative. It's not additional funding for neuroscience itself, but it's funding specifically for that technology. And so that's the way that we are going to get to this goal of mapping the brain. So we need to define what we want and figure out how we are going to get there. We are all going to do it together, no one is going to do it by themselves. We have talked about working with the National Labs; we have talked about bringing together a bunch of consortiums of neuroscience: researchers, clinicians, doctors, psychologists, computer scientists, physicists, and microelectronics. It's not just the field of neuroscience anymore. It's huge collaboration across all of the fields. We are going to need the technology to see maybe at every atom. We will need it to track the micro and the macro scale. There was a discussion about "it's my telescope and my microscope" related to an MRI machine. I thought that was a really good analogy. It's not just the 6 million dollars that we have in neuroscience research but it's another whole set of doors to open in talking about technology. It's not just in imaging; we've talked about the other components that go along with it. So we need to follow a road map that goes with tracking science to create the technology that can add to the scientific field afterwards. We need to coordinate all of our research together. If we do this right, we will actually be able to bring back our knowledge baseline from every human from here, up to here, based on the research that we have and how it will help the general population.

Thanks again for all of you who attended and a special thank you to our speakers. We look forward to seeing you all again soon.

PARTICIPANT BIOGRAPHIES



MARVIN CHUN, Ph.D.

Richard M. Colgate Professor of Psychology at Yale University

Dr. Marvin M. Chun is the Richard M. Colgate Professor of Psychology at Yale University, with joint appointments in the Cognitive Science Program and the Yale School of Medicine Department of Neurobiology. He also serves as the John B. Madden Master of Berkeley College. He received his Ph.D. from MIT and his postdoctoral training at Harvard University. His laboratory employs functional brain imaging to study visual attention, memory, decision-making, perception, and performance. Over the years, he has been supported by the NIH and NSF, and his research has been honored with early career awards from the US National Academy of Sciences and the American Psychological Association. His undergraduate teaching of Introduction to Psychology, one of the largest classes in Yale College, has been recognized with both the Phi Beta Kappa William Clyde DeVane Medal for Distinguished Scholarship and Teaching in Yale College and the Lex Hixon '63 Prize for Teaching Excellence in the Social Sciences. Beyond Yale, he serves on the Board of Directors for the Federation of Associations in Behavioral and Brain Sciences, and as a scientific advisor on the NIKE Performance Council.



PAUL VASKA, Ph.D.

Professor, Departments of Biomedical Engineering and Radiology at Stony Brook University, with a formal Joint Appointment at Brookhaven National Laboratory (BNL)

Dr. Paul Vaska is a Professor in the Departments of Biomedical Engineering and Radiology at Stony Brook University, with a formal Joint Appointment at Brookhaven National Laboratory (BNL). He specializes in developing novel imaging techniques for brain science and beyond, including the only imaging system that provides functional imaging across the whole brain of an awake and behaving rodent (RatCAP). He obtained his Ph.D. in Nuclear Physics from the State University of New York at Stony Brook and then transitioned to the field of medical imaging, initially by doing industrial research for a vendor of positron emission tomography (PET) scanners, which was ultimately acquired by Philips Medical Systems. In 2000, he was recruited by the PET Group at Brookhaven National Laboratory (BNL) led by Dr. Joanna Fowler, a pioneer in the field. He rose through the ranks to become Head of PET Physics in 2004, and Medical Scientist with tenure in 2008. In 2011, he became a Full Professor at Stony Brook University in the Department of Biomedical Engineering while maintaining his BNL appointment. He is an inventor on 4 patents and Co-Founder and initial CTO of a startup company that is commercializing his imaging technology.



JENNIFER BUSS, Ph.D.

**Research Fellow and Director, Center for Neurotechnology Studies
Potomac Institute for Policy Studies**

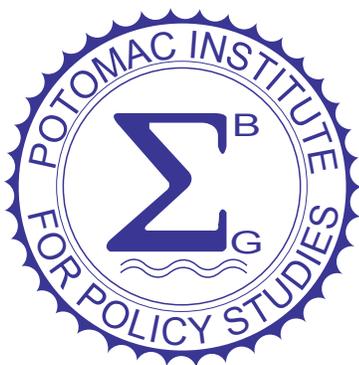
Jennifer Buss, Ph.D. is a Research Fellow at the Potomac Institute for Policy Studies. She is the Director of the Center for Neurotechnology Studies (CNS) at the Potomac Institute, where she leads a team studying issues in neuroscience technology and policy. Dr. Buss is a Fellow in the Center for Revolutionary Scientific Thought, a group at Potomac Institute that brings together individuals from a variety of backgrounds to foster discussion on science and technology futures from both an academic and policy perspective. In addition to these efforts, she has supported contracts for DMEA, OSD, and the Office of Corrosion Policy and Oversight. She is the Program Manager for the Rapid Reaction Technology Office contract for OSD in searching for innovative technologies to enhance government systems. Dr. Jennifer Buss was awarded a doctorate in biochemistry from the University of Maryland Department of Chemistry and Biochemistry in 2012.

SEEING ISN'T ALWAYS BELIEVING

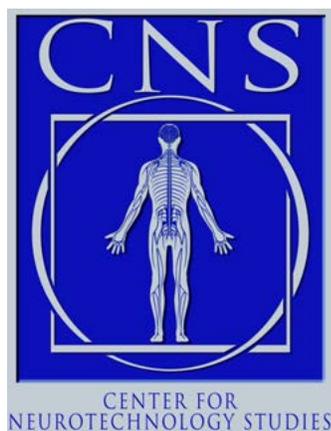
THE REALITIES OF IMAGING TECHNOLOGY AND NEUROSCIENCE

This seminar aims to discuss the future of imaging, how these technologies can be developed to provide a more in-depth map of the brain and its functions, and how knowledge gained from these technologies can impact and affect the lives of everyday citizens. The distinguished panel of neuroscientists and imaging specialists will provide their insight on how technologies like neuroimaging improve our brain health, spur new research and development, and help to accomplish our national science endeavors. Because this field holds such great promise, it warrants the development of policy options that will make brain mapping with new neuroimaging technology a reality. By bringing together researchers and academics involved in the brain sciences alongside policymakers and legislators, we hope to provoke a lively discussion from which novel policy ideas for the successful implementation of neuroimaging for brain mapping and other BRAIN Initiative efforts will emerge.

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