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14. ABSTRACT

Multiple sclerosis (MS) is the most common progressive neurologic disorder to occur in adults of working-age. Pathologically, MS is characterized by demyelination, immune-mediated inflammation and neurodegeneration within the central nervous system (CNS). Cognitive impairment is estimated to occur in up to 70% of all patients. In this study, the measure of cognitive impairment used, called intra-individual variability (IIV), can detect variability in each subject's performance over time. This is a sensitive indicator of cognitive impairment in individuals with neurological disorders including MS. Multiple types of brain imaging will be used to acquire data from participants, including Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET). Data from the first 10 subjects in each cohort has been acquired, pre-processed and both raw data and image analysis outputs have been put through extensive quality control/assurance analysis. The significance of our preliminary findings suggest we may be able to uncover early biological underpinnings of cognitive impairment, which could both improve our understanding of MS and help in the development of novel therapeutics for this impairment.

15. SUBJECT TERMS

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Abstract

Multiple sclerosis (MS) is the most common progressive neurologic disorder to occur in adults of working-age. Pathologically, MS is characterized by demyelination, immune-mediated inflammation and neurodegeneration within the central nervous system (CNS). Cognitive impairment is estimated to occur in up to 70% of all patients and is a major cause of disability, often striking during key years of productivity and family life. Despite longstanding recognition of cognitive impairment as a symptom of MS, two obstacles in measurement have limited understanding its biological basis, and therefore identifying targeted options for management. First is the absence of a sensitive and precise measure of cognitive impairment. Second is the absence of an index of disease status linked to brain pathophysiology and cognitive performance. This project overcomes both obstacles to link cognitive impairment to MS disease biomarkers.

In this study, participants with early stages of the relapsing-remitting subtype of MS (RRMS) will be studied. The measure of cognitive impairment we will use, called intra-individual variability (IIV), can detect variability in each subject's performance over time. This is a sensitive indicator of cognitive impairment in individuals with neurological disorders including MS. Multiple types of brain imaging will be used to acquire data from participants, including Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET). To reduce subject burden, we will use one scanner to simultaneously acquire both imaging parameters. The scanner is one of only a few in the world that simultaneously acquires PET and MRI images. During a one hour session, the PET/MRI scanner provides structural scans that allow estimation of volume and cortical thickness, as well as white matter tract integrity, which can relate information regarding demyelination, commonly associated with MS. At the same time, we will acquire PET images using a PET tracer called FDG, an analogue of sugar that allows us to quantify metabolism.

By analyzing the brains of MS patients using all of these techniques, we will create the most comprehensive profile of MS, greatly increasing our understanding of the biological differences that occur in MS and that are most closely related to differences in cognitive performance. The clinical implications of uncovering this correlation are tremendous. Most importantly, we would have an improved understanding of the MS disease process. This would improve both diagnosis and ability to provide prognosis.

Data from the first 10 subjects in each cohort has been acquired, pre-processed and both raw data and image analysis outputs have been put through extensive quality control/assurance analysis. This is performed through a semi-automated pipeline established by the Center for Understanding Biology using Imaging Technology (CUBIT), in which each slice of the raw images and every intermediate output of the image analysis pipeline can be examined, commented on, edited, approved and locked through an html interface. Of the 20 data sets received, one did not pass quality assurance inspection due to artifact in the image. For this reason, that subject's data was excluded from the following analyses. Ongoing quality improvement efforts include refining image analysis results using manual intervention.

As described in our application, structural MRI (sMRI) is sensitive to the neuro-axonal loss and demyelination that occurs in MS [1]. A recent meta-analysis of 18 studies of regional grey matter loss in RRMS found that, in all studies, loss was observed in the parietal regions. Our preliminary data confirms this finding with average cortical thickness measures being significantly lower in MS versus control subjects (Figure 1).

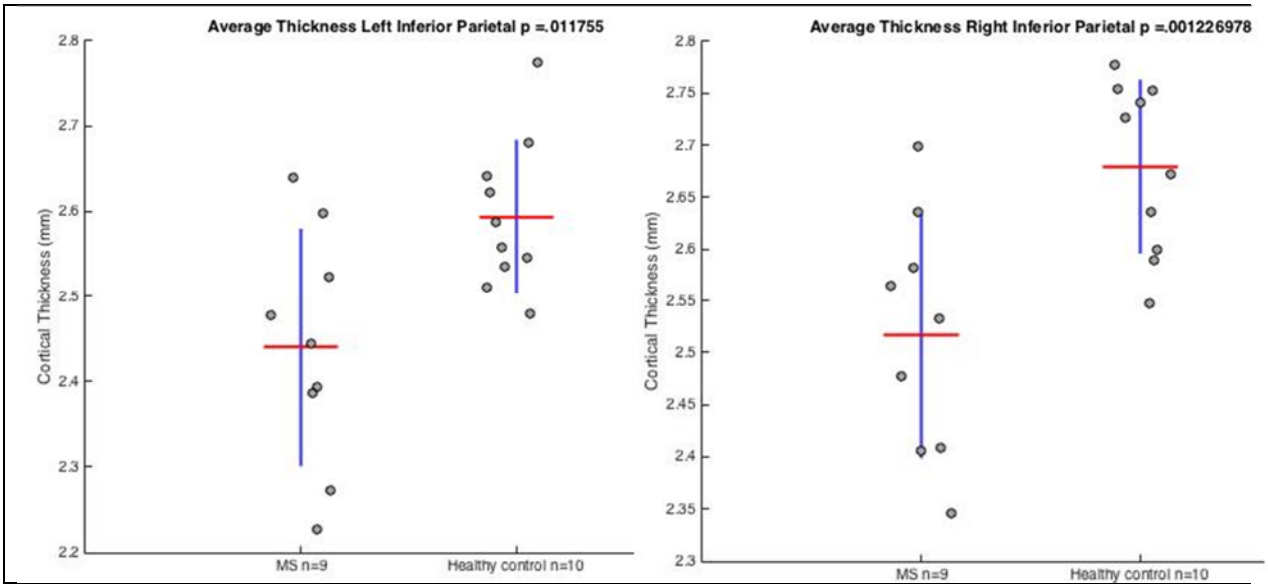

Figure 1: Average cortical thickness values in the left and right inferior parietal regions were lower in MS subjects than controls.

From dMRI, estimates of the directionality, water diffusion can be calculated throughout the brain. As such, dMRI is an optimal technique to detect demylination, axonal injury and cell death associated with MS. dMRI can provide an index of the health of the identified neuronal (white matter) tracts, called fractional anisotropy (FA). Higher FA values potentially reflect a parallel organization of axons and greater myelination. FA is a sensitive measure that can reveal pathology even in normal appearing white matter [2-4]. In a recent DTI study performed by our group, significant FA differences were found in the white matter tracts of the posterior thalamic radiation (connectivity between thalamus, occipital, and parietal regions), as well as between the frontal and occipital lobes [5]. The health of the thalamus, which is heavily involved with information processing [6], has also been related to cognitive decline [7, 8] Consistent with these findings, we observe significantly different FA in the right and left thalamus, left inferior parietal and left thalamus in MS patients versus controls (Figure 2).

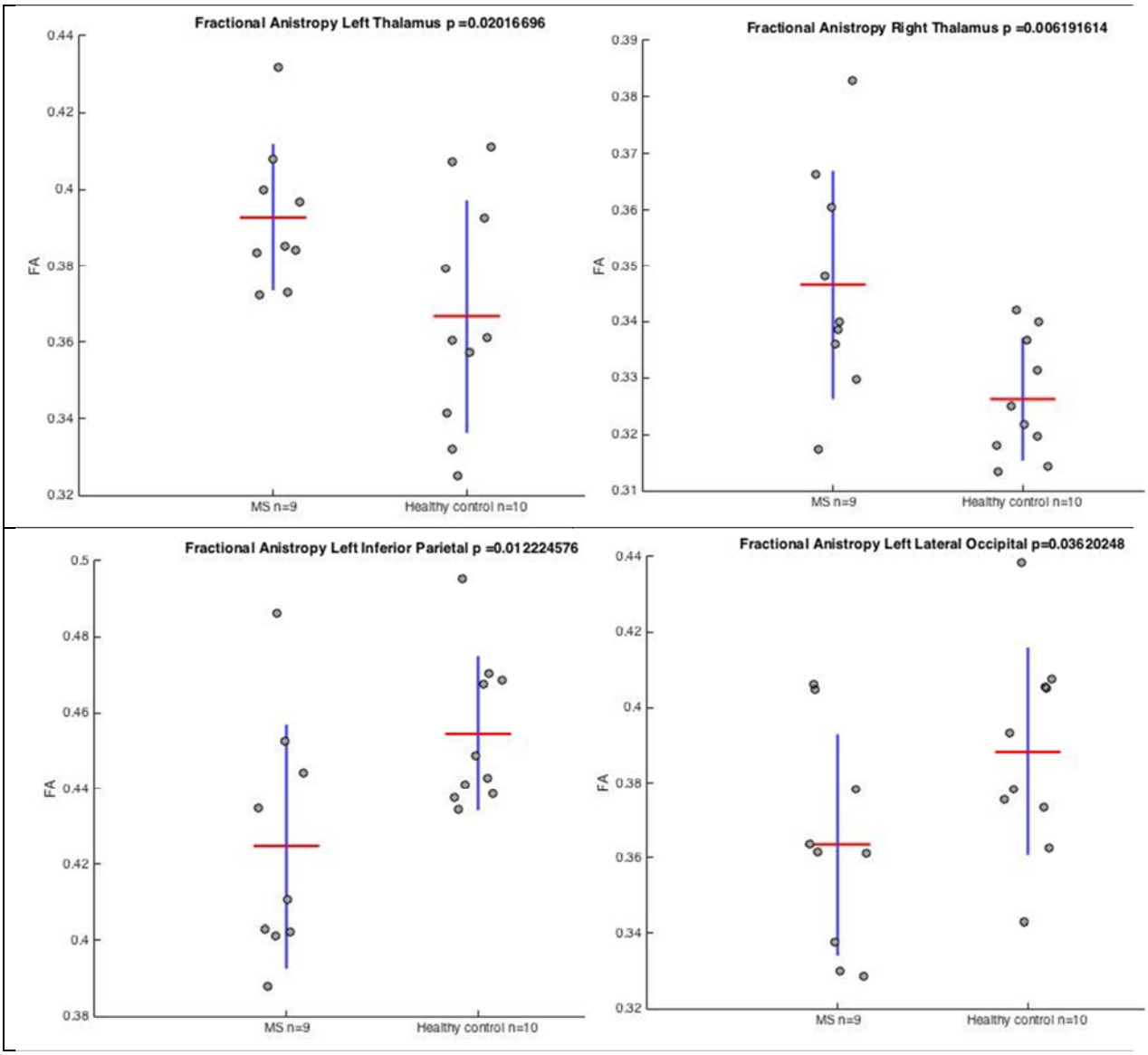

Figure 2: Average fractional anisotropy in the left and right thalamus (top), left inferior parietal (bottom left) and left lateral occipital (bottom right) was different in MS subjects than controls.

In a normal or healthy white matter region, there are multiple white matter pathways passing through, resulting in a higher FA since water molecules may travel in many different directions. In disease, if one or more of those pathways are destroyed or weakened, the FA will be lower. Our findings confirmed as analyzed with tractography, that the MS relative to the Control group had a lower FA in the regions examined.

In addition to examining image-derived biological differences between MS subjects and controls, this study aims to uncover the biological underpinnings of cognitive impairment. The relationship between cognitive IIV and white matter volume and/or integrity has been established in numerous contexts: in healthy controls [9-12], subjects with frontal lesions [13], and in development [14]. In DTI studies of the elderly, decreased

FA was associated with increased IIV [15]. However, this has not yet been established in MS. In exciting preliminary data, we show, for the first time, a correlation between gray matter atrophy, as assessed through cortical thickness, and both scores on an executive working memory task and our sensitive IIV (Figure 3).

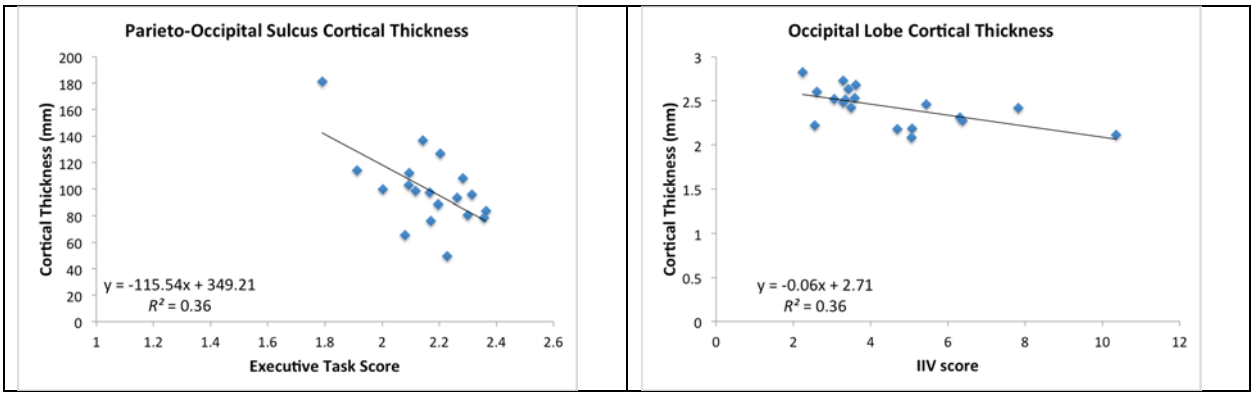

Figure 3: Relationship between cortical thickness in the parieto-occipital sulcus (left) and occipital lobe (right) and cognitive measures.

Though more subjects are needed to validate study hypotheses, this strong preliminary data reveals image-derived biological differences in regions related to MS and cognition, and therefore hypothesized as important in our study. In continued work, we will perform tractography from the dMRI images to identify specific pathways, as well as compare results across all modalities acquired. The significance of our preliminary findings, however, is that the results suggest we may be able to uncover early biological underpinnings of cognitive impairment, which could both improve our understanding of MS and help in the development of novel therapeutics for this impairment.

1. **INTRODUCTION:**

Cognitive impairment affects the ability to think and can include problems with the attention and information processing needed to learn and solve problems. This symptom represents a major concern for many individuals living with multiple sclerosis (MS). Unfortunately, no reliable treatments exist to help manage it. This is most likely for two reasons: (1) traditional tests of cognitive impairment in MS, which measure performance at only one point in time, are not sensitive enough and (2) the underlying causes of cognitive impairment are not well understood. In this study, we will address both of these challenges by using a precise indicator of cognitive impairment and correlating this measure with the largest amount of brain imaging data collected within a single subject to date. The ultimate purpose of this study is to use brain imaging to understand how the MS disease process causes cognitive impairment.

2. **KEYWORDS:**

Multiple sclerosis, cognitive impairment, neuroimaging, intra-individual variability, magnetic resonance imaging, positron emission tomography

3. **ACCOMPLISHMENTS:**

Through month 12 of the award, the below major goals and objectives were established in the statement of work. The accomplishment for each of these goals is detailed below each item.

-***Major Task 1 Study Set Up***
Target Month: 1-3
Completion: 1-3
Milestones achieved: *IRB and HRPO approval, certification of psychometrician and renewal of EDSS for LK, completion of MOP and clinical cognitive research database*

-***Major Task 2 Cognitive and clinical data collection of 25 MS and 25 healthy control participants***
Target Month: 4-24,
Completion Month: 1-12 60% of MS participants complete, 56% of control participants complete
Quarter Four Completion: 12% of MS participants complete, 12% of control participants complete
Milestones achieved: *First patient enrolled, progress report submitted re: clinical/cognitive findings on initial 20 participants (Report included in section above abstract).*

-***Major Task 3 Development of Neuroimaging Protocol***
Target Month: 1-3,
Completion: 1-3
Milestones achieved: *IRB submitted, staff all certified, neuroimaging MOP finalized*

-***Major Task 4 Neuroimaging data collection with quality control monitoring on all 50 subjects***
Target Month: 4-20,
Completion Month: 1-12 58% of subjects complete
Quarter Four Completion: 12% of subjects complete
Milestones achieved: *Collect neuroimaging data with quality control on first healthy control participant*

-***Major Task 5 Completion of data analysis of the relations between cognitive and imaging data***
Target Month: 21-24

- What opportunities for training and professional development did the project provide
Nothing to Report

- How were the results disseminated to communities of interest
Nothing to Report

- What do you plan to do during next reporting period to accomplish goals and objectives
During the next reporting period (months 13-16), we plan to continue neuroimaging data collection and cognitive testing with quality control monitoring toward the enrollment of the remaining 10 MS patients and 11 controls. We also plan to prepare abstracts to submit this work to relevant conferences and disseminate findings with through publications.

4. **IMPACT:**
- Impact on the development of the principal discipline of the project
The above results provide initial insight into the biological underpinning of cognitive dysfunction in MS. Once validated and expanded, results can be used to help develop new therapeutics or monitor treatment.

- Impact on other disciplines
Nothing to Report

- Impact on technology transfer
Nothing to Report

- Impact on society beyond science and technology
Nothing to Report

5. **CHANGES** (required to obtain written approval prior to changes):
Nothing to report

6. **PRODUCTS:**
Nothing to Report

7. **PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:**

- Individuals who worked on project (follow formant from quarterly report)

Name: *Lauren Krupp M.D.*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID): 0000-0003-3906-4485

Nearest person month worked: Y1Q4 - 0.225; Y1 - 0.9
Contribution to Project: Dr. Krupp has performed the baseline neurological assessment, addressed all clinical and research issues, and followed reports from the Clinical Coordinator's phone contacts. Dr. Krupp has ensured that the research accomplishments are consistent with the study timeline. She has met weekly with the Co-Is and study coordinator/psychometrician to monitor the study's progress.

Name: *Leigh Charvet Ph.D.*
Project Role: *Co-Investigator*
Researcher Identifier (e.g. ORCID ID): 0000-0003-4429-9713
Nearest person month worked: Y1Q4 - 0.425; Y1- 1.7
Contribution to Project: Dr. Charvet has directed the study coordinator/psychometrician in the day-to-day operations and overseen the neuropsychological assessment procedures and database creation during the study start-up. She has worked with the PI, Co-Is, and study coordinator/psychometrician to finalize the manual of operating procedures. She has taken responsibility along with the PI for quality control of all clinical and cognitive data entry. She has supervised the study coordinator/psychometrician regarding cognitive data collection and entry, and has met regularly with the PI on the progress of the study.

Name: *Christine DeLorenzo Ph.D.*
Project Role: *Co-Investigator*
Researcher Identifier (e.g. ORCID ID): 0000-0001-8035-2417
Nearest person month worked: Y1Q4 - 0.425; Y1 – 1.7
Contribution to Project: As the director of the image processing team (including programmer, data analysts, and IT support), Dr. DeLorenzo has ensured continuity of the project by overseeing the documentation of all image processing procedures, being the contact person for data or analysis issues, and providing daily guidance and support for the image analysis team.

Name: *Jie Yang Ph.D.*
Project Role: *Co-Investigator*
Researcher Identifier (e.g. ORCID ID): 0000-0003-3469-5931
Nearest person month worked: Y1Q4 - 0.300; Y1 – 1.2
Contribution to Project: Dr. Yang assisted in writing the analysis plan for the MOP and provides statistical consultation and support as needed

Name: *Kai Sherman*
Project Role: *Coordinator*
Researcher Identifier (e.g. ORCID ID): 0000-0003-2437-7892

Nearest person month worked: *Y1Q4 – 2; Y1 – 8*

Contribution to Project: Ms. Sherman is responsible for the step-by-step activities from implementing the database, producing participant enrollment logs, obtaining consent (after the PI has explained the study), scheduling the cognitive and MRI visits, performing neuropsychological testing and confirming that all scheduled visits are met and necessary data collected. She works very closely with Drs. Krupp and Charvet, as well as with the MRI image technician in ensuring that all aspects of clinical data collection take place in a timely manner, and that patients are scheduled at appropriate times for the neuroimaging.

- Change in active other support of PI or senior/key personnel:
  Nothing to Report

- What other organizations were involved as partners
  Nothing to Report

8. **Special Requirements**
   None

9. **Appendices:**

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