EM 7 Project report

New Therapeutics in Alzheimer's Disease (NTAD):MEG biomarker platform development	
Team members <u>funded</u> (full or part-time) by DPUK Andrew Quinn (Oxford), Leeza Almedoom (Oxford) In Cambridge- Juliette Lanskey, Ana Klimovich-Smith, Melek Karadag, Ece Kocagoncu **Team members involved with the project but <u>not</u> funded by DPUK** James Rowe and Rik Henson (University of Cambridge); Kia Nobre, Mark Woolrich, Masud Husain, Vanessa Raymont (University of Oxford); John Isaac and Giacomo Salvadore (Janssen); Michael Perkinton (MedImmune) and Stephen Lowe (Eli Lilly) **Location(s):** Oxford University Cambridge University Janssen MedImmune Eli Lily	**Total Funding awarded "NTAD study"** 823,000 Janssen (total after supplement for PET project) 130,000 DPUK 120,000 AZ 100,000 ARUK Plus, miscellaneous costs for meetings and workshops

Objectives	**Dependencies to and from other work packages, networks and themes**
The long-term goal is to arrest pre-symptomatic Alzheimer's Disease (AD) /Mild Cognitive Impairment (MCI). More specifically, this study aims to identify sensitive and tractable neurophysiological biomarkers for next generation experimental medicine studies based on MEG and EEG There are 2 research questions: A) Can we reliably measure the impact of AD/MCI on neuroplasticity and neurophysiology? B) Do the candidate neurophysiological and pathological biomarkers have the essential properties to support experimental medicine studies?	

Deliverables	**Milestones**	**Milestone deadline**	**Work package dependencies**	**Person(s) responsible**
Objective 1: Optimisation of 'trial ready' biomarkers of human Alzheimer neurophysiology				
D1.1 'Trial ready' biomarker available	M1.1.1 Establish functional biomarker test panel	M1.1.1 Complete	None	JBR JBR & JI
	M1.1.2 Completion of finance, legal and research governance arrangements	M1.1.2 Complete		JBR & JI
	M1.1.3 Partnership consensus on biomarker utility and priority protocol	M1.1.3 Jun 2020		
Objective 2: Using patients with symptomatic AD/MCI conduct MEG & EEG studies to validate experimental medicine paradigm				
D2.1 M/EEG metrics available related to (i) high level tasks of memory and plasticity available and (ii) low level features of robust well characterised cortical circuit physiology.	M2.1.1 Recruitment of first participant	M2.1.1 Complete	None	JBR (Cam) MW (Ox)
	M2.1.2 Recruitment of final participant	M2.1.2 6m after Covid 19		JBR (Cam) MW (Ox)
Objective 3: confirmation of normative properties and test-retest of the biomarkers				
	M3.1.1 Data acquired	M3.1.1 Complete	None	JBR (Cam)

D3.1 normative data and clinical test-retest measures will be undertaken in the first wave of baseline assessment				MW (Ox)
	M3.1.2 Provisional results	M3.1.2 Mar 2020		
Objective 4: Harmonised, validated MEG protocols and analyses for monitoring disease progression available				
D4.1 Protocols with base validation data	M4.1.1 Cross-sectional study readouts released	M4.1.1 Dec 2020	BioFIND	JBR and JI
Objective 5: Patient neuropsychological assessments				
D5.1 Neuropsychological, MRI and clinical profiling	M5.1.1 Cross-sectional data release	M5.1.1 Jun 2019	Imaging platform	JBR
	M5.1.2 Longitudinal data release and MRI	M5.1.2 Jun 2020		
Objective 6: Harmonised, validated MEG protocols and analyses for monitoring disease progression available				
D6.1 Protocols available	M6.1.1 Protocol consensus	M5.1.1 Complete		JBR & JI

Updates on delivery against milestones since last report

- M2.1.2 – final recruit at Cambridge complete Nov 2019 and follow up underway prior to COVID. Delayed start at Oxford due to facility refurbishment and critical equipment replacement but was underway Feb 2020 prior to COVID suspension. Suggest new deadline 6m after COVID suspension ends.
- M3.1.2 – data shared with all sites via DPUK servers. Cross-site pre-processing pipeline agreed, and test-retest results expected April 2020.
- M4.1.1 – on track for selected baseline data.
- M5 – longitudinal data on hold until after COVID. Cross sectional data shared within DPUK partners Jan 2020.
- M6 – processing protocol agreed by NTAD-analysis subgroup, with Stephen Lowe and statistician support from Lilly

Summary of plan to deliver on outstanding work (with dates)

- The timelines for completion of data acquisition are dependent on the opening of research activity and sites after COVID19. Currently working to an estimated 6m. Cambridge longitudinal follow up would remain on course to complete Nov 2020 if COVID restrictions are lifted by August. Oxford baseline data completion requires COVID-end-date plus 6m.
- On the issue of radiopharmacy capacity we await the impact of new measures put in place by the BRC but will also explore the potential to study participants at INVICRO.

Risks	**Mitigation**
1) COVID19 suspension of all data acquisition	1) Interim focus on analysis of baseline data and test-retest; and case identification by e-screening, in readiness for end of COVID suspension.
2) Financial – no-cost extension agreed by MRC, but Oxford data acquisition will run beyond this date	2) Oxford BRC to support latter stages of the study to ensure project completion
3) Scanner replacement at Cambridge part way through longitudinal follow up. Risk low, as very similar electronics in new scanner, although BIOFIND has found site effects on MEG with 'identical' scanners.	3) A group of older subjects underwent a NTAD-like protocol before and after the upgrade, to assess and if necessary, model the effect of scanner upgrade.
4) UCBJ PET capacity limitations in 2019	4) Cambridge BRC set in place new equipment and staffing Q1 2020 to increase capacity per month. The option of supplementary UCBJ at Invicro will be explored.

Please tell us the most successful outcome and what it means to dementia research

Our group has shown that MEG based studies of prodromal Alzheimer's is possible, both in terms of excellent patient tolerability, and data quality across sites, but also in the harmonisation of protocols and data integration. The overlap between NTAD, DFP and BioFIND groups has ensured a coordinated approach internationally.

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We are seeing initial results, with publications by the NTAD team of DFP and BIOFIND results relating neural dynamics to regional Tau accumulation, and data on cross-site replication of resting-state data. We are preparing a large data release of MEG acquired from about n~300 MCI and AD at multiple BIOFIND sites as a prelude to release of NTAD data. The Biomarker status and corollary data (MRI, cognitive) and MEG tasks continue to give NTAD data special value, but this is enhanced by the potential for replication studies of selected analysis.

Lessons Learnt

- While multi-site studies speak directly to the critical issue of scalability and reliability in future clinical trials, they also amplify the risks of local delays and dependency on specific equipment. With n=2 sites for data acquisition, this affected NTAD milestones. Although DFP has been delayed for other reasons, its use of 6 MEG sites introduces greater resilience to problems or delays at any one site, and a European network would be even more robust.
- Fortunately, the ability to share high volume MEG data and corollary MRI, PET and cognition, and the ability to integrate data across sites into a common analytical pipeline, has been less of an obstacle than anticipated a few years ago.
- The study protocol was very well tolerated (even enjoyed) by participants, and we have had very positive feedback. One-year retention is high. Investment in recruitment is essential. For recruitment even of a common disorder like MCI and AD, a large base cohort is required. With access to 15000 registrants on JDR, NTAD screened by phone ~600 volunteers, from whom ~100 eligible and interested participants were brought in for biomarker screening (PET and/or CSF), so as to reach 65 biomarker definite participants for the main study. A large and pre-screened biomarker-defined cohort would greatly facilitate such studies.
- The potential for MEG (and EEG) to reveal mechanistic insights into human pathogenic mechanisms is enhanced by developments in model-based and model-free analyses of neurophysiology. Examples of model-based analyses include the dynamic causal modelling of cortical microcircuits by NTAD teams led by Rowe and Singh, while model-free methods include the influential Hidden Markov Models developed by NTAD PI Woolrich to examine the impact of disease on non-stationary neural states.

Outcomes

PUBLICATIONS

Published

- Hughes LE., **et al. Biomagnetic biomarkers for dementia: A pilot multicentre study with a recommended methodological framework for magnetoencephalography**. Alzheimers Dement (Amst). 2019 Jun 14;11:450-462. doi: 10.1016/j.dadm.2019.04.009. eCollection 2019 Dec. PubMed PMID: 31431918; PubMed Central PMCID: PMC6579903.

This established the feasibility and reliability of MEG studies in dementia across multiple sites and scanner types. The study focussed on resting state, to examine MEG based classifiers. The main limitations were absence of biomarkers, and baseline data collection only.

- Kocagoncu, E., et al. **Tau pathology in early Alzheimer's disease disrupts selective neurophysiological networks dynamics** Neurobiology of Ageing (in press)

Here we show the relationship between regional accumulation of Tau (PET) and the impact on network connectivity expressed as efficiency and modularity graph metrics within principal frequency bands, as measured by MEG.

In preparation

- *New Therapeutics in Alzheimer's Disease (NTAD): protocol paper. Lanskey, J, Kocagoncu, E, Quinn, A, others TBC, Raymont, V, Isaac, J, Nobre, K, Woolrich, M, Rowe, JB.*

ENGAGEMENT ACTIVITIES

- Rowe J. Synaptic Health Symposium - A one-day workshop, and shorter follow up meetings, to engage academic and industry partners in Synaptic Health Research
- Rowe, J. Eastern AHSN Neurodegeneration and Dementia meeting – Synaptic Health and NTAD

PROTOCOLS

- This has been decided internally, but not yet published

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USE OF FACILITIES & RESOURCES

- Yes, the DPUK servers are used for dissemination and curation of NTAD data
- And the PET-MR has been used for amyloid imaging of NTAD participants and the UCBJ-PET imaging

FURTHER FUNDING

- Cambridge Trust, PhD studentship to J Lanskey
- NIHR Oxford Biomedical Research Centre co-funding of NTAD Oxford for recruitment and assessment
- NIHR Cambridge Biomedical Research Centre co-funding for recruitment

Project narrative

NTAD has proven a highly successful partnership between industrial and academic stakeholders in DPUK, and Lilly who were previously outside of DPUK. We overcame the challenges for the legal and financial agreements between such diverse sites, and then attained all the ethical and regulatory approvals. In 2018 we began baseline data acquisition, including the normative data and test-retest studies. Baseline data collection at Cambridge is complete, and cross-sectional analyses are underway while the longitudinal follow-up is partially completed (suspended under COVID restrictions). The closure of the Oxford MEG lab in Q4 2018 was followed by a long downtime for its replacement, re-opening Sep 2019. The pre-screening is advanced at Oxford for identifying the patient cohort, and the cognitive testing, biomarker assays, and baseline MEG/MRI testing had begun before COVID restrictions March 2020.

We meet monthly as a researcher steering group, and monthly in-between as an analysis group with the Lilly biostatistics team. The NTAD group has broadened, in association with the discussions over Synaptic Health programs in DPUK2, and the inclusion of Cardiff as a new site for MEG in the DFPh study, which is closely aligned to NTAD. Cardiff is a major MEG centre, hosting the 2019 MEG-UK conference, and leading the MRC partnership grant for MEG since 2015.

Analytical efficiency is planned by data partitioning data between sites, adoption of the common preprocessing framework, and cross-linkage of analysis and pipelines in other DPUK cohort studies (including CamCAN, MINDMAPS, BIOFIND and Deep-and-Frequent phenotyping). As a group, we have begun reporting MEG analyses, and MEG-to-PET comparisons are underway (one published, others pending), providing proof-of-concept and feasibility for NTAD tasks, pipelines and quality. Test retest data are to be presented April 2020 internally, with a view to publication summer 2020.