Dementias Platform UK
Medical Research Council

ANNUAL REPORT
2016-2017

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.

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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.

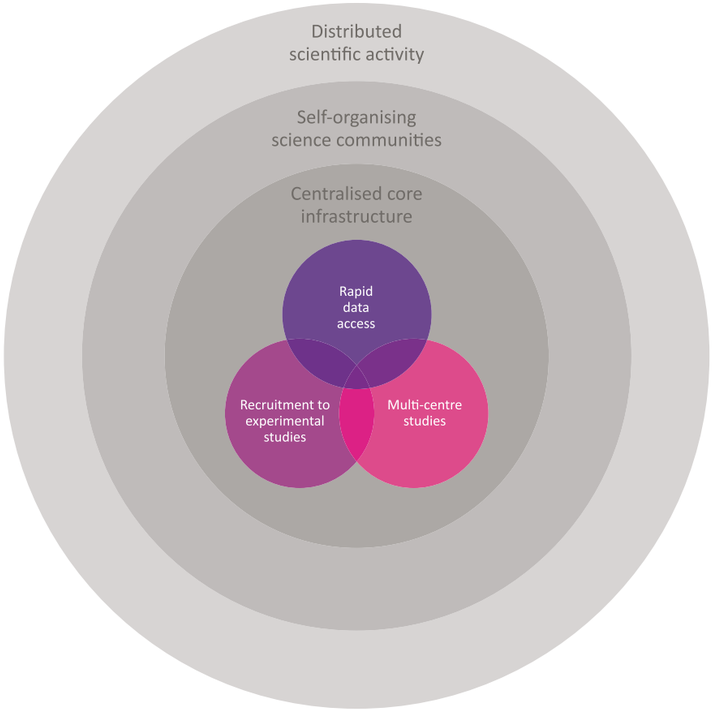

FIGURE 1: Overview of DPUK structures

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.

Professor John Gallacher
PhD AFBPsS CPsychol FFPH
Director of Dementias Platform UK

Professor John Gallacher

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.

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.

FIGURE 2: DPUK-funded scientists are working in universities and industry across the UK

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

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.

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

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.

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.

DPUK'S PLACE IN THE RESEARCH LANDSCAPE

DPUK is one of a growing number of international cohort-based data-sharing initiatives as research scientists and organisations around the world recognise the value of cohort study data. DPUK exists alongside these platforms, and provides a complete identify-access-analyse model for the research community.

Several cohort discovery and metadata platforms exist to describe the data that are available from a wide range of cohorts. GAAIN (the Global Alzheimer's Association International Network), IALSA (the Integrative Analysis of Longitudinal Studies of Aging), CLOSER 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.

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

FIGURE 3: DPUK is one of a number of initiatives which supports drug development for the diseases which cause dementia
Credit: iStock

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.

> In work looking at the biology of dementia, DPUK's Stem Cells network plays a key role.

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.

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Using the data portal, researchers are able to integrate data from a range of different types of cohort studies.[1]

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
European Prospective Investigation of Cancer – Norfolk
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 Neuroscience
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

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

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Marianne Talbot, participant in the English Longitudinal Study of Ageing (ELSA)

I love being a cohort member because it makes me feel useful. Every two years, I get a visit from someone armed with a very long questionnaire. Every four years a nurse comes to visit and give me a full physical. The information that I, and other cohort members, give will eventually bring about new diagnostic techniques, treatments, and hopefully even cures for the diseases that cause dementia. Surely that is worth two hours of my time once every two years?

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 CogNItive 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.

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.

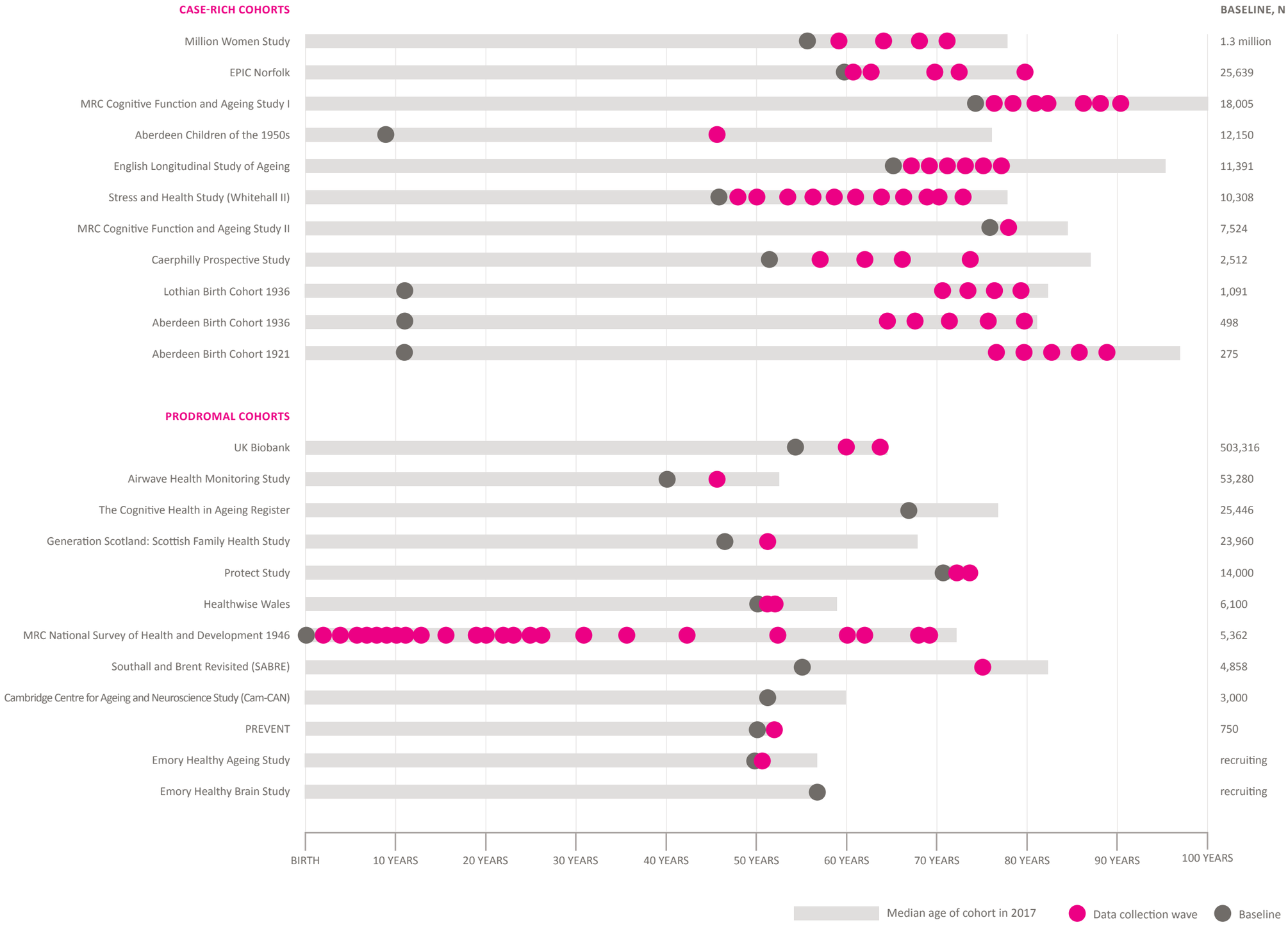


FIGURE 5: Data collection points in DPUK's case-rich population cohorts and prodromal cohorts. The genetic risk and dementia case cohorts are more recent studies and are not featured in this diagram. Find more information on the types of data available on the cohort directory at **portal.dementiasplatform.uk**

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.

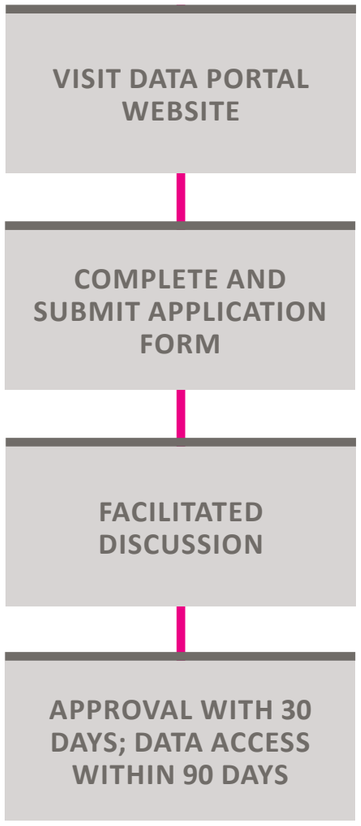


FIGURE 6: Streamlined data application process

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 to 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.

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.

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.

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 at two years will create a vast bank of imaging data that dementia researchers will be able to request access to through the DPUK 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. DPUK 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 DPUK 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.

DPUK1000 STUDY

Research group lead: Professor Simon Lovestone

We are trying to understanding the protein changes in the brain that are associated with Alzheimer's disease. We have met to design the study in terms of the risk stratification for population sample (using imaging and genetics data), the selection of biomarkers and the selection of outcomes. The population sample selection protocol will be finalised in late 2017. The sample analysis protocol will be finalised in early 2018. The inclusion of samples from the DPUK amyloid cohort is contingent on recruitment rates but is anticipated for early 2018.

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. DPUK continues to support recruitment to UCL's LRRK2 and Familial Alzheimer's disease cohorts.

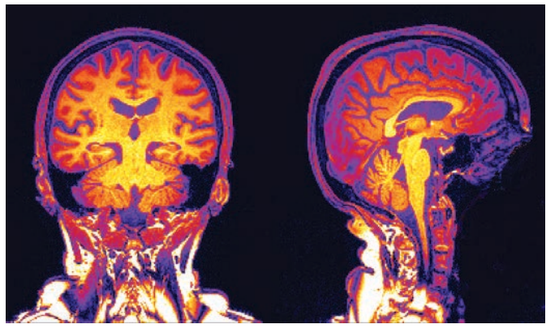


FIGURE 7: 3D anatomical brain scan of a participant from the National Study of Health and Development (the 1946 birth cohort)
Credit: Jonathan Schott

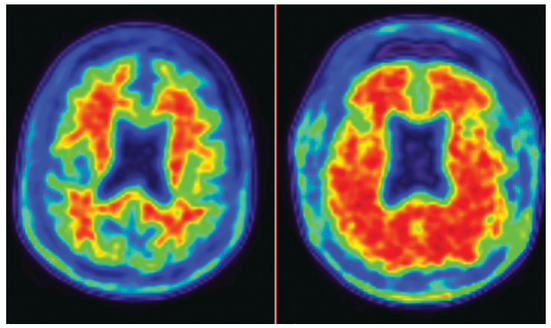


FIGURE 8: Amyloid PET scans showing amyloid positive (right) and amyloid negative (left)
Credit: Jonathan Schott

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 and structural MRI scans, and are donating blood and urine samples. Once collected, their data will be used to develop new ways of predicting brain amyloid status from MRI scans and will allow us to validate new blood and urine biomarkers.

> 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.

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 DPUK Imaging network. We have presented provisional data from the first 250 individuals at AAIC, 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

DPUK funds our study coordinator, a clinical fellow, an image analyst, and contributes to the funding of our imaging work. Building on the £1m seed funding from DPUK, 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 DPUK funding, allows for:

- Recruitment of study members from all round 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.

1,000 doses of the amyloid PET tracer Florbetapir (equivalent to around £900,000) has been kindly donated by AVID Radiopharmaceuticals (a wholly-owned subsidiary of Eli Lilly).

A Wellcome 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 £240,000 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 DPUK 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 Sea hero, 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.

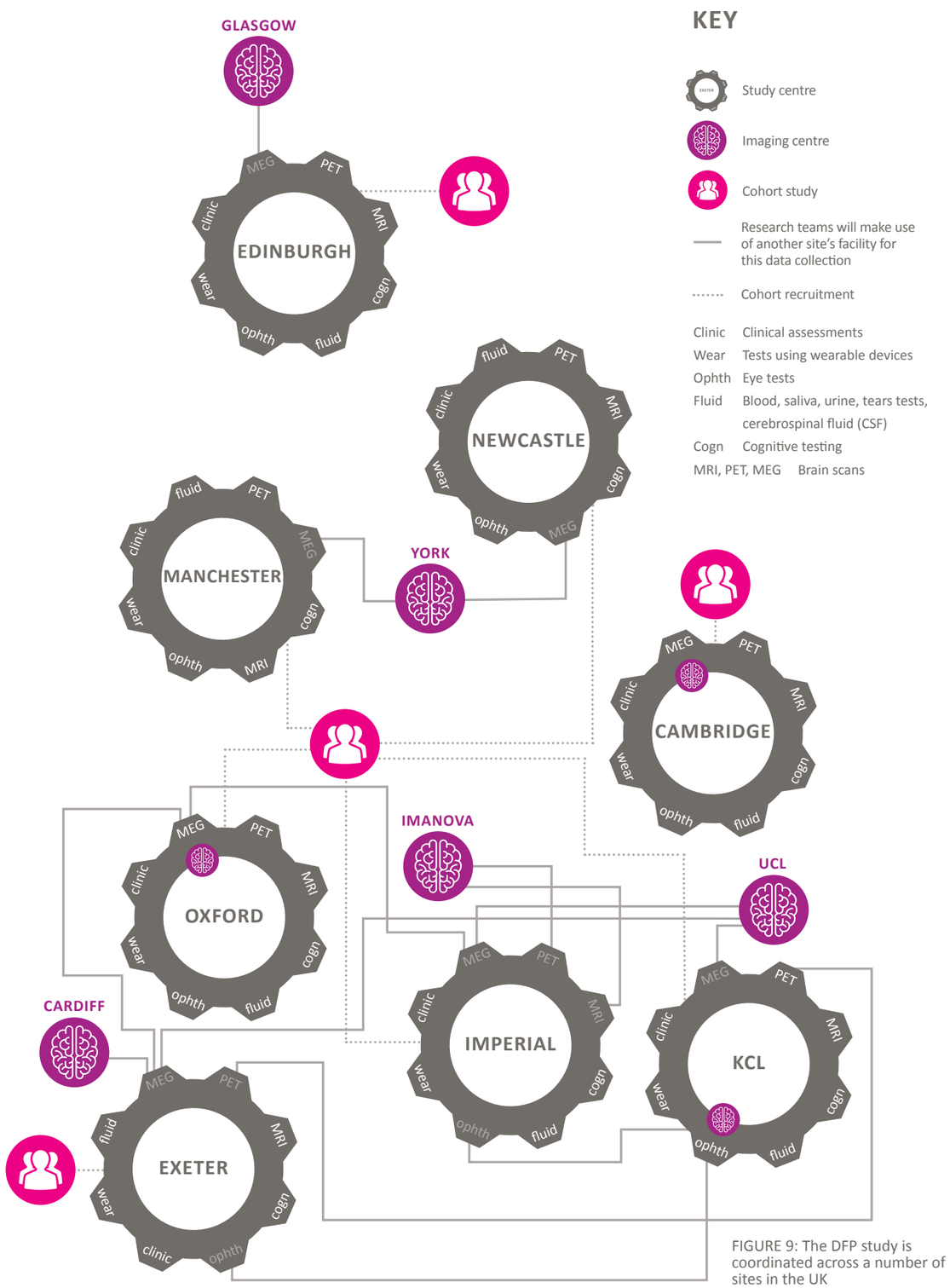


FIGURE 9: The DFP study is coordinated across a number of sites in the UK

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 cohort studies, GPs, hospitals and death records.

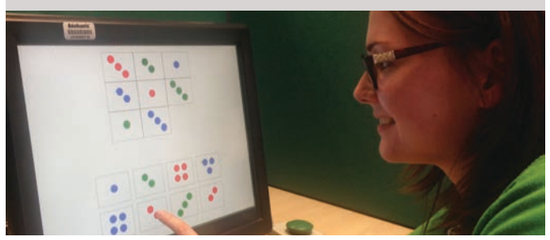
This year we have critically examined the evidence currently available for the accuracy of routinely-collected data in primary care, secondary care and death data, for the identification of MND, Parkinson's disease and dementia. We have found primary care data to be a promising resource for UK cohort 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 dementias 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.

FIGURE 10: DPUK researchers have developed an enhanced battery of cognitive tests that is being rolled out in the UK Biobank cohort
Credit: Chloe Fawns-Ritchie

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 CFAS 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.

FIGURE 11: Researchers can extract genetic material from saliva and blood samples
Credit: Wellcome Images/ UK BioBank

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.

Credit: Paul Tait

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.

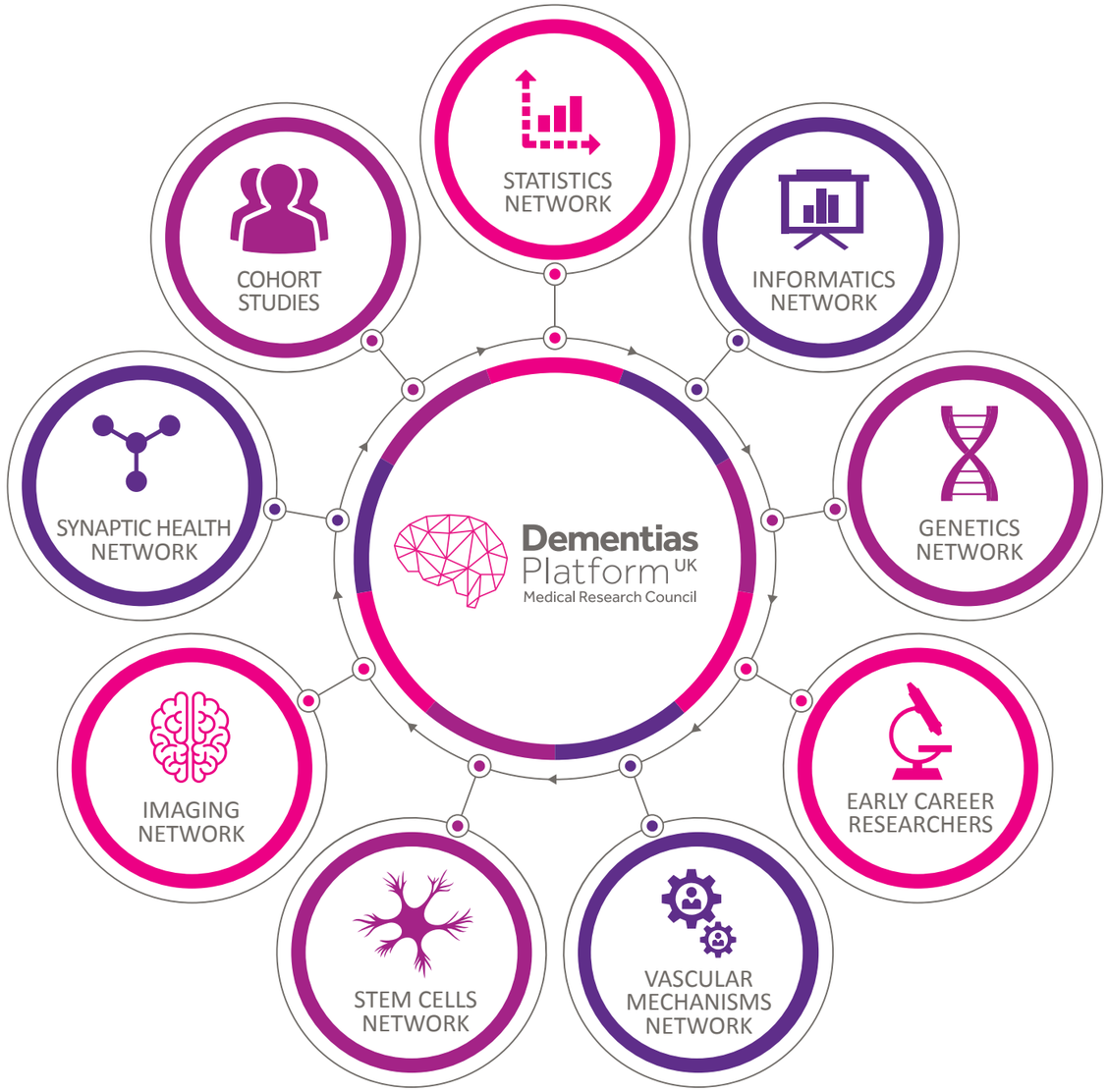


FIGURE 12: DPUK supports networks of scientists

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-J) 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.

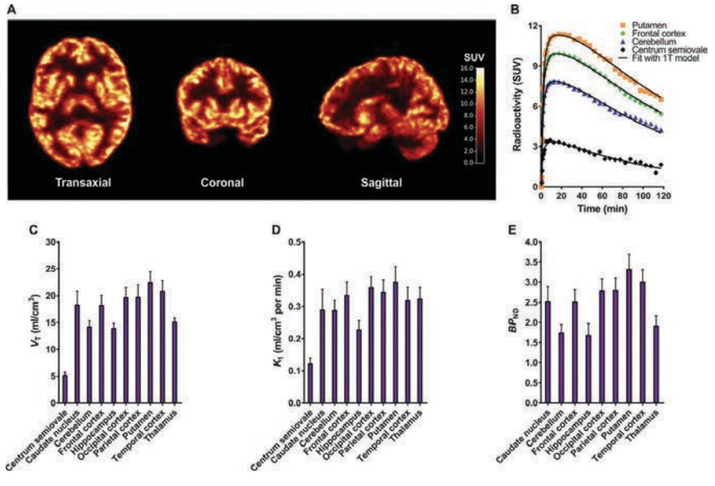


FIGURE 13: Synaptic PET images in the human brain
Credit: Sjoerd J. Finnema / Science Translational Medicine

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 Roxana Carare will be studying the mechanisms of fluid flow through brain tissue.

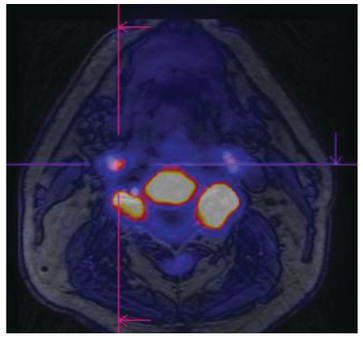
Other notable activities this year included a highly-successful international workshop on improving use of animal models in studies of small vessel diseases in Glasgow in Jan 2017, supported by the British Heart Foundation, Royal Society of Edinburgh, Alzheimer's Research UK and DPUK. We have also guest 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, neuropathologists, medical physicists, neuroscientists and vascular biologists, clinical trialists and representatives from industry.



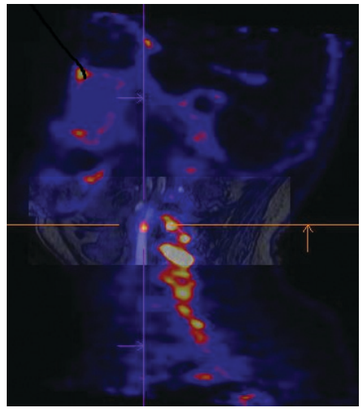


FIGURE 14: Researchers in the Vascular Mechanisms network use PET-MR imaging to show a PET tracer being taken up by a carotid plaque
Credit: Edinburgh Imaging QMRI & British Heart Foundation/University of Edinburgh Centre for Cardiovascular Science

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.

FIGURE 15: State-of-the-art PET-MR scanners are now ready to be used in multicentre imaging studies

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, as well how they regulate the neurons 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.

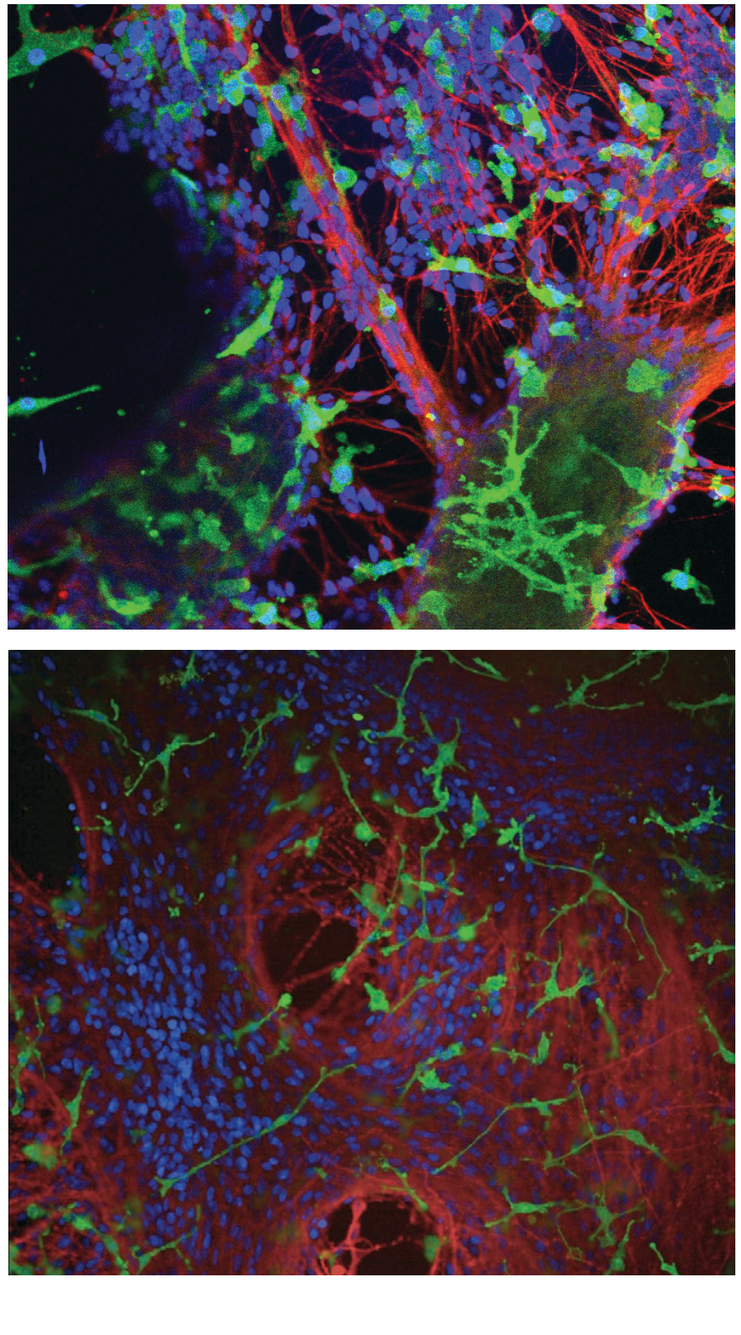


FIGURE 16: iPSC-derived microglia (green) in co-culture with iPSC-derived neurons (red) (nuclei are blue)
Image courtesy of Richard Wade-Martins / Stem cell reports

DPUK NETWORKS

INFORMATICS NETWORK

Network lead: Professor Simon Lovestone

We continue to develop an IT infrastructure which will allow for the storage and interrogation of the variety of data which is of most use to researchers investigating dementia.

A key focus of our work is the development of infrastructure to store and make use of complex data – from brain scans, wearable devices, post-mortem brains and genetic data. The imaging platform allows researchers to search imaging data that has been made available from cohorts via the central hub. Imaging data collected from the Deep and Frequent Phenotyping study (DFP) will be uploaded and made available to approved researchers through this platform. The wearables platform is being developed and will allow for data collected from a range of devices – gait sensors, GPS trackers, smart watches – to be stored centrally. As a study which collects a range of data, DFP will be the first to make use of this world-leading platform for the storage and integration of wearables data.

Work is progressing on the development of infrastructure to store and digitise data held by the brain banks. We are working on creating the technical capability to perform complex genetic analyses on DPUK data.

DPUK has supported the development of the CRIS platform, a database of de-identified patient records from 14 mental health trusts. As a platform which aggregates data from a number of separate trusts, CRIS represents a huge achievement as a resource for the research community. Work is currently in progress to link CRIS's clinical data with the UK Biobank cohort data.

Work continues to optimise these platforms and the data portal as a whole for use by the research community.

> A key focus of our work is the development of infrastructure to make use of the complex data collected from brain scans, brain banks and wearable technology.

GENETICS NETWORK

Genetics network lead: Professor Julie Williams

The Genetics network exists to facilitate research collaborations between cohorts wishing to carry out genetics-based research in any form.

The Genetics network was established this year. At our first meeting in May 2017, representatives from Edinburgh, Cardiff, Imperial, Brains for Dementia Research, Generation Scotland and UCL met to introduce their studies and plans for going forward. Since the initial meeting a number of possible collaborations have been identified. Researchers in Cardiff are working with the Chariot Pro cohort to expand their data collection with genotyping, data which Chariot Pro has not previously been funded to collect. This has led to the additional benefit of bringing another cohort into an ever-expanding Europe-wide genetics study - the Alzheimer Disease European DNA biobank (EADB).

Now that the genetics platform is live on the portal, we hope to continue to drive forward its development, to make it a research resource that is truly fit for purpose. We continue to meet regularly to share updates and identify potential new collaboration and funding possibilities.

EARLY CAREER RESEARCHER NETWORK

ECR champion: Professor Kim Graham

DPUK's Early Career Researcher (ECR) network was launched in May 2017, in a half-day workshop which took place the day before DPUK's annual scientific conference. The workshop was attended by ECRs from a range of universities who were able to feed into plans for how DPUK can involve ECRs in the work of the platform and facilitate more opportunities for ECRs.

Key themes to emerge from the workshop included the facilitation of networking opportunities, improvements to knowledge and skills, communications and career facilitators. DPUK's ECR champion, Professor Kim Graham, has consulted widely with other research funders and has set out recommendations for DPUK-focused activities in a paper which is under currently under review by the DPUK executive team. Updates on opportunities for ECRs will be shared through the DPUK newsletter and website.

Credit: Paul Tait

THE VALUE OF THE PUBLIC-PRIVATE PARTNERSHIP

Partnership has been at the heart of what we do since our inception in 2014. Researchers in academia and industry are benefiting from new perspectives brought about by the collaborations that DPUK facilitates. Dr Declan Jones and Dr John Isaac from Janssen Pharmaceuticals share their experience of the DPUK partnership.

Dr Declan Jones is a member of the DPUK executive team and was, until October 2016, co-lead (with Professor James Rowe) of the Synaptic Health network. Dr John Isaac took over co-leadership of this network when he joined Janssen in October 2016. The New Targets in Alzheimer's Disease study (NTAD) is funded through the Synaptic Health network and commences in November 2017.

Having been involved in DPUK from its initiation, we are experiencing first-hand the difference that DPUK is making to dementia research and the new opportunities that this innovative platform is providing for drug development.

The scientific and medical community is facing one of the biggest challenges of our time: how to prevent and treat Alzheimer's disease. Identifying new targets and developing new drugs is extremely difficult, and this is compounded by the very high cost and the long duration of clinical trials. In order to test the newest insights from research and development, our colleagues in industry and academia recognise the value of closer collaboration. This enables more rapid identification of drug targets, facilitates drug discovery and provides innovation in clinical biomarkers and clinical trial design.

However, collaborative research programmes also come with significant barriers: identifying the best collaborators and setting up the necessary legal agreements is often a lengthy process, particularly in cases where there is no precedent for work and studies of this type, and where multiple industry partners are involved. Also, as a result of the different worlds of academia and industry, there are significant hurdles in ensuring effective leadership and maximizing the output of such collaborative efforts.

In this environment, DPUK offers an opportunity as a platform for collaboration. Its networks are already bringing together scientists working on common themes and who share a passion for collaboration. DPUK's support for these networks, combined with the real prospect of cross-pharma and cross-academia collaborations supported by the DPUK infrastructure, is producing highly-engaged groups that are able to attract significant research resources to tackle difficult problems.

Through its legal framework, DPUK has set up pre-agreed conditions for collaboration, thereby facilitating such studies by minimising delay in establishing research agreements between members. DPUK has recognised the huge potential of patient cohort studies for Alzheimer's disease drug development and, by providing the forums in which our colleagues can develop new projects with partners in universities, it is invigorating the field, facilitating a much-needed new way of working and providing access to valuable new data resources from across the platform.

NTAD is one example of how this has worked well: this study, seeking to identify a new clinical biomarker for Alzheimer's disease progression based on magnetoencephalography (MEG), involves scientists at the universities of Cambridge, Cardiff and Oxford and at the pharma companies Janssen, Lilly, and MedImmune. The work is funded by research grants from DPUK, Alzheimer's Research UK and from funds and work-in-kind supplied by Janssen, MedImmune and Lilly as well as significant commitments from the universities. This is a great example of the collaborative spirit of DPUK and shows how DPUK is bringing the academic and industry communities together to address the challenge of dementia. There are similar examples in other areas of DPUK, and we hope that over the next few years this will be an increasingly common way to carry out research.

Dr John Isaac, Senior Director, Neuroscience External Innovations, Janssen Pharmaceuticals

Dr Declan Jones, Vice President, Neuroscience External Innovations, Janssen Pharmaceuticals

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DPUK's support for its networks is producing highly-engaged groups that are able to attract significant research resources to tackle difficult problems.

DPUK's academic and industry partners work together to drive the development of the platform's research infrastructure. We are also pleased to have links with the following organisations:

Find more information on the benefits of becoming a partner on the DPUK website

LOOKING FORWARD – PERSPECTIVE FROM THE MEDICAL RESEARCH COUNCIL

As described in the report, DPUK has made significant steps towards completing the setting up of infrastructure in informatics, imaging and stem cell lines which are core aims of the platform.

This infrastructure will enable dementia researchers from many sub-disciplines to have unprecedented access to the rich databases associated with diverse UK cohorts. The hope is that the accessibility provided by the data portal will encourage those not usually associated with dementia research to explore the data, bringing different perspectives and novel insights. The data from across the different cohorts can be compared and contrasted to gain further understanding of the environmental factors that contribute to the development or progression of dementia in individuals with varying degrees of genetic susceptibility.

The timely maturity of DPUK comes as the Dementia Research Institute (DRI), whose goal is to identify new targets for treatment of dementia, gathers momentum in its first year.

The timely maturity of DPUK comes as the Dementia Research Institute (DRI), whose goal is to identify new targets for treatment of dementia, gathers momentum in its first year. The multi-dimensional data gathered on individuals including genetics, imaging, lifestyle and other information will make possible early stage experimental medicine studies on well-characterised subjects with obvious benefits for understanding the impact of interventions. Dementia research in the UK is beginning to scale-up and add a much-needed sense of urgency to our attempts to understand how to diagnose, treat and prevent dementias, which have such a devastating impact on so many lives.

PUBLICATIONS

DPUK both funds scientific research and enables scientific research through its technology infrastructure and research group support.

Habitual exercise levels are associated with cerebral amyloid load in presymptomatic autosomal dominant Alzheimer's disease

Alzheimers Dement. 2017.

Brown BM, Sohrabi HR, Taddei K, Gardener SL, Rainey-Smith SR, Peiffer JJ, et al.

Presymptomatic atrophy in autosomal dominant Alzheimer's disease: A serial MRI study.

Alzheimers Dement. 2017.

Kinnunen KM, Cash DM, Poole T, Frost C, Benzinger TLS, Ahsan RL, et al.

Forced cell cycle exit and modulation of GABAA, CREB, and GSK3β signaling promote functional maturation of induced pluripotent stem cell-derived neurons

Am J Physiol Cell Physiol. 2016.

Telezhkin V, Schnell C, Yarova P, Yung S, Cope E, Hughes A, et al.

Multiplex High-Throughput Targeted Proteomic Assay To Identify Induced Pluripotent Stem Cells

Anal Chem. 2017

Baud A, Wessely F, Mazzacuva F, McCormick J, Camuzeaux S, Heywood WE, et al.

Study protocol: Insight 46 – a neuroscience sub-study of the MRC National Survey of health and development

BMC Neurology. 2017

Lane CA, Parker TD, Cash DM, Macpherson K, Donnachie E, Murray-Smith H, et al.

BDNF Val66Met moderates memory impairment, hippocampal function and tau in preclinical autosomal dominant Alzheimer's disease

Brain. 2016.

Lim YY, Hassenstab J, Cruchaga C, Goate A, Fagan AM, Benzinger TL, et al.

Inflammatory changes in very early Alzheimer's disease: friend, foe, or don't know?

Brain. 2016.

Schott JM, Fox NC.

Modeling the C9ORF72 repeat expansion mutation using human induced pluripotent stem cells

Brain Pathol. 2017

Selvaraj BT, Livesey MR, Chandran S.

Progressive Motor Neuron Pathology and the Role of Astrocytes in a Human Stem Cell Model of VCP-Related ALS

Cell Rep. 2017

Hall CE, Yao Z, Choi M, Tyzack GE, Serio A, Luisier R, et al.

Small vessels, dementia and chronic diseases–molecular mechanisms and pathophysiology

Clinical Science. 2016.

Wardlaw JM, Horsburgh K.

Hypercholesterolaemia and vascular dementia

Clinical Science. 2017.

Appleton JP, Scutt P, Sprigg N, Bath PM.

Using DTI to assess white matter microstructure in Cerebral Small Vessel Disease (SVD) in multi-centre studies

Clinical Science. 2017.

Croall ID, Lohner V, Moynihan B, Khan U, Hassan A, O'Brien JT, et al.

Reliability of an automatic classifier for brain enlarged perivascular spaces burden and comparison with human performance

Clinical Science. 2017.

González-Castro V, Valdés Hernández MDC, Chappell FM, Armitage PA, Makin S, Wardlaw JM.

Vascular basement membrane alterations and β-amyloid accumulations in an animal model of cerebral small vessel disease

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Held F, Morris AWJ, Pirici D, Niklass S, Sharp MMG, Garz C, et al.

Small vessel disease, neurovascular regulation and cognitive impairment: post-mortem studies reveal a complex relationship, still poorly understood

Clinical Science. 2017.

Love S, Miners JS.

Chronic cerebral hypoperfusion alters amyloid-β peptide pools leading to cerebral amyloid angiopathy, microinfarcts and haemorrhages in Tg-SwDI mice

Clinical Science. 2017.

Salvadores N, Searcy JL, Holland PR, Horsburgh K

New insights into mechanisms of small vessel disease stroke from genetics

Clinical Science. 2017.

Tan R, Traylor M, Rutten-Jacobs L, Markus H

Mechanisms of vascular disease in dementia: what does industry want to know?

Clinical Science. 2017.

Wren PB, Hill D, Lockhart A.

A review of key ethical and social issues in the development of Dementias Platform UK

DPUK Internal report. 2017

Atkinson S, Badger S, Milne R, Brayne C.

Assessing similarity to primary tissue and cortical layer identity in induced pluripotent stem cell-derived cortical neurons through single-cell transcriptomics

Human Molecular Genetics. 2016

Handel AE, Chintawar S, Lalic T, Whiteley E, Vowles J, Giustacchini A, et al.

Transcriptomic profiling of purified patient-derived dopamine neurons identifies convergent perturbations and therapeutics for Parkinson's disease

Human Molecular Genetics. 2017

Sandor C, Robertson P, Lang C, Heger A, Booth H, Vowles J, et al.

Neurological manifestations of autosomal dominant familial Alzheimer's disease: a comparison of the published literature with the Dominantly Inherited Alzheimer Network observational study (DIAN-OBS)

Lancet Neurol. 2016.

Tang M, Ryman DC, McDade E, Jasielec MS, Buckles VD, Cairns NJ, et al.

Guided self-organization and cortical plate formation in human brain organoids

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Mutations in valosin-containing protein (VCP) decrease ADP/ATP translocation across the mitochondrial membrane and impair energy metabolism in human neurons

J Biol Chem. 2017

Ludtmann MHR, Arber C, Bartolome F, de Vicente M, Preza E, Carro E, et al.

Booth HDE, Hirst WD, Wade-Martins R.
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J Exp Med. In press 2017.

Krejciova Z, Alibhai J, Zhao C, Krencik R, Rzechorzek NM, Ullian EM, et al.

Improving and accelerating the differentiation and functional maturation of human stem cell-derived neurons: role of extracellular calcium and GABA.

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Kemp PJ, Rushton DJ, Yarova PL, Schnell C, Geater C, Hancock JM, et al.

Neurons and neuronal activity control gene expression in astrocytes to regulate their development and metabolism

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Hasel P, Dando O, Jiwaji Z, Baxter P, Todd AC, Heron S, et al.

Presymptomatic cortical thinning in familial Alzheimer disease: A longitudinal MRI study.

Neurology. 2016.

Weston PS, Nicholas JM, Lehmann M, Ryan NS, Liang Y, Macpherson K, et al.

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Physics in Medicine & Biology. 2016.

Markiewicz PJ, Thielemans K, Schott JM, Atkinson D, Arridge SR, Hutton BF, Ourselin S.

iPSC-derived neuronal models of PANK2-associated neurodegeneration reveal mitochondrial dysfunction contributing to early disease

PLoS ONE. 2017.

Arber C, Angelova PR, Wiethoff S, Tsuchiya Y, Mazzacuva F, Preza E, et al.

Accuracy of routinely-collected healthcare data for identifying motor neurone disease cases: A systematic review

PLoS ONE. 2017.

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Mitochondrial hyperpolarization in iPSC-derived neurons from patients of FTDP-17 with 10+16 MAPT mutation leads to oxidative stress and neurodegeneration

Redox Biol. 2017.

Esteras N, Rohrer JD, Hardy J, Wray S, Abramov AY.

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Haenseler, W, Zambon F, Lee H, Vowles J, Rinaldi F, Duggal G, et al.

C9orf72 hexanucleotide expansions are associated with altered ER calcium homeostasis and stress granule formation in iPSC-derived neurons from patients with amyotrophic lateral sclerosis and frontotemporal dementia

Stem Cells. 2016.

Dafinca R, Scaber J, Ababneh N, Lalic T, Weir G, Christian H, et al.

ER stress and autophagic perturbations lead to elevated extracellular α-synuclein in GBA-N370S Parkinson's iPSC-derived dopamine neurons

Stem Cell Reports. 2016

Fernandes HJR, Hartfield EM, Christian HC, Emmanoulidou E, Zheng Y, Booth H, et al.

MAPT genetic variation and neuronal maturity alter isoform expression affecting axonal transport in iPSC-derived dopamine neurons

Stem Cell Reports. 2017

Beevers JE, Lai MC, Collins E, Booth HDE, Zambon F, Parkkinen L, et al.

Phenotypic screening identifies novel modulators of APP processing in human stem cell models of Alzheimer's disease

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Brownjohn PW, Smith J, Portelius E, Serneels L, Kvartsberg H, De Strooper B, et al.

A highly efficient human Pluripotent Stem Cell microglia model displays a neuronal-co-culture-specific expression profile and inflammatory response

Stem Cell Reports. 2017

Haenseler W, Sansom SN, Buchrieser J, Newey SE, Moore CS, Nicholls FJ, et al.

The role of astrocyte dysfunction in Parkinson's disease pathogenesis

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Extracellular monomeric and aggregated tau efficiently enter human neurons through overlapping but distinct pathways

In revision and online at bioRxiv. 2017.

Wassmer T, Evans L, Fraser G, Smith J, Perkinton M, Billinton A, Livesey FJ.

Dementias Platform UK
Medical Research Council

www.dementiasplatform.uk | portal.dementiasplatform.uk