Synaptic Health
Work Package 7

Dementias Platform UK
Medical Research Council

Objective(s):

To develop **Synaptic Health** as a theme for experimental studies by:
1) Facilitating the development of a synaptic plasticity research network
2) Identifying key and innovative research questions
3) Using the expert network to shape and prosecute a co-ordinated programme of research on synaptic plasticity and neuro-regeneration
4) Integrating the synaptic health network with other DPUK Experimental Medicine platforms and (inter) national initiatives

Overview Summary:

DPUK's investment in this work, establishing an active network of researchers from academia and industry focusing on synaptic health, has been one of its success stories. The network successfully secured funding for a Phase 0 experimental medicine study (New Targets in Alzheimer's Disease; 'NTAD') which is currently on-going and has started to generate important outputs. The network also identified tractable experimental medicine questions, secured new grant funding and contributed to on-going MRC studies (MINDMAPS and Deep and Frequent Phenotyping) as well as international initiatives (JPND) on data harmonisation and standardisation for MEG in dementia research. The network remains very active holding workshops and regular teleconferences to further progress these challenging studies; a new proposed study formed part of the experimental medicine theme for which funding has been sought for DPUK2.

Executive Summary:

This work package aimed to increase knowledge and awareness of synaptic health, developing a multidisciplinary research network from across academia and industry. The network has initiated innovative experimental medicine studies in synaptic health, including the NTAD study – a validation of a human neurophysiology longitudinal biomarker platform to support early-stage interventional studies and early-phase clinical trials; with increased sensitivity and mechanistic insights into human Alzheimer's disease pathogenesis.

The group has identified, and facilitated, broader opportunities for understanding synaptic health in dementia as part of national and international research initiatives. It has proved to be an excellent example of a successful public-private partnership with academics, clinicians and industrial company staff contributing to meet the challenge experimental medicine studies and planning for new treatment studies. This work led directly to a successful application from the DPUK Experimental Medicine fund for the NTAD study (MEG-based neurophysiological biomarker platform for AD), which is now recruiting patients and producing early promising results. This project benefits from additional industry investment to support a further PET study of synaptic health, connecting brain physiology and cognition.

Summary of Outputs: (as per Researchfish categories)

- Kocagoncu, E., Quinn, A., Firouzian, A., Cooper, E., Greve, A., Gunn, R.,Green, G., Woolrich, M.W., Henson, R.N., Lovestone, S., Deep and Frequent Phenotyping study team, Rowe, J.B., Tau pathology in early Alzheimer's disease is linked to selective disruptions inneurophysiological networks dynamics, Neurobiology of Aging (2020), doi: https://doi.org/10.1016/j.neurobiolaging.2020.03.009. Neurobiology of Aging, 2020 in press. https://doi.org/10.1016/j.neurobiolaging.2020.03.009
  This paper showed 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.

- Bischof G.N., Ewers M., Franzmeier N., Grothe M.J., Hoenig M, Kocagoncu E., Neitzel J., Rowe J.B., Strafella A., Drzezga A., van Eimeren T. Connectomics and molecular imaging in neurodegeneration. Eur. J. Nucl. Med. Mol. Imaging. 2019 46:2819-2830. doi: 10.1007/s00259-019-04394-5.

This review provides details of how the development of complex neuroimaging tools and the advancement of target –specific PET tracers can enhance our understanding of the in vivo characteristics, dynamics and principles in the progression of pathology in human neurodegenerative disease. It details how connectomics- investigation of brain network dynamics- offers the chance to examine the contributions of cell-autonomous and non-cell autonomous mechanisms. Models are proposed to address our understanding of neuronal dysfunction which account for observed clinical phenotypes.

- Preliminary analysis of the MINDMAPS UCBJ data vs MEG connectomics – publication pending Spring 2020

Collaborations & Partnerships

The main aim of the work package was the development of an active research network of experts in synaptic health able to identify tractable experimental medicine studies. This has been successful (see section on most successful outcome below). Network members also played a central role in the 2017-18 JPND initiative on harmonisation and standardisation of MEG for dementia research.

Further Funding

A successful application was made to DPUK for part funding for the NTAD study, designated EM7. Funding for this study has come from Janssen, AZ, ARUK and DPUK with Janssen providing additional funding for a PET study in 2019.

Next Destinations

Not applicable

Engagement Activities

The network remains active holding regular teleconferences and workshops to progress all studies in this area.

Influence of policy, practice, patients & the public

The network has been involved in international initiatives (JPND) on data harmonisation and standardisation for MEG in dementia research.

Research Tools & Methods

An agreed cross-site protocol for data processing has been developed.

Research Databases & Models

- Interim test retest MEG/EEG data set from 15 patients, test-retest analysis on the whole baseline 15 patients expected April 2020
- Baseline Cambridge data collection complete – follow up underway (prior to COVID19)
- Baseline Oxford data collection underway (prior to COVID19)

Intellectual property & licencing

Not applicable

Medical products, interventions & clinical trials

Not applicable

Artistic & creative products

None

Software & technical products

None

Spin outs

None

Awards & recognition

None

Other outputs & knowledge/future steps

None

Use of facilities & resources

None

Most successful outcome and what it means for future dementia research:

A successful active network of individuals from academia and industry was established focused on identifying the most tractable experimental studies in synaptic health. The network successfully applied to DPUK for funding to undertake the NTAD study (New therapeutics in Alzheimer's disease: MEG biomarker platform development, DPUK project EM7) and have made significant contributions to the MRC MINDMAPs and Deep & Frequent Phenotyping studies. By Early March 2020, the NTAD study has recruited more half of the patient and healthy controls and completed the test-retest evaluation of 15 patients. This test-retest data set is now being analysed across the

three sites (Cambridge, Oxford and Cardiff) and a data analysis pipeline has been agreed across sites.

Lessons learned:

A lesson learnt is that setting up experimental medicine studies at multi-sites in the UK is not straightforward. This is particularly the case when the funding involves research contracts and finance agreements with universities and industry partners. The funded NTAD study suffered significant delays to its start date caused by the negotiation of contracts. For this reason it is recommended that a framework for negotiations is developed or significant time for this activity factored in at the planning stage.

Other:

March 2020- COVID19 has now caused a pause on new patient recruitment and second visits at 12 months; it is currently unclear when the study recruitment can restart

Date of report: 30 March 2020