DPUK Imaging Network

Objective(s):

The Dementias Platform UK (DPUK) Imaging Network was established to facilitate and enhance the application of molecular imaging techniques to achieve the objectives of DPUK. Developing a network approach involving several major centres with imaging capabilities (see **Figure 1**) would improve sharing of ideas, technologies, best practice and procedures could be standardised.

During its first 5 years the network won multiple funding awards to develop UK PET capacity. In particular, was £24 million for a new network of five PET-MR scanners, strategically located to access the cohorts and enhance experimental medicine for dementia research with harmonised methods. Combined with the two PET-MR scanners at KCL and UCL this created the first national PET-MR clinical network internationally.

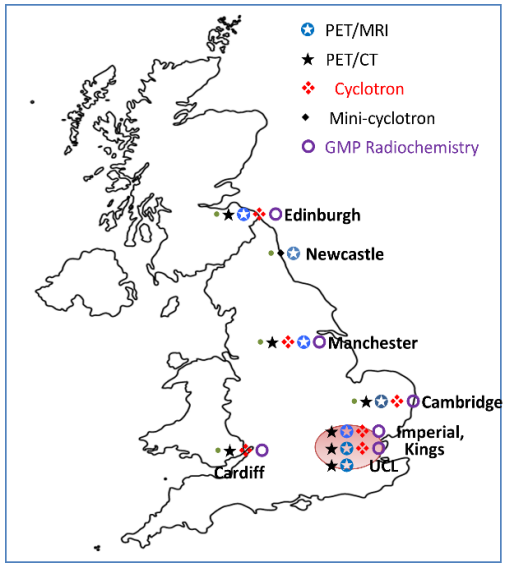

Figure 1. Dementia-Platform UK Imaging Network

During the period 2014-2019 building on the investments in capacity the objectives of the network were :

- MRI-PET site installations and qualification
- IT network implementation
- Harmonisation of PET-MRI scanning across network.
- Harmonisation of MRI scanning across network.
- Provision of standardised information for participants and regulatory applications
- New MRI-PET studies making use of the network

Overview Summary:

The Dementias Platform UK (DPUK) Imaging Network was established to create a network of UK Centres capable of facilitating and enhancing the application of molecular imaging techniques to achieve the objectives of DPUK. Complementing other DPUK Networks in Informatics and Stem Cells, the network approach would improve idea sharing, technology, best practice and facilitate standardisation of procedures.

The focus was on development of PET capacity. A new network of five PET-MR scanners, strategically located across the UK are now fully operational and linked with existing PET-MR scanners at KCL and UCL to establish the first national PET-MR clinical network. Separate strands of work focused on development of the DPUK imaging informatics infrastructure, harmonisation of scanning across the network, training as well as specific research studies.

Executive Summary:

The Dementias Platform UK (DPUK) Imaging Network was established to create a network of UK Centres capable of facilitating and enhancing the application of molecular imaging techniques to achieve the objectives of DPUK.

The focus was on development of PET capacity. A new network of five PET-MR scanners, strategically located across the UK are now fully operational and linked with existing PET-MR scanners at KCL and UCL to establish the first national PET-MR clinical network.

All the new PET/MR scanners in the DPUK Imaging Network are currently fully operational, with technical updates and improvements having been undertaken. An imaging informatics infrastructure based on the XNAT platform has provided a federated platform for managing, sharing and analysing neuroimaging data for dementia research (see project details and implementation). The harmonisation of scanning across the network is funded through a separate award to the Dementias Platform UK MR-PET Partnership (Work Package 17, due to end

September 2020) with a comprehensive approach including communications, training, regulatory aspects and governance.

Members of the Network are contributing to on-going DPUK funded studies including the Deep and Frequent Phenotyping Study (Work Package 16), Assessing models of AD risk and progression in Existing Cohorts using Tau PET imaging in combination with prospective follow-up (Experimental Medicine 10), and studies of amyloid in vascular dementia. In addition, there is involvement in the DPUK-linked programme MIND MAPS (Molecular Imaging in Neuro Degeneration-Mitochondria, Associated Proteins & Synapses).

Training remains at the heart of the Imaging Network. In particular, the MRI-PET Partnership Award Training Task Force initiated collaboration internationally aimed at developing training strategies for PET/MRI, particularly in Europe and the USA. It provided online training materials, plus standard templates for participant information sheets and consent forms to assist regulatory applications.

Summary of Outputs: (as per Researchfish categories)

Publications:

Published Papers

1) Mansur A, et al. - Characterization of 3 PET tracers for Quantification of Mitochondrial and Synaptic function in Healthy Human Brain: [^{18}F]BCPP-EF,[^{11}C]SA-4503,[^{11}C]UCB-J Journal of Nucl Med 2019 http://m.jnm.snmjournals.org/content/early/2019/07/18/jnumed.119.228080?papetoc
2) Mansur A, et al. Test-retest variability and reference region based quantification of [18F]BCPP-EF for imaging mitochondrial complex I in the human brain. – JCBFM in Press
3) IA Gilani IA., et al. Quantitative Data Driven Voxel-Wise Simulator (QVS): Application to 3D MP-RAGE Optimization for Harmonization of Multi-Centre Brain MRI Studies. P3322 Proc. Intl. Soc. Mag. Reson. Med. 27 (2019)
4) Andrews JPM, MacNaught G, Moss AJ, Doris MK, Pawade T, Adamson PD, van Beek EJR, Lucatelli C, Lassen ML, Robson PM, Fayad ZA, Kwieckinski J, Slomka PJ, Berman DS, Newby DE, Dweck MR. Cardiovascular 18F-fluoride positron emission tomography-magnetic resonance imaging: a comparison study. J Nucl Cardiol 2020 (Epub ahead of print]
5) Mada MO, Hindmarch P, Stirling J, Davies J, Brian D, Barnes A, Hammers A, Gulliver N,

Herholz K, O'Brien J, Taylor JP (2020). Competencies and training of radiographers and technologists for PET/MR imaging - a study from the UK MR-PET network. Eur J Hybrid Imaging. 4 (1), 1. doi: 10.1186/s41824-019-0070-6.

6) Holland N, Jones PS, Savulich G, Wiggins JK, Hong YT, Fryer TD, Manavaki R, Milicevic-Sephton S, Boros I, Hezemans FH, Aigbirhio FI, Coles JP, O'Brien J, Rowe JB (2020). Reduced synaptic density in progressive supranuclear palsy and corticobasal syndrome, revealed by [11C] UCB-J PET. medRxiv. 2020 Jan 1. doi: https://doi.org/10.1101/2020.01.24.20018697 .
7) Wilson H, Pagano G, de Natale ER, Mansur A, Caminiti SP, Polychronis S, Middleton LT, Price G, Schmidt KF, Gunn RN, Rabiner EA, Politis M. Mitochondrial Complex 1, Sigma 1, and Synaptic Vesicle 2A in Early Drug-Naive Parkinson's Disease. Mov Disord. 2020 Apr 29. doi: 10.1002/mds.28064.
8) Kocagoncu E, Quinn A, Firouzian A, Cooper E, Greve A, Gunn R, Green G, Woolrich MW, Henson RN, Lovestone S; Deep and Frequent Phenotyping study team, Rowe JB. Tau pathology in early Alzheimer's disease is linked to selective disruptions in neurophysiological network dynamics. Neurobiol Aging. 2020 Mar 17:S0197-4580(20)30086-5. doi: 10.1016/j.neurobiolaging.2020.03.009. Epub ahead
9) Wadhwa P, Thielemans K, Efthimiou N, Wangerin K, Keat N, Emond E, Deller T, Bertolli O, Deidda D, Delso G, Tohme M, Jansen F, Gunn RN, Hallett W, Tsoumpas C. PET image reconstruction using physical and mathematical modelling for time of flight PET-MR scanners in the STIR library. Methods. 2020 Jan 30:S1046-2023(19)30193-8. doi: 10.1016/j.ymeth.2020.01.005. Epub ahead of print. PMID: 32006678
10) Rhian S Convery , Jieqing Jiao , Mica T M Clarke , Katrina M Moore , Carolin A M Koriath , Ione O C Woollacott , Philip S J Weston , Roger Gunn , Ilan Rabiner , David M Cash , Martin N Rossor , Jason D Warren , Nick C Fox, Sebastien Ourselin , Martina Bocchetta , Jonathan D Rohrer *Longitudinal (18F)AV-1451 PET imaging in a patient with frontotemporal dementia due to a Q351R MAPT mutation.* ***Journal of Neurology, Neurosurgery and Psychiatry*** 2020, 91(1)
11) Firouzian, A., Whittington, A., Searle, G.E., Koychev, I., Zamboni, G., Lovestone, S., Gunn, R.N., on behalf of the Deep and Frequent Phenotyping study team *Imaging Aβ and tau in early stage Alzheimer's disease with [18F]AV45 and [18F]AV1451* **EJNMMI Research** 2018, 8(19)

12) Ivan Koychev, Jennifer Lawson, Tharani Chessell, Clare Mackay, Roger Gunn, Barbara Sahakian, James B Rowe, Alan J Thomas, Lynn Rochester, Dennis Chan, Brian Tom, Paresh Malhotra, Clive Ballard, Iain Chessell, Craig W Ritchie, Vanessa Raymont, Iracema Leroi, Imre Lengyel, Matt Murray, David L Thomas, John Gallacher, Simon Lovestone *Deep and Frequent Phenotyping study protocol: an observational study in prodromal Alzheimer's disease* **BMJ Open** 2019, 9(3)
13) Ivan Koychev, Roger N. Gunn, Azadeh Firouzian, Jennifer Lawson, Giovanna Zamboni, Basil Ridha, Barbara J. Sahakian, James B. Rowe, Alan Thomas, Lynn Rochester, Dominic Ffytche, Robert Howard, Henrik Zetterberg, Clare MacKay, Simon Lovestone, on behalf of the Deep and Frequent Phenotyping study team *PET Tau and Amyloid-β Burden in Mild Alzheimer's Disease: Divergent Relationship with Age, Cognition, and Cerebrospinal Fluid Biomarkers* **J Alzheimers Dis.** 2017, 60(1): 283–293

Meeting abstracts

1) IA Gilani, JS Thornton, MF Callaghan, M Wylezinska-Arridge, SJ Wastling, TA Yousry, DL Thomas. Quantitative Data Driven Voxel-Wise Simulator (QVS): Application to 3D MP-RAGE Optimization for Harmonization of Multi-Centre Brain MRI Studies. P3322 Proc. Intl. Soc. Mag. Reson. Med. 27 (2019)
2) Pagano G, et. al. - Mitochondrial Complex 1, Sigma 1 Receptor and Synaptic Vesicle protein 2A density in early *de novo* patients with Parkinson's Disease: an *in vivo* PET study. Presented at AAN 2019
3) Venkataraman, A. et. Al. –Quantifying mitochondrial and synaptic function in Alzheimer's disease using [18F]BCPP-EF, [11C]SA4503 and [11C]UCB-J PET imaging. Presented at AAIC 2019
4) Georgios Krokos, Jane MacKewn, Lucy Pike, William Hallett, Pawel Markiewicz, Anna Barnes, Marilena Rega, Tim D. Fryer, Roido Manavaki, Jose M. Anton-Rodriguez, Elizabeth Howell, Catriona Wimberley, Tim Clark, Gillian Macnaught, Paul Marsden and Julian C. Matthews; *Qualification of the Seven Dementias Platform UK PET-MR scanners for multicentre trials*; Oct 2019, IEEE MIC, Manchester
5) P.J. Markiewicz, J.C. Matthews, A. Barnes, J. Dickson, D. Thomas, J. Davies, W. Hallett, G. Krokos, J. Mackewn, P. Marsden, E. da Vita, J. Sterling, G. Delso, G. Macnaught, T. Clark, C. Wimberley, G. Thompson, J. Anton-Rodriguez, I. Vamvakas, A. Watkins, R. Maxwell, E. Howell, R. Manavaki, T. Fryer, V. Lupson, M. Mada, V. Rhodes-Bradford, J. Wardlaw, J-P.

Taylor, J. O'Brien, A. Hammers, S. Ourselin, N.Fox, K. G. Herholz, F. Barkhof; *Characterisation of PET/MR scanners for brain imaging in Dementias Platform UK clinical trials;* Oct 2019, IEEE MIC, Manchester

6) Papanastasiou, G., Rodrigues, M., Wang, C., Heurling, K., Salman, R. & Macnaught, G.; *Pharmacokinetic analysis of 18F-flutemetamol uptake in cerebral amyloid angiopathy using PET-MR imaging;* Conference proceeding, PSMR, 2019
7) Papanastasiou, G., Rodrigues, M., Wang, C., Heurling, K., Salman, R. & Macnaught, G.; *Quantitative assessment of 18F-flutemetamol uptake in cerebral amyloid angiopathy using a reduced PET-MR acquisition time frame*; Conference proceeding, PSMR, 2019
8) Wang, C., Papanastasiou, G., Tsaftaris, S., Yang, G., Gray, C., Newby, D., Macnaught, G. & MacGillivray, T.; *TPSDicyc: Improved Deformation Invariant Cross-domain Medical Image Synthesis*; Conference proceeding, PSMR, 2019
9) Catriona Wimberley, Mark Rodrigues, Gerry Thompson, Joanna Wardlaw, Edwin J.R. van Beek, Rustam Salman, Gillian Macnaught; *MRI for attenuation correction of brain PET data in hybrid PET-MR imaging*; March 2019, ISMRM workshop on MR value, Edinburgh
10) Catriona Wimberley Michael Stringer, David Thomas, Enrico Devita, David Brian, Kenneth Dolan, Adam Waldman, Gerry Thompson, Edwin Van Beek, Gillian Macnaught, Craig Ritchie, AMYPAD consortium; *Correlating estimated brain perfusion parameters between 18F-Flutemetamol PET and ASL-MRI during simultaneous PET-MRI*; Oct 2019, PET is Wonderful meeting, Edinburgh
11) Andrews, J., Macnaught, G., Moss, A., Doris, M., Pawade, T., Adamson, P., Lucatelli, C., Newby, D. & Dweck, M.; *18F-Flouride Positron Emission Tomography Magnetic Resonanace versus Positron Emission Tomography Computerised Tomography in valcular and coronary heart disease: a comparison of attenuation correction methods;* Mar 2019, *Journal of the American College of Cardiology.* Vol. 73. Conference contribution
12) Macnaught, G., Andrews, J., Brian, D., Dolan, K., Robson, P. M., Fayad, Z. A., Clark, T., Fletcher, A., Fenchel, M., Semple, S., van Beek, E., Newby, D. & Dweck, M.; *An Evaluation of Radial GRE Attenuation Correction Maps for Cardiac and Coronary PET-MRI Studies*; Jun 2018, International Society of Magnetic Resonance in Medicine.
13) Papanastasiou, G., Rodrigues, M., Salman, R. & Macnaught, G.; *Quantitative analysis of 18F-flutemetamol uptake in cerebral amyloid angiopathy using hybrid PET/MR imaging*. PSMR congress, 2018

14) *Wang, C., Macnaught, G., Papanastasiou, G., MacGillivray, T. & Newby, D.; Unsupervised learning for cross-domain medical image synthesis using deformation invariant cycle consistency networks.*; *PSMR congress, 2018*
15) Kaczynski J, Williams M, Whiteley W, Dennis M, Wardlaw J, Macnaught G, Tavares A, Jansen M, MacGillivray T, Forsythe R, Tambyraja A, Dweck M, Chaudhury R, van Beek EJR, Newby D.; *Early experience with 18F-Fluoride Positron Emission Tomography- Magnetic Resonance Imaging in patients with Acute Neurovascular Syndrome.*; SHARP (Scottish Heart and Arterial Risk disease Prevention), 2018
16) Macnaught G, Brian D, Dolan K, Robson PM, Fayad ZA, Clark TP, Fletcher A, Frenche M, Semple S, van Beek EJR, Newby DE, Dweck MR. *An evaluation of radial GRE attenuation correction maps for cardiac and coronary PET-MRI studies*. ISMRM 2018
17) Kaczynski J, Williams M, Whiteley W, Dennis M, Wardlaw J, Macnaught G, Tavares A, Jansen M, MacGillivray T, Forsythe R, Tambyraja A, Dweck M, Chaudhury R, van Beek EJR, Newby D. Early experience with 18F-Fluoride Positron Emission Tomography- Magnetic Resonance Imaging in patients with Acute Neurovascular Syndrome. SHARP 2018
18) Kaczynski J, Williams M, Wardlaw J, Macnaught G, Forsythe R, Whiteley W, van Beek EJR, Newby D*. Early experience with 18F-Fluoride Positron Emission Tomography- Magnetic Resonance Imaging in patients with Acute Neurovascular Syndrome*. ECR 2019.
19) Dickie B, Scott L, McFadden J, Parker GJM, Herholz K, Matthews J, Parkes LM 'Impact of amyloid-B and cardiovascular risk on blood brain barrier integrity in patients with mild cognitive impairment' *28th Annual Meeting of the International Society for Magnetic Resonance in Medicine* (2020).
20) Scott L, Dickie B, McHugh D, McFadden J, Priest AN, Parkes LM 'Characterisation of microvascular blood flow, exchange and structure using multi-diffusion time DWI' *28th Annual Meeting of the International Society for Magnetic Resonance in Medicine* (2020).
21) McFadden J, Matthews J, Lohézic M, Parker GJM, Parkes LM, 'Optimisation of QSM measurements of venous oxygen saturation' *27th Annual Meeting of the International Society for Magnetic Resonance in Medicine* (2019).

Thesis awarded: Rodriguez M (Supervisors Al-Shahi Salman R, Wardlaw JM, Dhaliwal K), Multi-modality imaging assessment of cerebral small vessel disease biomarkers after stroke due to spontaneous intracerebral haemorrhage; 2019, University of Edinburgh; paper in preparation: Amyloid in ICH-related cerebral small vessel disease, a PET-MRI study.

Collaborations & Partnerships
The Imaging Network was established as a collaborative network. Industrial partnerships : GE Healthcare , Siemens, Invicro
Further Funding
Following the establishment of the Imaging Network successful applications included for a new network of five PET-MR scanners (£24 million, MRC) and the Dementias Platform UK MR-PET Partnership (Work Package 17, £1,058,747, MRC). Members of the Network are also involved in a separately funded project, MIND MAPS (Molecular Imaging in Neuro Degeneration-Mitochondria, Associated Proteins & Synapses, MRC). A range of PET-MR studies at each Centre funded by GE Healthcare.
Next Destinations
None
Engagement Activities
See above in terms of abstracts published at meetings and conferences. The Network has implemented an effective communications framework as part of its objectives and training has been emphasised.
Influence of policy, practice, patients & the public
The MRI-PET Partnership Award Training Task Force initiated collaboration internationally aimed at developing training strategies for PET/MRI, particularly in Europe and the USA. Validated and standardised information sheets and consent forms are available online to facilitate regularoty applications in the UK/EU; online training for MR-PET operations were also developed.
Research Tools & Methods
A standard phantom has been purchased for all sites for the purposes of scanner QA Gold Standard Phantoms FUNSTAR phantom https://www.goldstandardphantoms.com/funstar PET-MR scanning protocols have been developed and implemented as part of the DFP and harmonisation studies. Methods for the data management of imaging data have been developed and implemented across sites including the upload of image and raw scan data to the DPUK Imaging Informatics Data Management system, and the collection of case report data using REDCap. Study procedures have been developed, implemented and documented in a guidebook.

Research Databases & Models
Data can be analysed using GSP Cloud, cloud-based image platform for the analysis of MRI QA data https://www.goldstandardphantoms.com/gsp-cloud. The imaging data collected as part of this study, will be uploaded in DICOM format directly to the DPUK Imaging Informatics Data Management system (https://info.dpuk.org), which is based on XNAT (https://www.xnat.org).
Intellectual property & licencing
None
Medical products, interventions & clinical trials
The Network is involved in DPUK funded experimental studies as described above.
Artistic & creative products
None
Software & technical products
None
Spin outs
None
Awards & recognition
None
Other outputs & knowledge/future steps
None
Use of facilities & resources
The Network utilises the DPUK Imaging Infrastructure.
Most successful outcome and what it means for future dementia research:
For the first time, a network of PET centres was created that linked methods advances and researchers across major UK Centres. The focus was on dementia imaging for early detection and monitoring, but the network also has supported diffusion of advanced PET methods for cardiology, oncology and other application areas.
Lessons learned:
While this investment has expanded the availability of this new class of imaging hardware tool, challenges remain. The availability and cost of radiotracers remains the major limiting factor. A consequence of this has been that critical expertise in radiochemistry, radiopharmacology and modelling and clinical applications for advanced PET research is still insufficient and there are few

robust training opportunities. This risks a failure to exploit the resources that have been put in place for future patient benefit.
Team Members and Leads:
Franklin Aigbirhio[1], Edwin Van Beek[2], David Brooks[3], Azedah Firouzian[4], Tim Fryer[1], Nick Fox[8], Roger Gunn[4], Alexander Hammer[9], William Hallett[4], Karl Herholz[5], Clare Mackay[6], Marius Mada[1], Paresh Malhotra[7], Julian Matthews[5], Ross Maxwell[3], John O'Brien[1], Jan Passchier[4], Laura Parkes[5], Ilan Rabiner[4], John-Paul Taylor[3], David Thomas[8], Joanna Wardlaw[2], Catriona Wimberley[2], Paul Matthews[7]. [1]Cambridge, [2]Edinburgh, [3]Newcastle, [4]Invicro, [5]Manchester, [6]Oxford, [7]Imperial, [8]UCL, [9]KCL The leads for the network have been as follows: **2014 -19** Prof Paul Matthews (Imperial), Prof Nick Fox (UCL), Prof Franklin Aigbirhio (Cambridge) **2019** - Prof Franklin Aigbirhio (Cambridge)
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