DPUK: Using the power of cohorts to accelerate the development of new treatments for dementia

We are an intellectually generous community sharing data, best practice and technologies.

We are a creative community harnessing new ideas, new technologies and new ways of working.

We are a collaborative community inviting all stakeholders to join our programmes and shape our activity.

We are an enabling community, facilitating the leverage of further resources for dementia research.

The DPUK Annual Report for 2016 - 2017 was collated and edited by Beatrice Shelley, with Jennie Hall, Anna Myers and Ivan Koychev. The team would like to express thanks to all DPUK colleagues who contributed to the report.
INTRODUCTION

This report covers the period July 2016 - June 2017, setting the scene for project completion as we move into the final stages of the current programme.

The strategy underlying all DPUK activity is to build a core infrastructure, use this as critical mass around which to gather science communities, and support these communities in obtaining funding for distributed research programmes (Figure 1). To date, from the MRC and industry core funding of £16m, a further £120m has been awarded, contributing to 18 programmes of research using the DPUK infrastructure from both academic and industry sources.

FIGURE 1: Overview of DPUK structures

This third year has been one of development in ethos, science support and scientific activity.

ETHOS

DPUK operates in a fast-changing world, where dementia research funding remains a poor relation. The MRC-funded dementia infrastructures, the Dementias Platform and more recently the Dementias Research Institute, representing significant investments in UK dementia research, are as much about changing thinking about dementia research as changing how we do it. The need for intellectual generosity between colleagues, collaboration across disciplines and partnerships across stakeholder groups, becomes more apparent with every year without a new treatment becoming available. In this report I would particularly like to acknowledge the hard work and dedication of the growing community of scientists who recognise the wider value of the DPUK enterprise, and support it through the sharing of data, specialist knowledge and (most of all) ideas.

SCIENCE SUPPORT

DPUK structures are designed to make doing good science easier. Our focus is on using the core infrastructure to develop a pipeline for dementia-focused experimental medicine (EM). This involves rapid access to longitudinal data via our data portal, recruitment to highly-targeted studies through a clinical studies register, and the ability to conduct multicentre studies using our imaging, Stem Cells and Informatics networks.

Over this year we have populated the data portal with data for over 560,000 individuals and look forward to adding a further 1.5 million individuals during the next 12 months. The security, convenience and cost-effectiveness of a central repository for cohort data is attractive to many research groups, particularly as the size and complexity of their datasets grows. The DPUK model of ‘bringing researchers to data’ is proving increasingly popular, with cohorts from the Republic of Ireland, France, South Korea and China joining the collaboration.

Recruitment to highly-targeted studies is particularly challenging in dementia due to difficulty in identifying individuals with sufficiently detailed background information. In anticipation of the data portal being populated we have begun work to create a clinical studies register that will recruit from the data portal to highly-targeted, dementia-focused EM studies.

SCIENCE ACTIVITY

DPUK is an enabling infrastructure. Although we fund studies both directly and indirectly, the potential of DPUK will be realised through researchers exploiting our infrastructure to prepare competitive grant proposals for diverse funding sources and in developing our relationships with industry. Over the last year six awards totalling £12m have been won by DPUK research teams from a variety of funders.

Epictetus observed that ‘no great thing is created suddenly’. This is certainly true for a complex, multi-layered project like DPUK. For the remainder of the project we look forward to continuing to develop the core infrastructure and conducting our first tranche of multicentre studies, further supporting the development of science communities and further expanding the envelope of dementia funding for distributed research.

"Over this year we have populated the data portal with data for over 560,000 individuals and look forward to adding a further 1.5 million individuals during the next 12 months."

Professor John Gallacher
PhD, FIBiol, PhD ChS, FFPH
Director of Dementias Platform UK
HIGHLIGHTS FROM ACROSS THE PLATFORM IN 2017

Scientists in universities and industry up and down the UK are working on joined-up research programmes, developing and enhancing DPUK’s infrastructure and data resources for use by dementia researchers worldwide. See below for highlights from our third year.

The DPUK Stem Cells network has produced a bank of iPSC stem cells from selected participants in two DPUK cohorts for use in future studies of brain cells affected by Alzheimer’s disease.

The CRIS platform aggregates de-identified data held in 14 mental health trusts, enabling researchers to search over 2 million clinical records.

Our genetics platform is now operational, providing a suite of new tools which enable researchers to work with genetics data through the DPUK data portal.

The data portal development team is working with cohort principal investigators and data managers across the UK and beyond. DPUK has data deposit agreements in place with seven institutions, allowing for the upload of data from 21 cohorts to dedicated secure storage on the DPUK infrastructure. Currently data for 560,000 individuals are available.

DPUK’s cognitive assessment researchers have developed an enhanced battery of cognitive tests which is now being adopted by UK Biobank.

Researchers in London have scanned 450 members of the 1946 birth cohort using the latest amyloid PET-MR scanning technology. Once processed, valuable de-identified data from this age-matched population cohort will be made available to researchers worldwide through the DPUK data portal.

The Vascular Mechanisms network has secured a joint award of £1.2m from the Stroke Association, British Heart Foundation, Alzheimer’s Society and DPUK for a pioneering large-scale study investigating links between stroke and vascular dementia.

Brain scan data are now being uploaded to the imaging platform, allowing researchers to search and request imaging data that has been securely shared through the central hub.

DPUK researchers have won European funding to investigate the value of real world evidence in Alzheimer’s disease.

FIGURE 2: DPUK-funded scientists are working in universities and industry across the UK.
DPUK’S PLACE IN THE RESEARCH LANDSCAPE

DPUK is a data repository, enabling centralised data storage, curation and access management. The DPUK model is exclusively bringing researchers to data.

Several cohort discovery and metadata platforms exist to describe the data that are available from a wide range of cohorts. GA(A)IN (the Global Alzheimer’s Association International Network), IALSA (the Integrative Analysis of Longitudinal Studies of Aging), CLUSTER and JPND the global cohort portal (the EU joint programme in neurodegenerative research database) are all online resources which allow researchers to find out what data is available. Individual researchers are then provided with contact details to make data access requests for each cohort they are interested in. EMIF-AD, an Alzheimer’s disease-specific research programme of the European Medical Information Framework, focuses on Alzheimer’s disease cohorts. Like the non-disease-specific databases, EMIF-AD allows researchers to search and find out what type of data is available to them, and additionally helps researchers coordinate access requests. DPUK, by contrast, provides a new model of fast, easy and secure access to data. DPUK focuses on population cohorts and operates exclusively a ‘bringing researchers to data’ model. Data are held within a single secure environment enabling centralised data storage, curation and access management. A range of metadata discovery tools is provided, in addition to standard and bespoke statistical analysis tools. From discovering what data are available through to the integration and analysis of those data securely online, DPUK is a one-stop shop for dementia researchers looking to work with a wide range of cohort data.

DPUK is one of several UK initiatives which contribute to drug development. The Dementia Research Institute, ARUK’s Drug Development Alliances, the Translational Research Centres for Dementia and the Joint Dementia Research initiative operate in different stages of the drug development pipeline – from looking at the biology of the disease through to the identification of molecules with the potential to modify disease progression, and the trialling of new treatments in people. DPUK contributes at all of these stages.

In work looking at the biology of dementia, DPUK’s Stem Cells network plays a key role. Thanks to the network of six high-throughput stem cell processors, UK-based scientists are able to investigate the nature of brain cells using the most up-to-date technology. As scientific understanding into the different biological mechanisms of dementia grows, there is increasing need for researchers working in ‘experimental medicine’ – investigation undertaken in humans – to be able to work with research participants for whom we already hold a lot of information. DPUK enables researchers’ access to these ‘highly-characterised participants’ through the data portal and integrated informatics platforms. By enabling access to highly-detailed cohort data – including complex data from brain scans and genetic testing – DPUK facilitates highly-specific studies at this stage.

DPUK’s Imaging network is also set up to facilitate improved experimental medicine. The network of seven PET/MR scanners facilitates multicentre studies, allowing scientists to see inside the brain in unprecedented detail in sites across the UK. In these ways, DPUK is facilitating a new generation of highly-specific experimental medicine studies, with much greater promise of leading to effective treatment.
DPUK COHORTS

DPUK is bringing together individual-level data for 2 million participants from 44 cohort studies into a research resource of unprecedented detail for its size and theme. Our clinical, imaging, genetic and wearables data provide vital sources of insight for dementia researchers. DPUK technologies are being developed to optimise the rich variety of data that are collected by cohort studies.

Using the data portal, researchers are able to integrate data from a range of different types of cohort studies.

CASE-RICH POPULATION COHORTS
These large population studies have followed adults into their 70s, 80s, and some beyond – a stage in life when the risk of dementia substantially increases in the population. These studies provide sufficient case numbers of dementia with which to better characterise risk and protective factors associated with the dementias, as well as to study trajectories of disease progression.
- Aberdeen Birth Cohort 1921
- Aberdeen Birth Cohort 1936
- Aberdeen Children of the 1950s
- Caerphilly Prospective Study
- MRC Cognitive Function in Ageing Study I
- MRC Cognitive Function in Ageing Study II
- English Longitudinal Study of Ageing (ELSA)
- Lothian Birth Cohort 1936
- Million Women Study
- Whitehall II

PRODROMAL POPULATION COHORTS
These large population studies are following adults in their forties and fifties, before clinical symptoms of dementia appear in the majority of cases. This stage of life is critical for understanding the multiple risk and protective factors that contribute to onset of dementia, given the long pre-symptom (“prodromal”) phase of dementia, and for understanding the disease progression in its early stages.
- Airwave Health Monitoring Study
- Cambridge Centre for Ageing and Neurosciences
- Cognitive Health in Ageing Register
- Emory Healthy Ageing Study
- Emory Healthy Brain Study
- Generation Scotland: Scottish Family Health Study
- Healthwise Wales
- MRC National Survey for Health and Development 1946
- PREVENT Research Programme
- Platform for Research Online to investigate Genetics and Cognition in Ageing
- Southall and Brent Revisited
- UK Biobank

DEMENTIA CASE COHORTS
These cohorts involve the study of patients with a diagnosis of dementia or related neurodegenerative disease. They often involve frequent follow-up and extensive assessment of individuals, in order to characterise the progression of the disease pathology and/or clinical symptoms, or to understand the care needs of individuals and their families. Many of the studies involve a healthy control group of participants.
- Amyloid imaging for Phenotyping LEwy body dementia
- Brains for Dementia Research
- Cambridgeshire Parkinsons Incidence from GP to Neurologist
- Project Cygnus
- Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-PD
- Identifying Predictors of dementia with Lewy bodies in People with MCI
- Neuroimaging of Inflammation in Memory and Other Disorders
- Oxford Parkinson’s Disease Centre Discovery Cohor
- Parkinson MRI Imaging Repository: Part 2 Database
- Parkinsonism: Incidence and CogEry heterogeneity in Cambridgeshire

GENETIC RISK COHORTS
Genetic risk cohorts include individuals who carry genetic mutations that increase their risk of specific dementias or a closely-related neurodegenerative disease (ie Parkinson’s and Huntington’s diseases). Disease onset and progression is followed up by cognitive and neuropsychiatric assessments, measurements of symptoms and biological signs of the disease, and brain imaging.
- Dominantly Inherited Alzheimer Network
- GENetic Frontotemporal dementia Initiative
- Track HD

Cohort studies are research studies carried out on the same group of people regularly over a number of years. At regular intervals, the people who take part in these studies may sit cognitive tests, undergo brain scans, complete lifestyle questionnaires and undertake blood tests. Taken together, this information provides valuable insights into the causes and potential treatments for diseases like Alzheimer’s.

1Some studies belong in more than one category, eg Whitehall II, and Generation Scotland, particularly where age at recruitment is broad.
DPUK COHORTS

DPUK cohorts contain data on lifestyle and cognition going back 50 years and more in some studies. Taken together with the insights we have from more recent tests and brain scans in these and other studies, the DPUK cohorts are a data resource of unprecedented breadth and depth for dementia researchers.

The diagram indicates active data collection points in these studies. Some studies are ongoing, whereas others are closed. Many of the studies link to electronic records and so may follow up participants on an ongoing basis according to these records. The age at each wave is the mean age of participants; median age is used in cases where mean age isn’t published. These data are based on current available information from websites and journal publications.

FIGURE 5: Data collection points in DPUK’s case-rich population cohorts and prodromal cohorts. The genetic risk and dementia case cohorts are more recent studies and are not featured in this diagram. Find more information on the types of data available on the cohort directory at portal.dementiasplatform.uk
IN FOCUS: DATA PORTAL

The DPUK data portal brings together – for the first time – data from UK and international cohorts into a single research hub, enabling secure and cost-effective data storage, curation, linkage and access management. The portal allows researchers to access multiple independent datasets, enabling rapid confirmatory analyses, innovative data analysis and the triangulation of evidence from many different types of data, including complex data. Over this past year the user experience of the portal has been enhanced, new utilities added and further data uploaded.

REFRESHED WEBSITE
DPUK is committed to providing a transparent and guided journey for researchers from the moment they arrive onto the DPUK website and subsequently onto the data portal landing site. To achieve this the portal website has been revised, providing greater access to metadata and a streamlined data access process. The DPUK data management team is available to respond to queries and help researchers navigate their way through the various portal tools.

NEW ANALYSIS PLATFORMS
DPUK aims to provide an integrated analysis environment. Over the last year we have brought our genetics analysis platform into the data portal so that its functionality can be extended from case-control analyses to cohort-based analyses. This allows researchers to conduct gene-environment interaction analyses and link genotype and lifestyle to risk of dementia, as well as use specialist genetics analysis toolsets such as PLINK.

The DPUK imaging informatics platform has become operational, with initial imaging data being uploaded. This XNAT-based platform operates a hub and node model, with the hub being based in the DPUK data portal and nodes at imaging centres around the UK. Early adopter studies, such as the Deep and Frequent Phenotyping study from the University of Oxford and the Cambridge Centre for Neuroscience and Ageing cohort, are now uploading imaging data to their local nodes. The system of nodes allows local and central web-based management of imaging data.

INCREASING THE ACCESSIBILITY OF COHORT DATA
The data portal now holds phenotypic data from eight UK cohorts: UK Biobank, the English Longitudinal Study of Ageing, ICICLE-PD, CamPaIGN, Generation Scotland, CFAS, CFAS II and the Cambridge Centre for Neuroscience and Ageing. The Oxford Parkinson’s Disease Centre Discovery cohort is also sharing data to the portal. These cohorts provide data for 560,000 individuals.

Now that the portal platforms are fully integrated we are accelerating our upload of genetic and imaging datasets.

Researchers can now benefit from Stata 15 as standard when accessing cohort data via the portal, as well as the other pre-installed statistical and data management software available, including RStudio, Eclipse, SPSS and SQL Server Management Studio.

FIGURE 6: Streamlined data application process

DPUK is happy to announce collaborations with the University of Hong Kong Neurocognitive Disorder cohort and the Northern Ireland Cohort for the Longitudinal study of Ageing (NICOLA) and PRIME, from Queen’s University Belfast.

All cohorts and data listed on DPUK discovery tools such as the cohort matrix and directory are available for data access. We welcome applications for data access from any bona fide researcher.
BETTER DATA

The medical information held by longstanding population and cohort studies is of immense value in studies of dementia. Our investment in enhancing this longitudinal information is enabling the creation of uniquely rich research data resources.

IMAGE DATA FOR THE DATA PORTAL

Research group lead: Professor John Gallacher

Repeat brain and body imaging 10,000 UK Biobank participants over two years will create a vast bank of imaging data that dementia researchers will be able to access to use any dementia in the DPURK data portal. This year we have completed the background work for the re-imaging protocol and look forward to beginning repeat imaging in early 2018. Amyloid is one of the brain proteins associated with Alzheimer’s disease. DPURK is funding PET brain imaging for amyloid in 500 individuals from the National Study of Health and Development. See ‘In focus’ opposite.

GENETICS BIOSTATISTICS

Research group lead: Professor Julie Williams

We have developed, and continue to advance, state-of-the-art risk stratification methods for Alzheimer’s disease using polygenic risk scores and other analytical techniques. These risk stratification algorithms are available for application to DPURK cohorts. We are preparing exemplar analyses to test the utility of the data portal for cross-cohort analyses linking genetic, population and routinely-collected data.

MAKING USE OF FAMILIAL DISEASE STUDIES

Research group lead: Professor Martin Rossor

Rare familial forms of Alzheimer’s disease are studied in a number of smaller cohorts. By bringing together these studies we will be able to gain insights into both the genetic forms of dementia and other non-genetic forms. DPURK continues to support recruitment to UCL’s UKRR2 and Familial Alzheimer’s disease cohorts.

500 INDIVIDUALS SCANNED FOR AMYLOID

We have now scanned nearly 450 of the 500 and are on track to complete collection of relevant data by the end of 2017. We have published our study protocol and shared our scanning methods and systems for electronically collecting and storing imaging and clinical trials data across the DPURK Imaging network. We have presented provisional data from the first 250 individuals at AAC, the major annual Alzheimer’s disease conference, demonstrating that around 1 in 5 individuals who don’t show any symptoms has significant brain amyloid, and comparing different methods of determining the extent of brain amyloid deposition.

COLLABORATIVE FUNDING SECURED

DPURK funds our study coordinator, a clinical fellow, an imaging analyst, and contributes to the funding of our imaging work. Building on the £1m seed funding from DPURK, we have secured significant external funding both to run the wider Insight 46 study and to undertake specific additional analyses. We have received around £3.1m from Alzheimer’s Research UK and £900,000 from the Wolfson Foundation which, combined with the DPURK funding, allows for: Recruitment of study members from all around the UK and bringing them to London for testing; Scanning, data collection and analysis; Employment of the extensive study team – including doctors, psychologists, administrative staff, statisticians, epidemiologists, image analysts, data managers, and biomarker experts – required to run this study.

Over this year we have populated the data portal with data for over 560,000 individuals and look forward to adding a further 1.5 million individuals during the next 12 months.

IN FOCUS: AMYLOID DISCOVERY COHORT

Research group leads: Professor Jonathan Schott, Professor Nick Fox, Professor Marcus Richards

Running clinical trials to determine if new treatments can prevent or slow the development of cognitive impairment depends on identifying individuals who are in the earliest stages of developing Alzheimer’s disease. Current research criteria allow for various stages of early ‘preclinical’ Alzheimer’s disease to be determined using amyloid positron emission tomography (PET) scans – an invasive and costly test. We are looking to identify preclinical Alzheimer’s disease using more widely available, less invasive and less costly tests, including MRI and new tests in blood and urine.

We are investigating 500 members of the 1946 birth cohort – individuals all born in mainland Britain in the same week, who are taking part in an intensive study to investigate pre-symptomatic Alzheimer’s disease. These individuals perfectly matched for age and originating from all over the UK – are undergoing amyloid PET imaging by structural MRI scans, with urine and blood samples. Once collected, their data will be used to develop new ways of predicting brain amyloid status from MRI scan and will allow us to validate new blood and urine biomarkers.

A Welcome PhD Training Fellowship (around £180,000) has been awarded to one of our clinical fellows (Dr Parker) to analyse aspects of the imaging work. Around £340,000 has been awarded by the Brain Research Trust to allow for detailed genetic analyses of Insight 46 (ongoing), which will enable us to explore the extent to which genetic and life-course factors influence the development of different diseases, which lead to dementia and influence biomarker findings.

NEXT STEPS

As we complete the data collection phase, we will start the detailed analyses, making appropriate data available in due course for collaborative work via the DPURK data portal. We are in the process of applying for additional funding to undertake novel biomarker analyses from the blood samples we have collected. We plan to see all individuals for a second visit (funded through ARUK and Wolfson) to assess change in clinical, cognitive, imaging and biomarker parameters over time. We anticipate that our analyses will provide:

1. Major insights into how genetic risk factors and life-course data influence the development of Alzheimer’s disease and vascular dementia
2. Information about how these combine to influence the development of late life cognition and dementia
3. Data to inform the design of the next generation of clinical trials aiming to prevent the onset of Alzheimer’s dementia.
MULTICENTRE STUDIES

Experimental medicine involves many challenges, including the need to conduct studies at multiple sites. To streamline this process, DPUK is using its imaging network to develop standardised procedures across sites for governance, data collection and data management. DPUK’s first multicentre study is the Deep and Frequent Phenotyping study (DFP).

DEEP AND FREQUENT PHENOTYPING STUDY

Lead: Professor Simon Lovestone

One of the principal challenges for the dementia research community worldwide is how we can study the brain in the very early stages of the disease. Damage in the brain can start to occur up to 15 years before we see symptoms of Alzheimer’s disease and researchers need to be able to investigate and test interventions at this critical early stage. At present, proving that a new early-stage treatment works is difficult because any symptoms will be a long way off. The DFP study aims to address this by creating a database of different measures – blood proteins, retinal scans, brain scans, gait analysis – which will be tracked as the disease develops. In the future we will be able to use the data gained through DFP to understand if early interventions are working.

This year we developed DFP’s study design and methods, incorporating feedback from people who took part in the pilot study. We have extended the range of measurements we will take to include new digital technologies that allow for cognitive testing using smart phones and video-audio recording to assess spoken language, as well as linking measures of cognitive performance to SeaHero, a widely-used app for cognitive testing. We have worked with Alzheimer’s Society to produce videos which inform the volunteer participants about the tests they will complete as a participant in studies like DFP. We have received ethical approval for DFP and look forward to initiating the work across all sites in early 2018.

DFP is the most detailed study into preclinical Alzheimer’s disease for its size in the world. Currently work is underway to recruit 250 suitable participants for the study from a number of DPUK cohorts. To date the research team are recruiting from UK Biobank, EPIC and the Generation Scotland cohorts. The figure opposite shows how this first multicentre study works with these DPUK cohorts and how the extensive programme of testing will be coordinated across eight different study centres and four imaging centres.

It also sheds more light on DFP’s long name: ‘deep and frequent’ refers to the in-depth nature of the measurements that are taken from each of the 250 participants. Each tooth of the cog shows the different tests that participants will undertake at their local study: MEG scans, PET scans, MRI scans, cognitive tests, blood and urine tests, eye tests and tests using wearable devices.

Not all of the study sites have the capacity to do every type of testing required in this study so some participants will travel to nearby centres for certain tests. Enabling research teams to make use of facilities in other centres is a key reason underlying DPUK’s work in setting up standardised protocols for use with the new research infrastructure in the UK.

DFP is the most detailed preclinical Alzheimer’s study for its size in the world. All the anonymised data collected from DFP will be made available to bona fide researchers through the DPUK data portal.

DFP starts in early 2018. In this year-long study, the research volunteers will undergo a range of different tests designed to uncover the earliest signs of Alzheimer’s disease, and how we can prevent it at those early stages.

“DFP is the first study to systematically investigate the use of wearable and digital technology alongside the well-established methods – MRI and cognitive tests – in a population of the most interest for disease modification: those people who are in the very early stages of Alzheimer’s disease.”

Dr Ivan Koychev, Clinician Scientist for DPUK and DFP lead in Oxford.
METHODS DEVELOPMENT

DPUK has an ongoing programme of methods development to improve the quality and range of data available to dementia researchers. DPUK-funded work is making recommendations on best practice for the use of routinely-collected data, cognitive assessment, brain donation, ethical and legal issues and biostatistical methods.

ROUTinely-collECTED DATA

Research group lead: Professor Cathie Sudlow

We are working with real world data, looking to determine how this can help us better understand neurodegenerative diseases such as dementia. We want to produce robust methods to identify cases of dementia or other neurodegenerative disease, such Parkinson’s or MND, from data routinely gathered by primary care data to be a promising resource for UK cohort research. Following on from these comprehensive assessments we have produced updated research guidance which we are making available to any researcher working with UK Biobank data. This guidance will allow researchers to simply and accurately identify participants in the UK Biobank cohort with neurodegenerative conditions, so that individual research projects can be sure that they are working with the information from the correct participants.

COGNITIVE ASSESSMENT

Research group lead: Professor John Starr

We are working with UK Biobank to improve the cognitive testing that it administers, and are focusing on implementing this in the 100,000 participants who are currently undergoing brain scans.

We have developed an enhanced battery of computer-administered cognitive tests. This was rolled out at the UK Biobank imaging assessment at the end of 2016 and data collection is ongoing. We will be validating the cognitive measures that UK Biobank uses, which we will do once we receive the tests in a form that can be administered face-to-face.

Dementias Platform UK marks a new phase in the development of data science and experimental medicine for dementia research in the UK. We examined ethical, social and practical issues related to the development of the data portal, cross-cohort data platform and the potential re-contact of participants from existing cohort populations by undertaking empirical research with both participants and researchers.

We have identified and provide recommendations to researchers in the following areas:

- Ethical practices in the development of a cross-cohort data-sharing platform
- Re-contacting cohort participants for experimental medicine studies
- Participants’ social and ethical concerns around data-sharing and linkage
- Social and ethical issues around re-contacting cohort participants for experimental medicine studies.

For further detail on these recommendations, please refer to our report, available by contacting dpuk@psych.ox.ac.uk.

BRAIN DONATION

Research group lead: Professor Carol Brayne

It is important to be able to link the variety of data gathered by DPUK cohorts to tissue information which is relevant to dementia research: brain tissue and iPSC stem cells. We are working on identifying which of the DPUK cohorts would be in the best position to facilitate this type of study.

We have agreed a process for researcher access to tissue banks. Two cohorts – BDR and UK Biobank – have been identified as most suitable and work is underway to agree procedures for tissue donation.

By the end of the year we aim to have established options for the collection of brains at scale.

BIOSTATISTICS METHODS

Research group lead: Professor Sylvia Richardson

We are developing statistical methods that would allow us to use DPUK cohort data, for example genetics and basic demographics, to differentiate those people who are more likely to develop dementia or deteriorate faster than others. We are testing whether we can do this with both single as well as repeated measurements. We are also developing methods to see if we can increase the certainty of predictions of who is at risk of developing dementia by combining a number of complex measures, including brain imaging, urine and blood biomarkers.

We have used the CPAS cohort data to test whether genetics can be used to identify groups that are more likely to decline faster. We were therefore able to identify high-risk genetic variants linked to cognitive decline and which would be particularly promising for use in selecting people most suitable for clinical trials. We are also building statistical simulations of clinical trials that can be used to plan recruitment, and select the most effective measures to determine whether interventions tested in clinical trials are working.

We are looking forward to working with data from the other DPUK cohorts to test our methods with longitudinal data and scenarios where multiple types of measures are available.
COMMUNITIES OF SCIENTISTS WORKING TO DEFEAT DEMENTIA

DPUK promotes high-quality science by bringing together experts to develop strategic research proposals. As the biological mechanisms and pathways which lead to dementia are complex, and developing effective interventions will require us to work across traditional discipline boundaries, we encourage the formation of interdisciplinary groups. By supporting the collaboration of geneticists, statisticians, vascular experts and our cohort communities, we are enabling the cross-fertilisation of the ideas that we need for a breakthrough in dementia research.

Support we provide to the DPUK networks

- Travel expenses to enable meetings between scientists based at different sites.
- Administrative support for grant applications.
- Training opportunities.
- Co-funding to increase competitiveness when making grant applications.

The support we provide to the DPUK networks facilitates knowledge-sharing and the development of best practice.

FIGURE 12: DPUK supports networks of scientists
DPUK NETWORKS

SYNAPTIC HEALTH NETWORK
Network leads: Dr John Isaac and Professor James Rowe

Synapses are the chemical connections between neurons and as such are absolutely fundamental to brain function. There is emerging evidence that a loss of synapses precedes the death of neurons and is a major cause of the early symptoms of Alzheimer’s disease. We aim to better understand whether new interventions aimed at preventing synaptic loss and promoting synaptic function are having the desired effect in patients by developing new ways of measuring synapse number and function in living people – something which has never been done before.

NEW RESEARCH PROPOSALS

The Synaptic Health network ran a two-day workshop in March 2017 to identify new areas for collaboration with a view to developing new research proposals. This was followed up by a meeting of the network during the Alzheimer’s Association International Conference in London in July 2017. At the workshop and subsequent meeting the network discussed a research proposal focused on the use of a new recently-developed PET ligand (UCB-1) that specifically labels synapses. We agreed on an outline project proposal in which synaptic PET imaging was complemented by other clinical and preclinical experiments to determine its utility in measuring synaptic loss in Alzheimer’s disease. This project will build on work from the Mindmaps study. In additional discussions at the workshop there was interest in the role of sleep in promoting synaptic health in dementia; further discussions are ongoing on this theme.

NEXT STEPS

The New Targets in Alzheimer’s Disease (NTAD) study is the largest to come out of the Synaptic Health network, thanks to a collaborative funding effort from DPUK, ARUK, the Universities of Oxford, Cambridge and Cardiff, and the industry partners involved in the study: Janssen, Lilly and MedImmune. The study, which is due to get started in late 2017, will measure the electrical activity of the brain using magnetoencephalography (MEG) while participants complete visual recognition tasks. We hope to identify whether the MEG signal is a useful/sensitive biomarker of early decline in cognitive performance observed in Alzheimer’s disease.

We are now looking at the next step for the grant proposal on the use of synaptic PET imaging: the plan is to bring this proposal forward for funding as part of the DPUK renewal.

“ In additional discussions at the workshop there was interest in the role of sleep in promoting synaptic health in dementia."

FIGURE 13: Synaptic PET images in the human brain
Credit: Sjoerd J. Finnema / Science Translational Medicine

VASCULAR DISEASE MECHANISMS NETWORK
Network leads: Professor Joanna Wardlaw and Dr Paul Wren

Epidemiological, genetic, neuroimaging and clinic-pathological data indicate that vascular mechanisms are fundamental risk factors for dementia. We look to increase understanding of vascular disease in dementia and enable vascular basic and human sciences to be integrated into dementia research.

COLLABORATIVE FUNDING

Over the past year we have achieved significant funding success, including a £1.2m award by the Stroke Association, British Heart Foundation, Alzheimer’s Society and DPUK for our ‘Rates, risks and routes to reduce vascular dementia’ (R4VAD) project. The project will track changes in memory and thinking skills in over 2,000 stroke survivors across the UK and will start in 2018.

From the same funding call we were also successful in securing two other grants for lab studies: a multicentre group led by Professor Karen Horsburgh will be looking at developing models for studying small vessel disease, and Dr Rosana Carare will be studying the mechanisms of fluid flow through brain tissue.

Other notable activities this year included a highly-successful international workshop on improving use of animal models in studies of small vessel diseases in Glasgow in Jan 2017, supported by the British Heart Foundation, Royal Society of Edinburgh, Alzheimer’s Research UK and DPUK. We have also guest edited a special edition of Clinical Science on ‘Small vessels and chronic diseases’ with a superb set of invited review papers and original papers debating the potential mechanisms and long-term effects of brain microvascular disease.

NEXT STEPS

The Stroke Association award is being used to carry out the multicentre R4VAD study. The stroke survivors who take part will complete regular tests to assess their memory and thinking skills, give blood samples and undergo brain scans. Their results will be used by the research team, who will work together to generate insights from this rich and detailed data. Outputs will include reliable data on cognition long-term after stroke, stratified by prior cognition, stroke and patient-related variables, improved risk prediction, and understanding the influence of neuroimaging, vascular, inflammatory and genetic markers.

The project will develop an infrastructure and strong national foundation that means future studies will be easier and cheaper to undertake, as well as being quicker, because suitable individuals will have been identified already. The study is planned to start in early 2018 once the regulatory approvals have been obtained and the study set up. The study builds on infrastructure and expertise that is already in place in expert-stroke centres, for large multicentre clinical trials in stroke, and the Stroke and Dementia Clinical Research Networks.

“ Over the last year, we have increased the group membership by five to broaden our representativeness and expertise. The group comprises stroke physicians, old age psychiatrists, neurologists, neuroradiologists, cardiologists, neuropahtologists, medical physicists, neuroscientists and vascular biologists, clinical trialists and representatives from industry."

FIGURE 14: Researchers in the Vascular Mechanisms network use PET-MR imaging to show a PET tracer being taken up by a carotid plaque
Credit: Edinburgh Imaging OMRI & British Heart Foundation/University of Edinburgh Centre for Cardiovascular Science
DPUK NETWORKS

IMAGING NETWORK
Network lead: Professor Paul Matthews
Following the installation of five PET-MR scanners in sites across the UK, we have this year undertaken testing to ensure that the scanners are calibrated correctly and the output from each site is comparable. We have evaluated the quality of scans and are now in a position where we can run multicentre imaging studies. In this way, we are preparing for the first use of these scanners in two large-scale studies which have an amyloid PET imaging component: the amyloid imaging to prevent Alzheimer’s disease initiative (AMYPAD) and the Deep and Frequent Phenotyping study (DFP).

We have worked with informatics colleagues to set up a networked IT infrastructure – XNAT – which represents a significant step forward for multicentre imaging studies. This cloud-based storage allows for imaging data collected in studies to be stored centrally rather than on individual servers on each hospital site. This infrastructure, known as the Imaging Platform, is online within the DPUK data portal and is configured so that the imaging data can be linked with other data types that have been collected on these participants.

Further work is planned to optimise the technical performance of the scanners, which are at the cutting edge of scanning technology in the UK at present.

We are preparing for the first use of the Imaging network scanners in two multicentre studies, both due to get started in 2018.

STEM CELLS NETWORK
Network lead: Professor Richard Wade-Martins
There is widespread scientific interest in the role of microglia – cells which support neurons in the brain. We are interested specifically in how microglia help clear harmful proteins in the brain.

STANDARDISED PROTOCOLS
This year we have developed standardised, highly-efficient procedures which can be used to investigate the role of microglia in neurodegenerative disease. We have developed common approaches to generating iPSC stem cells from skin and blood cells, converting iPSC stem cells to microglia and imaging these cell cultures using the Opera Phenix microscope to better understand their nature.

BANK OF iPSC STEM CELLS
In addition, we have created two banks of iPSC stem cells based on individuals selected from two DPUK cohorts – 24 from the 1936 Lothian birth cohort and 20 from the DFP pilot study. These will be used in future studies interested in linking the characteristics of the patients to the neuronal cells generated from their iPSC stem cells. Our study into Parkinson’s disease patients is an early example of the type of work we can do with the iPSC stem cell bank: we have found that dopamine neurones generated from Parkinson’s disease patients were found to accumulate proteins typical for the disease and showed problems with mitochondrial function. Further research will focus on whether and how neurones generated from Alzheimer’s patients differ in how they breakdown amyloid, compared to people who are cognitively normal.