Final Project Report WP 7

Synaptic Health

- **Introduction**

This workpackage was set up to facilitate the development of an active research network in the new area of synaptic health, to identify tractable experimental medicine studies. The idea was to accelerate and intensify ambitious research in the area of synaptic health in dementia, drawing on the expertise of individuals from both academia and industry. This network has been successful with a DPUK-funded experimental medicine study (EM7) and significant contributions to the MRC MINDMAPS project and the physiology dimension of the Deep and Frequent phenotyping study.

- **Specific contributions from the Synaptic Health Network**

(i) The group has founded the NTAD project, New Therapeutics in Alzheimer's disease (CI Rowe), with direct funding from DPUK. Following pilot work, and completion of contracts, the study has been actively recruiting since May 2018. Supplementary industry funding for an extension study with synaptic-PET is likely to be approved for start in January 2019.

The expertise provided to this project illustrates the success and appetite for multi-disciplinary and multi-partner collaboration, facilitated by DPUK. Although the major financial contributions to NTAD have come from Janssen, AZ-Medimmune, DPUK, ARUK, and the Universities themselves, there are many additional pharma and academic partners who have made intellectual and in-kind contributions through our Workshops, EM study planning, and sharing of unpublished data.

A study such as this has proven to be very attractive to industry and we continue to remain open to enquiries from other potential partners who wish to contribute either to this project, or the new EM study in Synaptic Health that being developed as part of the DPUK renewal application.

<u>Industry Funding Partners</u>

Janssen: M/EEG, clinical trial design, biomarkers,

AstraZeneca-MedImmune: clinical operations and biomarkers

Lilly: MEG and clinical trial design, statistics

<u>Academic Partners</u>

Cambridge: Project lead, M/EEG, biomarkers, MRI, neuropsychology (PET from 2019)

Oxford: MEG/EEG, biomarkers, MRI, neuropsychology

Cardiff: analytical support, biophysical modelling

(ii) Individuals from the Synaptic Health Network have been involved in augmentation of the MRC MINDMAPS program at Invicro (CI Rabiner, Matthews). MEG is being undertaken on the AD/MCI patient participants, for piloting the correlation of synaptic loss to impairments in cognitive physiology. Recruitment for this study is near completion.

(iii) The physiology component of the Deep-and-Frequent phenotyping study, DFPh (CI Lovestone/Raymont), with successful implantation of the M/EEG paradigms at Cambridge, Oxford, Glasgow, Cardiff and UCL sites. The study is poised and awaiting the main launch of recruitment. We are about to submit a neurophysiology paper from the DFPh Pilot study (Kocagoncu et al), building on Cope et al's Brain 2018 demonstration of connectivity based progression of tau pathology but with added insights to the frequency specificity of relevant connectivity.

(iv) In addition, members of the academic (Henson/Rowe and ECRs) and industry (Lowe/Lilly, Jones) partnership in the synaptic health theme were central to the 2017-18 JPND initiative on harmonisation and standardisation of MEG for dementia research. The report has been submitted to JPND and a paper with recommendations and proof-of-concept analysis has been submitted for publication. This project built in EU-wide data sharing and transparency of research methods, which represent a continuing culture shift in this area of cognitive neuroscience for dementia research.

(v) Some of the key data underlying the design of the Synpatic Health proposals in NTAD/DFPh have now also been published (eg. Sami et al, Brain 2018), while the Hidden-Markov modelling of fast-transient neurocognitive microstates has been replicated in a DPUK cohort (CamCAN) and extended to a cohort of patients with AD/MCI (Nesbitt et al, in prep).

(vi) The advent of new PET ligands for pre- and post-synaptic targets over the last 18 months has led to new investments in synaptic health imaging at both Invicro/Imperial and Cambridge, including new translational studies of early dementia. Pilot studies will be completed in 2019, and are expected to be a game-changer in providing quantitative biological tools to study the impact of pathology on human neural systems that occur in AD, and other disorders, long before cell death and atrophy.

(vii) The Synaptic Health theme's public-private partnership has ensured an open forum to accelerate broad-based knowledge and readiness of these tools for dementia research in the UK through its regular meetings and culture of precompetitive sharing.

(viii) The Synaptic Health team will hold a third workshop in London on 11th January 2019 to consolidate progress, to bring in new partners into the program, and to develop plans for experimental medicines research in this area as part of the transition to DPUK2.

- **Conclusion**

DPUK's investment in this workpackage to establish an active network of researchers in synaptic health has been one of its success stories. The network has been successful in identifying

tractable experimental medicine questions and in gaining new grant funding to conduct the research. The studies are challenging but the experimental work is progressing well and interest in this area is key area of dementia research is growing nationally and internationally, with its direct pathway to impact through new therapeutic strategies to prevent or limit the brain changes that lead to dementia.

- **Recommendations**

Synaptic Health is a rapidly progressing research area that is continues to justify its support through the public-private partnership of DPUK. This is reflected in the decision to invite the Synaptic Health group to submit a project for inclusion as part of the renewal application to the MRC. We remain excited about possibilities in this area and are actively discussing the work with potential partners, to build on the initial success DPUK has had with investment in this area.