"MEG Bio-Markers for Alzheimer's Disease- A Pilot Study"

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5 million people in the US alone have Alzheimer's Disease(AD). There is, in addition, an intermediate condition between normal and AD called "mild cognitive impairment"(MCI). MCI often (but not always) progresses in time to AD. Because there is as yet no effective cure for AD there is a need for tools that would enable its detection at an early stage and guide therapies or the discovery of possible therapies.

This proposal concerns analysis of a unique MagnetoEncephaloGraphy (MEG)-based study of patients with Alzheimer's Disease (AD) and healthy cognitively normal control subjects. The data were gathered at the University of Pittsburgh Medical Center(UPMC) during the course of the last year with funding that enabled (but was limited to) the collection of these data.

The study was designed to address the question:" Is there a MEG biomarker for Alzheimer's Disease?"

There is a growing interest in Brain Imaging for early detection of AD (based on morphology, metabolism or even available amyloid tags for PET imaging). We feel that MEG's promise, which goes beyond imaging metabolism, is to directly image cognitive function. Uniquely so, because MEG is the only available noninvasive technique that images rapidly and clearly enough to capture the neuronal signaling that is a fundamental manifestation of AD.

In the proposed activity, these data will be analyzed using the methodologies for which the team of Fernando Maestu is widely recognized and the results will be reported in the appropriate scientific journal.

This activity will be partially sited at Princeton University where, since the Princeton Neuroscience Institute was formed 10 years ago, there has been exploratory discussion about a possible MEG activity. The development of new non-cryogenic sensors (Atomic Spin Magnetometry) for MEG in the Physics Laboratory of Dr. Michael Romalis (across the street form PNI)- with the potential for significant improvement in sensitivity, imaging and ease of use- has played into this interest.

<u>Scope of request</u>
We are seeking funding to carry out the analysis of the above-mentioned patient study. Our group combines a familiarity with the study itself and the analytical tools for which the Madrid group is well known. Funding is required for a 6 month effort, including 2 investigator meetings (UPMC, Princeton, Madrid), full time research

support of Dr. Bajo (at Madrid rates, but to also support a 6 week residency at the PNI), 50% support for Dr. White, who will be project manager and 5% support for Drs. Becker and Romalis. Computing resources will be contributed by Madrid.

6 month vs. 12 month

Although this project would achieve these goals with the 6 month effort outlined above, this proposal requests, at small additional cost, to fully capitalize on the interest of the proponents, as well as Princeton and others with whom we have discussed this project (ie INCF, Simons Data and Wolfram Research). In particular, Madrid would like to enable Dr. Bajo to do re-analyses enabling a further critical examination of the statistical tools. Drs. White and Romalis would like to do an evaluation of the potential impact of Dr. Romalis' new technology (ASR). Finally, in conjunction with INCF, Wolfram and tacitly (ie using some of their computing resources) Simons Data there is a broad interest in adding visualization tools to what is now used and to explore combining MEG data with other current imaging tools now curated by ADNI, for example.

The additional cost over the 6 month analysis would increase the overall cost by ~30% yielding a total of ~$140k. while opening up a fruitful line of investigation, for which PNI expects to be supportive.

Context:

MEG can provide an effective bio-marker for AD with significant promise for early detection and as a tool to guide therapies (1). A range of metrics derived from MEG are capable of distinguishing between cognitively normal individuals, and MCI and DAT patients (1). Functional connectivity is severely disrupted not only in DAT and MCI, but also in individuals with subjective memory complaints (SMC). Bajo (2) proposed a biphasic model describing the changes in expression of MEG-identified neural networks such that individuals with SMC underexpress networks, individuals with MCI overexpress networks, while those with DAT underexpress networks to a large degree.

The current state-of-the-art of in vivo amyloid imaging suggests that the temporal sequence of events leading to DAT may not be as straightforward as once believed (3). Technologies that are able to detect alterations in connectivity (4), especially those measuring synaptic activity (1), may become the most sensitive indices of AD pathology, and may be useful for tracking disease progression and response to therapy.

Prof. Maestu's team has had particular success analyzing MEG connectivity to discriminate MCI from normal cognition, and those MCI patients who progressed rapidly to dementia from those who are stable (5). An alternative is to use partial directed coherence (6), a Granger causality method in the frequency domain, that gives both directional interactions and frequency specific maps. Drs. Maestu and Becker have examined the relationship between functional connectivity and breakdown in white matter in amnestic MCI (7); with Dr. Bagic and the MAGIC-AD group, they have also demonstrated the ability to identify individuals with MCI (versus controls) with a reasonable sensitivity and specificity. Thus, MEG is able to

detect pathological changes at the level of the individual subject, and in the context of the very rich imaging and biomarker data set, with longitudinal follow-up, will provide a unique window on the relationship between AD pathology and the development of DAT.

In spite of the range of evidence that demonstrates the relative merits of MEG for the analysis of functional connectivity on the spectrum of AD pathology (e.g., (2,7—14,17)), it remains the case that the clinical applicability of these biomarkers is not firmly established. As a first step in the process, it is necessary to demonstrate the reliability (measured over a few minutes) and stability (measured over weeks) of any derived neuronal networks. This is important, because to the extent that these networks are stable, then it means that they are an ideal biomarker for tracking the natural history of the disease, and also for examining the effects of various pharmacological and non-pharmacological therapies on disease progression. Although we have previously demonstrated high reliability and stability of measures of relative power in young adults (15), and Dr. Maestu's team has demonstrated the stability of neural networks in young adults, there are no extant data regarding the reproducibility of these functional connections in older adults, or those with dementia.

For the current project, we will utilize resting state (eyes open and eyes closed) and task-based MEG measured at two sessions, two weeks apart. For the task-based MEG, we have additional within-session reliability measures that will also be included in the analysis. These data were acquired from 10 healthy control subjects and 8 with Probable AD.

We will utilize state-of-the art methodologies, primarily based in graph theory, to identify critical brain networks, and the extent to which these networks are reproducible across imaging sessions. We will examine both "established" networks (e.g., default node network (16), executive control network, salience network (18)) as well as empirical networks derived from the data (i.e., those that maximally distinguish between patients and controls). Our null hypothesis is that within-subject, the networks remain stable, and the extent to which an individual subject expresses the network does not change over time. To the extent that we must reject the null hypothesis (i.e., the network is not stable, or the expression of the network changes over time) we will then determine the underlying cause of the breakdown in network integrity — for example, the extent to which this represents losses in network segmentation (6, 8).

The results of this analysis will be instantly translatable into clinically-relevant research, and will allow us to begin the process of expanding and analytic methodologies with the confidence of the inherent stability of the data. This means that newly developed methodologies from laboratories at Princeton University will be easily adapted into this workspace. In addition, because of Dr. Bajo's close contact with the Princeton Neuroscience Institute, his expertise will greatly facilitate the translation of analytic tools from hi physics research to MEG.

(a workshop on these topics can be found here: http://indico.cern.ch/event/324890/) and the talks themselves could be provided separately if useful.

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