New Therapeutics in Alzheimer's Disease (NTAD): MEG biomarker platform development
Start date: 1 July 2017. **Completion date: 30 June 2020**

Overall objective(s): 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:
1) Can we reliably measure the impact of AD/MCI on neuroplasticity and neurophysiology?
2) 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:				
D1.1 'Trial ready' biomarker available	M1.1.1 Establish functional biomarker test panel	M1.1.1 Complete		JBR
	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		JBR & JI
Objective 2:				
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		JBR (Cam) & MW (Ox)
	M2.1.2 Recruitment of final participant	M2.1.2 Complete		
Objective 3:				
D3.1 Normative data and clinical test-retest measures will be undertaken in the first wave of baseline assessment	M3.1.1 Data acquired	M3.1.1 Dec 2019		JBR (Cam) & MW (Ox)
	M3.1.2 Provisional results	M3.1.2 Complete		
Objective 4:				
D4.1 Protocols with base validation data	M4.1.1 Cross-sectional study readouts released	M4.1.1 Dec 2020 (was Sep 2019)	BioFIND	JBR and JI
Objective 5:				
D5.1 Neuropsychological, MRI and clinical profiling	M5.1.1 Cross-sectional data release	M5.1.1 Dec 2019	Imaging platform	JBR
	M5.1.2 Longitudinal data release and MRI	M5.1.2 Jun 2020		
Objective 6:				
D6.1 Protocols available	M6.1.1 Protocol consensus	M5.1.1 Jun 2020		JBR & JI

Updates on delivery against milestones since last report

- M2.1.2 Recruitment of final participant

Cambridge baseline recruitment complete (Nov 2019), with completion of test-retest subgroup (M3.1.1), and 12m follow up studies underway

- M3.1.2 Provisional results

Face to face meeting of NTAD group and interim analysis (Aug 2019) – all partners represented.

- M4.1.1 Cross-sectional study readouts released

Data freeze of AD-50, HC-15, and Re-test-15 planned Dec 2019, with dissemination ongoing via DPUK servers to partners. Interim internal results Q1 2020, and publication Q2 2020.

- We have changed the CSF analysis screening, reducing turnaround time from eight to 2-4 weeks.

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

- Oxford recruitment now underway, after new MEG facility opened Sep 2019. Experience of JPND, BRC and NHS recruitment in Cambridge shared, and 'pre-screening' has already identified a high proportion of the necessary Oxford cohort. Vanessa Raymont leading Oxford recruitment.
- The request to share baseline data via BIOFIND study portal has been agreed in principal after initial NTAD analyses, in parallel to DPUK release expected Q4 2020 for baseline data (M4.1.1). Will establish largest accessible MEG-dementia dataset worldwide.
- The UCBJ PET uplift to NTAD was delayed due to radiopharmacy development and cyclotron replacement Q1 2019, and phased capacity for ^{11}C synthesis. Additional Cambridge BRC investment agreed Sept 2019 to increase ^{11}C production. QC good and initial BPnd maps indicate sensitivity to disease, and in accord with MINDMAPS data. Janssen aware of delay and discussion initiated with MRC regarding no-cost extension options.
- Longitudinal data expected to be completed Cambridge Nov 2020, Oxford March 2021
- New Cam, Ox and Lilly statistical methodology group meeting monthly. Main NTAD investigator TC meetings continue monthly. JPND BIOFIND Meg-biomarker report published (overlap with NTAD investigators) and good practice adopted (M6.1.1) with NTAD specific protocols expected for release Q3 2020 with publications.

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)

Risks	**Mitigation**
1) Delays imply overrun beyond June 2020	1) MRC discussions regarding NCE, and sites committed to additional resourcing to complete proposal
2) Initial costs for analysis staffing not sufficient.	2) Additional BRC, fellowship and PhD studentship funding identified, adding value to NTAD.
3) PET production delayed	3) New BRC investment in ^{11}C capacity for UCBJ
4) Alignment to DFPh protocol reduced by delay in DFPh	4) (i) Minimisation of deviance between MEG procedures, MRI and neuropsych during DFPh NoSA amendments and sequence updates (ii) analysis protocols for NTAD draw on DPFh pilot data analyses.

Outcomes

The interim analysis of NTAD data presented internally at the face to face meeting in August confirmed the success of data sharing of high volume MEG data, and the planned analysis pipelines for each task/method proposed. Interim test-retest data indicated good or excellent ICCs/between session correlations for principal measures. We anticipate the Dec 2019 data freeze supporting publications related to trial-ready methodology for MEG, and effects of AD on physiology.

The NTAD team have made a major contribution to the EU-JPND initiative for standardisation and harmonisation of EMG biomarkers for dementia (Hughes et al 2019) and have prepared the multicentre neurophysiology component of the forthcoming Deep and Frequent Phenotyping study (first consent Oct 2019), and pilot data analysis (Kocagoncu et al).

NTAD is lined with initiatives including MRC MINDMAPS study, to pilot the relationship between synaptic ligand PET and neurophysiology, and analysis is underway of the relationship between synaptic density and MEG biomarkers by region. The MINDMAPS AD paper has been presented at conference and full paper submission expected soon.

- **Hughes LE, Henson RN,** Pereda E, Bruña R, López-Sanz D, **Quinn AJ, Woolrich MW, Nobre AC, Rowe JB,** Maestú F; BioFIND Working Group. 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. **Bold are NTAD investigators**,
- Kocagoncua, E, Quinn, A, Firouziand, A, Cooper, E, Greve, A, Gunnd, R, Green, G, Woolrich, MW, Henson, RN, Lovestone, S, Deep and Frequent Phenotyping study team and Rowe, JB. Tau pathology in early Alzheimer's disease disrupts selective neurophysiological networks dynamics

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, so that preliminary cross-sectional analyses can be underway while the longitudinal follow-up is approaching. 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 MRI have begun. 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 between sites, and by cross-linking with comparative analysis and pipelines in other DPUK cohort studies (including CamCAN and Deep-and-Frequent phenotyping). These related studies have begun reporting their MEG analyses, and MEG-to-PET comparisons are underway, providing proof-of-concept and feasibility for NTAD tasks, pipelines and quality as we approach the completion of baseline data at the first site (Cambridge, Nov 2019).