POSTON RESEARCH LABORATORY

Stanford MEDICINE

Stanford Neurology Research Report

Dear Members of Our Research Community,

We, at the Poston Lab and the Stanford Movement Disorders Center, would like to take the opportunity to express our sincere gratitude for your time and participation in our research on Parkinson's disease and parkinsonian disorders. Your dedicated participation lies at the heart of our scientific research. As a show of thanks, here is an update on our progress to date.

We have been hard at work compiling and interpreting valuable information given to us by research participants. The fruits of our efforts will soon be available for shared access in the scientific community. Please see Page 3 for more information.

Special thanks from the Poston Lab Research Team!

Research Recruitment

With the help of our research assistants, we have considered over 434 individual cases for research.

We are actively recruiting participants with diagnoses of Parkinson's disease, and healthy controls over the age of 70.

Diagnosis	**#**
Parkinson's disease (PD)	252
Atypical Parkinsonism (MSA, PSP, CBD)	23
Mild Cognitive Impairment & Early Alzheimer's Disease	24
Healthy Control	135
Total Enrolled	**434**

Recruitment for New Research Studies!

- **New PET Study** - We recently started recruiting individuals with Parkinson's disease for two PET/MRI scans to examine patterns of protein (amyloid) build up and inflammation (microglial activation) in the brain. The ability to measure amyloid accumulation and microglial activation provides a critical opportunity to further the understanding of Parkinson's disease, monitor disease progression, and assess disease modifying treatments.
  - **For more information, please contact Marian Shahid at (650) 723-0060 or mshahid@stanford.edu.**
- **Stanford Alzheimer's Disease Research Center (ADRC)** - The NIH, with the National Institute for Aging (NIA), approved funding for the new Stanford Alzheimer's disease Research Center (ADRC) and we have had a very successful year of recruitment and data collection! Our Center's theme is understanding early memory problems in people with Parkinson's disease and Alzheimer's disease.
  - **For more information, please contact Christina Wyss-Coray at (650) 721-2409 or ADRCstanford@stanford.edu.**
- **Pacific Udall Center** - In July 2016, Stanford became the lead site for the Pacific Udall Center: A Morris K Udall Center of Excellence in Parkinson's Research, which is one of eight Centers funded by the NIH and the National Institute for Neurological Disease and Stroke (NINDS). Pathology Chairman Dr. Tom Montine and Dr. Kathleen Poston are leading the Stanford team. Together with University of Washington and Oregon Health Sciences University (OHSU), the Pacific Udall Center's mission is to understand the genetic contributions to Parkinson's disease memory problems and balance problems.
  - **For more information, please contact Meagan Adams at (650) 721-5274 or udallcenter@stanford.edu.**

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Pacific Udall Center
NIH Center of Excellence for Parkinson's Disease Research

A·D·R·C for healthy brain aging

Looking at cognition in people with Parkinson's disease from a different angle: how do tiny strokes and their location in the brain affect cognition?

People with Parkinson's disease are at risk of developing cognitive impairments; however the exact cause is unknown and it is likely that there are many different contributing causes. We used data acquired on MRI scans to determine if tiny strokes might play a role. At the 2018 Annual Meeting of the American Academy of Neurology and the 2018 Society for Neuroscience Annual Meeting, Dr. Patricia Linortner and Mr. Colin McDaniel showed that these tiny strokes increase the risk of having problems with attention, memory and executive function, such as the time it takes a person to complete a mental task. These effects become especially apparent when these strokes are larger or next to fiber tracts that transfer information between different regions of the brain. Treatment of stroke risk factors (like blood pressure or diabetes) could help slow down the progression of some cognitive difficulties in people with Parkinson's disease, which we plan to investigate in future studies.

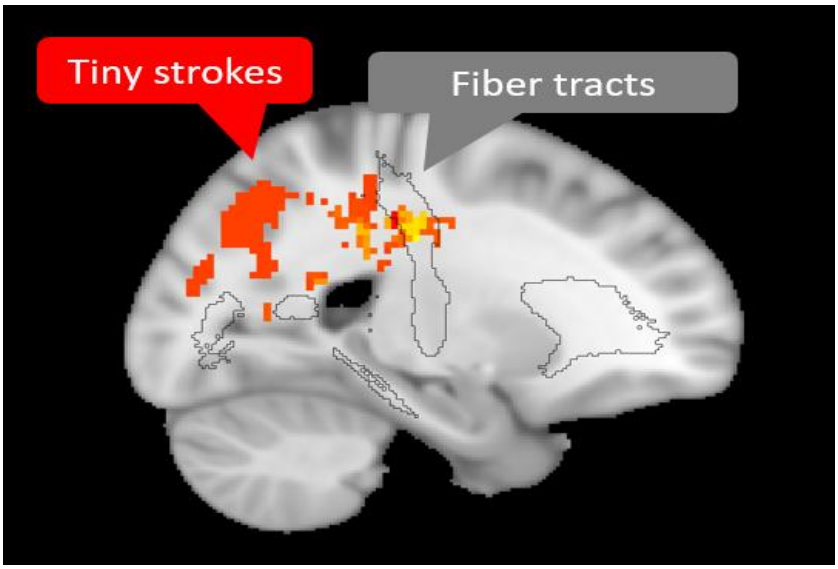

Figure 1: Tiny strokes near fiber tracts in the brain.

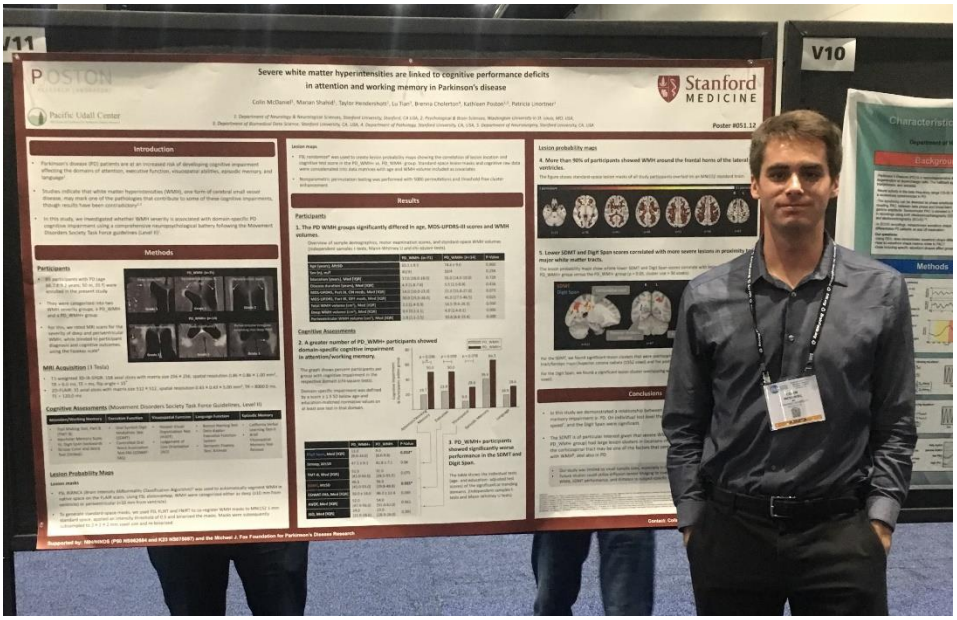

Figure 2: Mr. Colin McDaniel presenting at the 2018 Society for Neuroscience Meeting in San Diego, California.

Maintaining Information

Ever wondered how our brain works to keep phone numbers in our head until the moment we jot it down on a piece of paper? It's done by a brain process called 'working memory.' Working memory refers to the ability to actively maintain and manipulate information in your mind. You generally rely on this ability when you are keeping track of lists in your head or attending to conversations.

We tested a similar process in the MRI scanner in people with Parkinson's disease, both while they were on and off their dopaminergic medications. We asked research participants to view a single number probe and respond based on whether it matched with one of the five numbers they saw previously (Figure 3). From this study, we found that some individuals' working memory improve when they take their dopaminergic medications, whereas others don't demonstrate such improvements. We are currently investigating which clinical characteristics indicate whether an individual's working memory improves, or does not improve, with dopamine. This can help inform how to best prescribe medications that optimize cognitive functioning.

Further, working memory is known to be facilitated by the frontal lobes of the brain (as shown by the red activation in the brain images below) in coordination with other regions, such as the subcortical regions. This ability can be disrupted in Parkinson's disease, which is thought to be driven by a decrease in dopaminergic input from the subcortical regions to the frontal lobes.

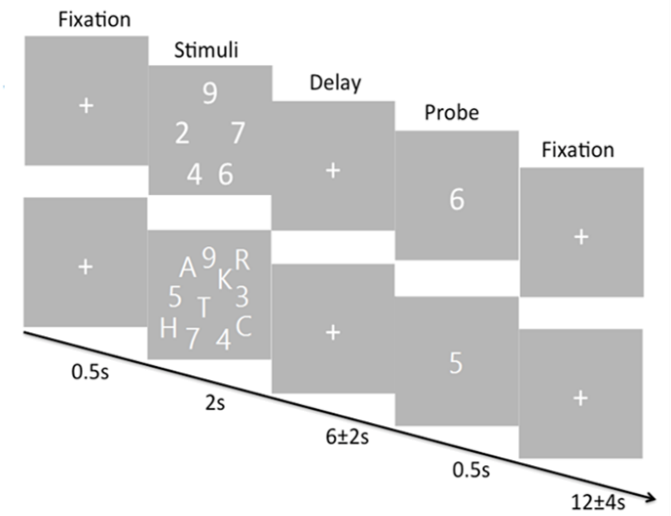

Figure 3: Sternberg task – the working memory task participants complete inside the MRI scanner.

Previously, Dr. Kathleen Poston demonstrated that a subcortical region, the putamen, demonstrates compensatory activity in Parkinson's disease during this working memory task. Therefore, Poston Lab researchers, Dr. Sephira Ryman and Ms. Jeehyun Kim, are in the works to extend this finding and better understand the interaction between the putamen and the frontal lobes of the brain. Understanding this system will enable researchers to develop effective means to intervene and improve cognitive functioning in individuals with Parkinson's disease.

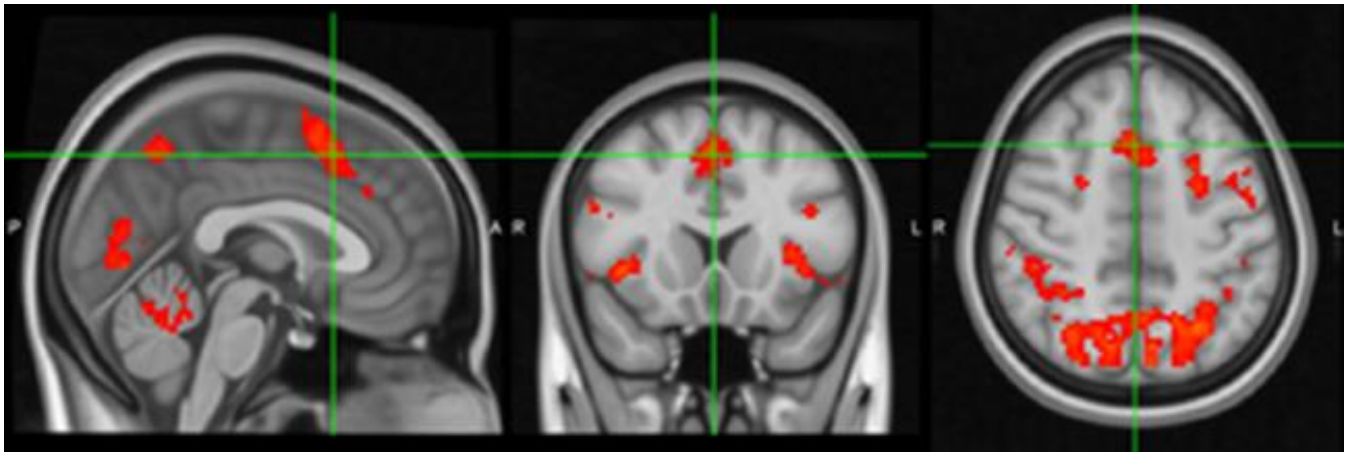

Figure 4: Frontal cortical regions involved in the working memory task.

How much can a brain at rest tell you?

Turns out your resting brain actually tells quite a bit. The 10 minute 'resting-state' functional MRI scan acquired from our research participants allows us to analyze natural brain fluctuations and provides a functional framework underlying basic brain operations. In previous studies, the regions of the brain that control motor activity (termed the 'motor network') has less synchronized fluctuations in people with Parkinson's disease, compared to people who do not have Parkinson's disease. This could be one mechanism that leads to the motor symptoms experienced by patients. In the Poston Lab, we are studying whether the synchronized fluctuations associated with both cognitive and motor symptoms are inter-linked. We have found that a brain region, called the anterior insula, might be responsible for this link. The insula is well known for its role in gating of attention and allowing us to switch our attention to different stimuli.

While the typical 'resting-sate' functional MRI analysis method is to average all of the data collected over the 10 minute duration of the scan, this average representation might be a gross simplification and may miss critical information that can help us better characterize important brain changes over short periods of time. Therefore, we have decided to take a non-stationary approach to analysis. Dr. Christian La and Ms. Nessa Kim are exploring how analyzing the changes in synchronized fluctuations over time might be a novel metric for understanding brain flexibility and overall brain health. This could be particularly interesting in people with Parkinson's disease and helpful in understanding the mechanism underlying motor and non-motor symptoms. Initial results from this investigation have been presented at the *6th Biennial Resting State Brain-Connectivity Conference* 2018 in Montreal, Canada, and the manuscript is currently being prepared for publication.

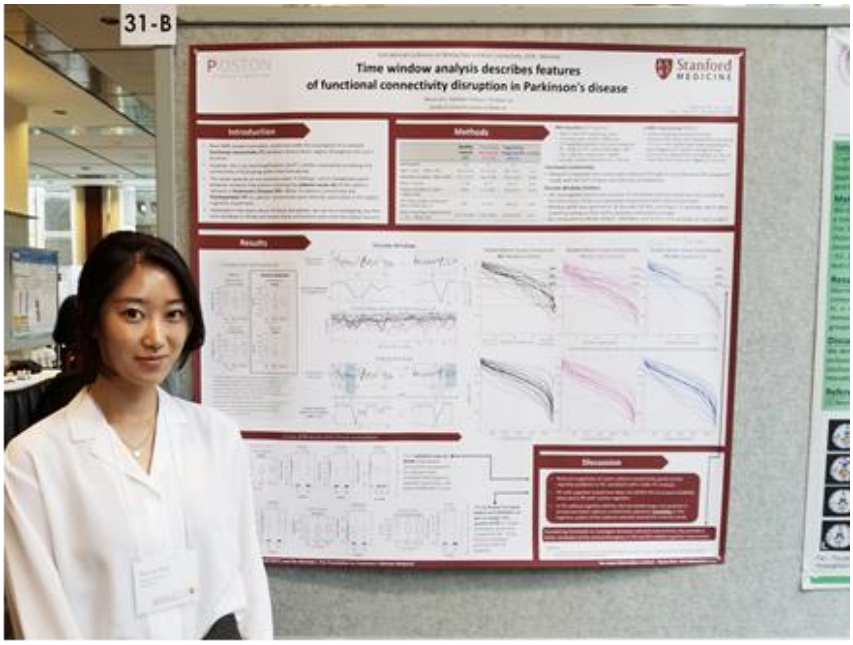

Figure 5: Ms. Kim presenting at the 2018 Biennial Resting State Brain Connectivity Conference in Montreal, Canada.

Scientific Papers

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