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TITLE: Imaging Effects of Neurotrophic Factor Genes on Brain Plasticity and Repair in Multiple Sclerosis

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
The objective of this study is to develop a better biomarker for multiple sclerosis (MS) by combining genotype and imaging data. In this study, patients with MS undergo neurological evaluation to confirm diagnosis and determine disability level. They have blood drawn for genotyping, and undergo magnetic resonance imaging sensitive to focal and diffuse effects in brain (including cortical thickness and subcortical volume measures, lesion volumetry, and voxel-based morphometry and diffusion imaging). We are continuing to progress with screening, enrollment, and scanning of participants, with 79 patients having enrolled and completed study procedures or screened in to the study and in the process of scheduling. Although recruitment was initially slower than we hoped on this study, we have taken major steps to increase visibility and awareness of the study among patients and referral sources, and our recruitment rate significantly increased and continues to increase as a result. We continue to devote significant effort to maintaining and enhancing study visibility and awareness among referral sources and patients to maximize recruitment, and we fully anticipate that the momentum in recruitment will continue to grow as we go forward. We have encountered no adverse events. We continue to log and back up all data, and complete ongoing QA and data entry. A first batch of TaqMan genotyping (N=47) has been completed and a second batch will be sent in the Winter 2012. We are preparing a conference submission on brain-derived neurotrophic factor genotype and regional gray matter volumes (Hypothesis 1-A). We continue to have regular research meetings, and monitor the budget/expense with our Grants Manager.
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Introduction

Background. Conventional MRI provides a useful biomarker for multiple sclerosis (MS) clinical trials, but conventional imaging is insensitive to many of the neural changes in the disease and a better biomarker is needed. The proposed study will combine multimodal MRI, to capture the full range of neural changes in the disease, with genotype data to develop a more sensitive and comprehensive biomarker for the disease. Neurotrophic factor genes related to brain plasticity and repair will be targeted for this purpose because of their probable moderating effects on neural damage in MS. Objective. The objective of the proposed study is to develop a better biomarker for MS by combining genotype and imaging data. Specific Aims. We will combine data regarding neurotrophic factor genotype and imaging to: (1) Assess specific a priori hypotheses regarding effects of specific neurotrophic factor polymorphisms on specific brain imaging, (2) Assess both additive and interactive models of effects of genes within each of the three neurotrophic factor gene families on imaging of gray and white matter integrity, and (3) Determine the optimal linear combination of genotype and imaging data to predict concurrent level of disability in MS. Study Design. Patients with MS (N=200) will undergo neurological evaluation to confirm diagnosis and determine disability level. They will have blood drawn for genotyping, and will undergo MR imaging sensitive to both focal and diffuse effects in gray and white matter, including cortical thickness and subcortical volume measures, lesion volumetry, and voxel-based morphometry and diffusion imaging. Regression and symbolic modeling will be used to address the specific aims. A number of data reduction and other procedures will be used to minimize Type II error. Impact. This research will set the stage for future longitudinal research assessing the obtained imaging-genotype biomarker as a predictor of disease course and treatment response. Ultimately this research will improve the clinical care of patients with MS by increasing prognostic accuracy and enhancing our ability to identify optimal treatment protocols for individual patients. Development of a more sensitive and comprehensive biomarker will contribute to drug discovery and clinical trials in MS.

Body

We are continuing to progress with screening, enrollment, and testing. We have encountered no adverse events and our IRB/Human Subjects approvals are current. We have completed the following recruitment/enrollment steps:

- 446 patients have completed basic screen or been referred to the study
- 286 passed basic screen and we have attempted to contact for full screen
- 147 have completed full screen; additional 34 in active recruitment
- 53 had enrolled as of June 30, 2011
- 79 have now enrolled and completed study procedures, or are in the process of scheduling

The funds for this study were released to us in October 2009, which is when we started recruiting. Recruitment was slower than anticipated in the early stages of the research, and we are therefore part-way through the recruitment goals we had set for year 2 in the statement of work. However, we have taken major steps to increase visibility and awareness of the study among patients and referral sources, and our recruitment rate has significantly increased and continues to increase as a result. In addition to advertising through the MS Center at Dartmouth, we have reached out to other departments (e.g., Radiology, Urology) where MS patients are seen at our medical center, and have made our study pamphlets available to the physicians who see these patients and in the waiting areas. Our medical center’s neuro-opthalmologist, who routinely sees patients with optic neuritis (who may be eligible for the study), is now also participating in referring to the study. We have also obtained the assistance of our hospital’s patient education center, where study pamphlets are displayed, and we have had a number of self-referrals from individuals who saw our research advertised there. In addition to increasing visibility and awareness of the study throughout our medical center, we have also reached out to area MS Clinics in Lebanon, NH, Concord, NH, Manchester, NH, and Burlington, VT, and we have identified several additional clinics to include. We also created new study letters that are signed by each patient’s MS neurologist to introduce the study to patients from these area clinics, as well as our own MS Center. We have seen a significant increase in referrals from both the area clinics and from within Dartmouth-Hitchcock Medical Center since instituting these changes. We have also attended MS patient-oriented conferences, made presentations, and displayed our study materials, to increase visibility of the study, and these strategies have also been helpful in increasing recruitment. We continue with our other basic recruitment strategies, including working closely with physicians and nurses at the MS Center at Dartmouth and notifying patients my mail about our study opportunities. Together, these efforts have paid off with significantly increased recruitment. We have also been able fill a previously vacant part-time research coordinator position, so starting in January 2012, we will have additional needed help to further enhance recruitment and enrollment. We will continue to devote
significant effort to maintaining and enhancing study visibility and awareness among referral sources and patients to maximize recruitment, and we fully anticipate that the momentum in recruitment will continue and grow.

We continue to use our established procedures for acquiring, logging and backing up all data, and completing ongoing QA and database entry. The genotyping occurs in batches; the blood samples are securely stored in our Molecular Diagnostics Laboratory in the interim. A first batch (47 samples) was sent for TaqMan-based genotyping this Spring and we have received the results, performed QA, and entered them in the study database. We intend to send a second batch in the Winter 2012. We are analyzing data for an initial report regarding the relationship between the brain-derived neurotrophic factor Val66Met polymorphism and gray matter volume in prefrontal cortex, striatum and hippocampus on voxel-based morphometry (Hypothesis 1-A), and anticipate having these data ready to submit for conference presentation by the Spring 2012. Final findings from this study will be available when we complete data collection. We are having biweekly to weekly research meetings, and additional meetings as needed, and we are monitoring financial and administrative issues with our Grants Manager.

**Key Research Accomplishments**
- This study’s final key findings will be reportable when we have completed data collection.

**Reportable Outcomes**
- One grant application was awarded to add a cognitive testing component to this study (National MS Society RG4264A3)
- We have submitted one grant application to perform a longitudinal follow-up of patients enrolled in this study.

**Conclusion**

The overall objective of this study is to develop a better biomarker for multiple sclerosis (MS) by combining genotype and imaging data. Currently, there is a great deal of unexplained heterogeneity in the symptom expression and clinical progression of MS. This study aims to improve scientific understanding of the neural and genetic basis of this heterogeneity, identify protective and risk factors, and inform and develop an integrated imaging genetics approach for use as a biomarker in MS. We have taken significant steps to increase visibility and awareness of this study among referral sources and patients, and this resulted in a substantial improvement in recruitment. We will continue to devote significant effort to maximizing enrollment and we anticipate that recruitment will continue to go well as we go forward. We have encountered no adverse events. We continue to log and back up all data, and complete ongoing QA and data entry as planned. The blood samples are securely stored in our Molecular Diagnostics Laboratory. The first batch of TaqMan genotyping (N=47 patients) has been completed, and a second batch will be completed in the Winter 2012. Preliminary data/image analyses are being completed as the data are acquired. We are preparing a preliminary report regarding the relationship between the brain-derived neurotrophic factor Val66Met polymorphism and gray matter volume in prefrontal cortex, striatum and hippocampus on voxel-based morphometry (Hypothesis 1-A), and anticipate having these data ready to submit for conference presentation by the Spring. Final key findings will be reportable when we complete data collection. We continue to have regular research meetings, and monitor the budget and expenses with our Grants Manager.

**References** NA

**Appendices** NA

**Supporting Data** NA