Feasibility of Utilizing the Infinitome Program to Evaluate Abnormal Large Scale Brian Networks in Alzheimer's Disease

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Clinical Study Protocol

08/11/2020

Sponsor
HealthPartners Institute

This study will be conducted in compliance with the protocol, IND regulations and other applicable regulatory requirements.

Participant Contact Project Narrative

1. *Summary*

The Infinitome Program from Omniscient has the ability to study abnormal brain networks or connectomes using resting state functional MRI (rs-fMRI). This technology, which visualizes brain networks in three dimensions, was originally developed to ensure neurosurgeons avoid inadvertently lesioning cognitively eloquent brain regions during surgical operations. The potential of Infinitome in identifying connectome dysfunction for neurodegenerative diseases such as Alzheimer's disease has yet to be explored. This diagnostic technique may play a critical role for identifying disease brain networks that may benefit from targeted interventions in clinical trials.

2. *Study aims*

To determine the feasibility of utilizing Infinitome Program for the evaluation of network dysfunction in Alzheimer's disease. We will report the rate of completion of rs-fMRI, rate of completed analysis of images using the program, and list the abnormal networks as identified by the program.

3. *Background, Rationale, Significance*

In 2009, the Human Connectome Project (HCP) commenced one of the most ambitious neuroscientific initiatives to map the brain [1,2]. This project identified 379 functional areas of the brain and gained insight into how they are connected, and how they related to neurological illness. This data has provided neuroscientists for the first time in history the ability to view the brain not merely as a structural entity, but rather as an individualized network system.

Unfortunately, the HCP has had little impact on clinical care. The techniques necessary to produce connectomic maps were feasible in research settings, but not clinical ones. Much of the work depends on the ability to perform rs-fMRI imaging as well as diffusion tensor imaging, both techniques that are time-consuming and impractical for clinical practice [3]. At the same time, structural brain MRIs are too often read as "normal," even though a patient may carry a chronic, life-changing diagnosis of Alzheimer's disease or Lewy body dementia. These observations suggest that structural MRIs lack precision for the detection of brain abnormalities in patients with neurodegenerative diseases.

The Infinitome Product developed by Omniscient was created to accelerate connectomic research and provide application of rs-fMRI findings to the clinical setting. The product is cloud-based, accessible via internet browser, and has the capability to analyze rs-fMRI data from a clinic-based image server (see attached Omniscient Overview pdf file). The program allows for personalized connectome mapping, which enables visualization of brain networks with great accuracy, regardless of brain lesions. Furthermore, the developers have used machine learning to measure connectivity between subregions and how they compare to normal controls. For instance, the default mode network (DMN) has been found to function abnormally in Alzheimer's disease [4]. This technology has the capability of comparing the DMN in a suspected Alzheimer's patient with a cohort of controls from the HCP.

This feasibility study may provide helpful clinical information relating to the underlying disease process and guide our practice. Furthermore, this information will be helpful in guiding our decision about purchasing a subscription to Infinitome for future clinical research. In addition the results will add preliminary data for a future grant applications that will utilize the program to detect abnormalities in AD and guide individualized treatments.

4. *Approach*

   a. *Study design*

This is a prospective feasibility imaging study in patients with AD.

   b. Population

      i. Inclusion/Exclusion Criteria

         Inclusion Criteria

1. Patients with a diagnosis of mild, moderate, or severe Alzheimer's disease
2. Age: 40 – 90 Years

3. Patients who are clinically indicated for an MRI

Exclusion Criteria

1. fMRI contraindicated (eg. Implantable device, pacemaker, metallic implants, etc.)
2. Subject unable to tolerate sitting for a one hour fMRI
3. Other concerns as determined by the investigator

ii. Sample Size

We plan to enroll 4 patients

c. Data collection process

1. Dr. Rosenbloom will identify potential study patients via scheduled clinic (or video visits) and ask patient/caregiver if they would like information about a research study and potential study participation.

2. If patient/caregiver indicates they would like more information, Dr. Rosenbloom, shares the info with the research staff, and let patient/caregiver to expect a call from the research staff

3. Research staff reaches out to the patient/caregiver with a phone call (phone script attached), and patient/caregiver is offered an informed consent form to read on their own time. If the patient/caregiver requests additional time, then the research staff schedules a phone appointment to answer any questions, and to complete the electronic consent via REDCap. This process will be conducted prior to the scheduled imaging visit.

4. After completion of the informed consent process and upon confirmation of eligibility (I/E criteria), subject will undergo added imaging (research sequences).

5. Once the scan is complete, the data will be de-identified and uploaded to the Omniscient Cloud server. Once processed by the Infinotome program, the results will be collected by the research team and stored in a secure server. This information will also be shared with the patient and family.

i. Consent

Potential research subjects will be informed that participation in this study is voluntary and that their decision to participate will not reflect upon their relationships with the Center for Memory and Aging, Regions Hospital, or HealthPartners. Subjects will be informed that they can withdraw from the study at any time and will be given a copy of the consent form.

With the electronic consent via REDCap the patient/caregiver providing consent will be able to review the consent form themselves and sign electronically with a stylus, touch screen, or cursor using a signature field in REDCap. After the individual has received the link and can view the consent form, the research staff member will go through the consent form with the individual as would be typical in person. If the patient/caregiver consents to participate, then they will sign via REDCap. After the signed consent form is received by study staff, the research staff member will sign another signature field and email a copy to the same email address to which the link was sent.

ii. Data sources

- Electronic medical records (EMR)
- Case Report Forms
- MRI Imaging
- Infinitome Program

d. Intervention, treatments

There is no proposed treatment intervention.

Imaging protocol described below: Once settings are in place, apply these parameters for the BOLD imaging (what we call a T2*EPI sequence)

Resting state fMRI

- 3 × 3 × 3-mm voxels
- 128 volumes/run
- TE = 27 ms
- TR = 2.8 s
- field of view = 256 mm
- flip angle = 90˚
- Run time about 8 min

Diffusion imaging protocol

- one b0 baseline image
- B1000
- At least 30 and ideally 50-60 directions+ one baseline b0 scan
- FOV=25.6 cm
- slice thickness 2mm
- 0 mm gap between slices with no overlap
- full brain coverage
- isotropic voxels
- square 128x128 matrix
- 1 average/NEX
- axial foot to head slice prescription
- DTI done before contrast images

e. Outcomes/endpoint and other variable definitions, and instruments used

Since this is a feasibility study, we are mainly evaluating the ability of the Infinitome program to detect connectome abnormalities in AD subjects.

- *Rate of Completion of rs-fMRI* – % of subjects who completed the sequence of the fMRI protocol
- *Rate of Completed Analysis* - %of subjects whose images were uploaded and analyzed by the Infinitome program
- *Type of Abnormal Networks Identified* – All the abnormal networks as identified by the Infinotome program (categorical) – such as default modal network..

Variable Name	**Data Source (patient survey, EMR, claims, registry)**	**Purpose (sample identification, description, grouping variable, study endpoint, predictor, covariate)**	**Measurement Scale (binary, continuous)**
Demographics (e.g., Age, Gender)	EMR	Description	Continuous, Binary
AD severity	EMR	Description	Categorical
MoCA (Montreal Cognitive Assessment)	EMR	Description	Continuous
fMRI – Program numbers and Post-processed Images	MRI and Infinitome program	Description/endpoint	Descriptive/Continuous

g. Statistical analysis plan

Demographics and baseline characteristics of study participants will be summarized using descriptive statistics (mean and standard deviation, median, and proportions, as appropriate).

We will report the proportion of successfully completed rs-fMRIs and completed Infinitome analyses. If all 4 rs-fMRIs are completed and at least 3 of 4 Infinitome analyses are completed, we will consider this feasibility study a success.

We will also explore and report if any and which networks are identified as abnormal by the Infinitome program. The Infinitome output provides pairwise dysfunction between structures/areas within each network. We will report the number of patients who have dysfunction in the DMN, overall, as well as the number of pairwise structures within the DMN are dysfunctional. We may report on several other networks, if abnormality is shown.

h. No inferential statistics will be conducted for this study. We do not anticipate being able to definitively report areas that have dysfunction in persons with Alzheimer's; however, this preliminary data will be very important for future larger studies.*Power analysis or statement of precision*

If all 4 rs-fMRIs are completed and at least 3 of 4 Infinitome analyses are completed, we will consider this feasibility study a success. With a sample size of 4, we will be able to estimate a success rate of 75% to within a 95% confidence interval of +/- 21.7% assuming a true success rate of 75%.

i. Strengths and limitations

Strengths of this application include the fact that we are testing a novel program that leverages HCP data to determine dysfunctional connectomes in AD. This work has never been done before with this software and could lead to the design of clinical trials for targeted treatments to dysfunctional networks.

Limitations of this study include the low number of subjects, but we are merely performing a feasibility study to justify standard use of the Infinitome program in clinical research

5. Setting/Environment/Organizational feasibility

The study will be conducted at HealthPartners Neuroscience Center, specifically the Center for Memory and Aging. This location is appropriate in that it is an established multidisciplinary clinic developed specifically for evaluating patients with dementia. It is adequately staffed and equipped to serve this population.

As this study involves in-person visits, here is a description of how the visits will be conducted

- Visit would be added onto existing clinical care order. The only in-person visit is an increase in the amount of time for an already ordered clinical care MRI. NSC procedures would be followed. No additional scripting will be added.
- We plan to do the consent virtually. No in-person contact for consent process.

6. Risks and Benefits

The risk is overall minimal for patients. Structural MRI is a routine diagnostic procedure at HealthPartners, and the resting state portion merely requires an additional 8-15 minutes of scan time. The patient may experience claustrophobia with the narrow imaging space.

7. Data Confidentiality and Privacy

Omniscient uses an industrial grade cyber security that is superior to what is offered at the leading medical device companies. No personal health information is stored on servers and only de-identified scans stored on a dedicated edge node on an encrypted MinIO instances. Patient data is only accessed through authenticated calls form Kubernetes pods contained in the VPC. The web service requires user authentication. Only the data related to a specific facility can be retrieved through authenticated calls and are restricted to their use.

For other data that is collected, the tools will be developed internally (i.e. CRFs and source documents). This data collected will be stored electronically and remain confidential and secure (e.g. secured server, encrypted data, password protected file)

8. Timeline

- June- July 2020 – IRB submission
- August -September 2020 – Enrollment and Data Collection
- September -October 2020 - Compile and Report

9. Dissemination/Sharing Results/Integration and Impact

Study results will be used to provide preliminary data for future grants and clinical trial work. In addition, the study results and background may be presented during neurology/CMA conferences, grand rounds, and within the HealthPartners Research Foundation newsletter.

10. References

1. Fox MD. Mapping symptoms to brain networks with the human connectome. *New England Journal of Medicine.* 2018;379(23):2237-2245.
2. Glasser MF, Smith SM, Marcus DS, et al. The human connectome project's neuroimaging approach. *Nature neuroscience.* 2016;19(9):1175-1187.
3. Lv H, Wang Z, Tong E, et al. Resting-state functional MRI: everything that nonexperts have always wanted to know. *American Journal of Neuroradiology.* 2018;39(8):1390-1399.
4. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings of the National Academy of Sciences.* 2004;101(13):4637-4642.