Proposal Working Draft for Simons Foundation Funding

July 4, 2015

**1)Specific activity that is proposed for funding support:** This proposal concerns analysis of a unique MagnetoEncephalography(MEG)-based study of Alzheimer’s patients and controls which was recently carried out at the University of Pittsburgh Medical Center(PUMC) under a prior grant. The study was designed to address the question:” Is there an MEG biomarker for Alzheimer’s Disease (AD)?” In the proposed activity, the data collected at PUMC 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 .

1.1The proposed activity brings to the problem the team of Fernando Maestu at Madrid, which has a history of collaboration with Drs. James Becker and Anto Bagic at PUMC. Maestu’s group has a record as a world-class team in the analysis of MEG data- particularly in connection with AD. They propose to contribute the computing resources required for the analysis.

1.2 The analysis of these data will be carried out primarily in Madrid by Maestu’s group but under this proposal some of the analysis will be performed remotely at Princeton (under the auspices of PNI). This overall proposal will be managed from Princeton, with Dr. Michael Romalis as scientific contact and Dr. Sebastian White as Project Manager. Maestu proposes to make available at PNI (under terms to be worked out with PNI management) his postdoctoral fellow, Dr.xx., who has significant experience in MEG and an interest in career opportunities managing MEG facilities in the US.

PNI is contemplating the addition of a MEG facility to its laboratory activities and has also an interest in exploring the potential of new Atomic Spin Rotation technology for MEG developed by Dr. Romalis.

Dr. White moved this year from Rockefeller to work with the Princeton team at CERN but is also spending 1 day/week at the EU Human Brain Project as a visiting scientist. In this activity he is exploring the potential for integration of MEG data with other imaging modalities- ie as in ADNI. Dr. White was active in the initial discussions, which led to the Alzheimer’s study at PUMC.

1.3 The proposal requests funding support for scientists active in this project at Princeton ( Dr. White and Dr. XX, each for a period of ~3 months) , for the student/postdoc carrying out the analysis in Madrid, and finally for (~2) investigator meetings involving PUMC, Princeton and Madrid. The latter are expected to occur at the start of the analysis as well as for preparation of writing the publication. A limited support will be required for preparing and documenting the data protocols at PUMC. We are confident that this overall project can be carried out with an external funding support of $120k. Additional discussions about the contribution of Princeton (ie enabling the visiting appointment of Dr. XX to PNI) and Madrid (ie their proposed contribution of the computing resources) are aimed at achieving the maximum benefit to the scientific agendas of both institutions.

2) **Context:** The principals in this proposal are confident that MEG can provide an effective bio-marker for AD with significant promise for early detection and as a tool to guide therapies. Drs. Maestu , del Pozo and collaborators have already published extensively on this topic and the question has led to a seminal paper by an international interest group (AD-MAGIC collaboration). There is also, in the literature, a study which shows that the same tools could be applied to early stages of autism.

Nevertheless, we recognize that there is rapid progress in other areas, which could lead to new chemical biomarkers, etc.

But we believe that there is a wider context, which makes funding this study attractive.

MEG data on the current topic have, up to now, been more readily available from European research institutions than the US. In the US the clinical driver for MEG is primarily related to Epilepsy.

However Dr. Romalis recently received a DOD award to develop MEG tools for the study of severe brain damage.

In patient treatment, electrophysiological tools are becoming widespread as a growth area. Examples are: deep brain stimulation, magnetic therapy(real name?),…. Wearable (EEG) devices targeted at cognitive therapy for cases of ADD and PTSD are entering the market and “neurobiofeedback “ is receiving considerable interest as an alternative to pharmaceuticals or talk therapy.

In addition, the proponents of this proposal feel that this is a good time to assess the research and clinical potential of MEG- particularly in the context of PNI’s interest in starting activity in MEG, in general.

There are a number of topics which could be given renewed attention in the context of our proposed activity:

1. are there alternatives to addressing the spatial resolution limits of commercial MEG imagers? (the benefit of MEG is already established in the time domain- since it is the only non-invasive imaging tool that can respond at a speed appropriate to that of neuronal signaling).
2. Related to a) is the issue of whether this is the most fruitful approach in the first place. If MEG patient data are to be integrated with other modalities-such as PET and fMRI- perhaps we shouldn’t be thinking of it as voxel data. The MEG imaging problem, after all, is related to the fact that each MEG sensor combines signals from multiple sources. The methodology currently used performs a “functional connectivity” analysis on >100 waveforms, sampled at ~1kHz- but the “connectivity” criterion is somewhat limited by the multiple source issue. There may be benefit to post-processing these data within the context of models of signal propagation- analogous to the way that crystallographers have short-circuited resolution limits through the use of “phasing”.
3. There is an interest, which extends beyond Princeton, in evaluating the potential of the new Atomic Spin Rotation MEG sensors, coming from the atomic physics lab of Dr. Romalis. It is not yet clear which aspect of this technology could have the most impact- ie-higher sensitivity, elimination of cryogens (vs. current SQUID technology) allowing better proximity to the skull, flexibility and lower cost, potential for eliminating need of costly shielded enclosures, etc. Clearly the collaboration that this proposal brings together could be a fruitful one for addressing these questions.

( 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.