Association of British Neurologists

Clinical Research Training Fellowship

November 2018

ABN Clinical Research Training Fellowship Scheme

The objective of the ABN's Clinical Research Training Fellowship scheme is to encourage the brightest UK neurology trainees in undertaking world-leading clinical neuroscience research for improving the care of those with neurological conditions and to develop new links between the funders of research and clinical trainees.

Research in clinical neuroscience lags far behind research in cancer and heart disease in funding and in the recruitment and retention of research personnel. It is vital that the next generation of neurologists is trained in research and discovery.

The ABN Clinical Research Training Fellowships support 3-year clinical research training fellowships in neurological disciplines resulting in a PhD. Each fellowship costs approximately £210,000 over the 3 years including £10,000 per annum allowance for consumables.

Since its launch in 2009 the scheme has supported the research projects of 25 new fellows. Brief summaries of the work of our 17 current fellows are given on the following pages.

We are grateful to all funders, reviewers, interviewers, administrators as well as applicants and supervisors who make this process possible.

Viorica Chelban	**ABN/Multiple System Atrophy Fellow 2017** **Institute of Neurology, London**

Defining clinical and genetic biomarkers in Multiple System Atrophy

The UK MSA clinical and sample bio-bank was created and to date includes 42 longitudinal cases, 54 cross-sectional cases, serum, plasma, CSF, DNA and RNA.

Results achieved and future research:

- Phenotype and Natural history. A comprehensive questionnaire and clinician review was completed for 94 MSA patients. A similar protocol was applied to patients with PSP and CBD for ultimately identifying differential clinical biomarkers in atypical parkinsonian disorders.
- MRI brain. 20 patients have baseline scans, 10 patients have 2 follow-up scans and 5 patients completed 3 yearly MRI. All patients had extensive neuropsychology assessment performed with each scan. The neuroimaging analysis is performed in collaboration with Dr John Rohrer, Dementia Research Centre.
- Serum and CSF. 20 CSF and plasma matched samples have been collected. The samples are prepared for biomarker's analysis in collaboration with the Institute of Neuroscience in Goteborg, Sweden and the UCL Leonard Wolfson Biomarkers Lab.
- DNA. MSA patients are undergoing whole genome sequencing as part of the 100 000 Genomes England Project. To date 32 MSA genomes have been generated. Recruitment will end in October and analysis will follow next year.
- RNA sequencing from blood tissue and brain tissue. The blood RNA extraction and sequencing was completed. The brain RNA extraction was completed for all 64 samples and will be sequenced next. Analysis of both blood and brain RNA will be performed in parallel.

Ingrid Hoeritzauer	ABN/Patrick Berthoud Charitable Trust Fellow 2015 Western General Hospital, Edinburgh

The Clinical Features and Prognosis of Scan-negative Uro-Neurological Disorder

I have completed recruitment for my prospective study and have written two drafts of the final paper. To optimise the study follow-up I will carry out a notes review in the next two weeks and add this to the current information. All other papers from the PhD have been written and submitted (n= 15) or are nearing submission (n=3). My PhD will be written around seven key papers which will be published (n=4 published, n=1 returned for corrections, n=2 draft). All papers and writing will be completed by November 2019.

With two neurosurgical colleagues we have commenced a prospective UK wide study of cauda equina syndrome in conjunction with the British Neurosurgical Trainee Research Collaborative (https://www.bntrc.org.uk/current-projects). To date 89 patients have been recruited and 40 centres have expressed an interest in taking part. We aim for 500 patients which will be the largest prospective study of cauda equina syndrome in the world.

After returning from maternity leave next year I will seek Post-doctoral research funding.

Grace McMacken	ABN/Guarantors of Brain Fellow 2015 Newcastle University

Adrenergic Signalling at the Neuromuscular Junction and Congenital Myasthenic Syndromes

My current research focuses on disorders of the neuromuscular junction, particularly congenital myasthenic syndromes (CMS).

My laboratory based research focuses on exploring the effect of treatments for these conditions in animal models, supervised by Prof Hanns Lochmüller. Using zebrafish models of myasthenic syndromes, we showed that adrenergic agonists have a direct effect on neuromuscular junction development and do so via a cyclic AMP and mediated pathway (McMacken *et al* Hum Mol Genet 2018). I am currently carrying out follow-up studies investigating the effect of these drugs in CMS mouse models.

My clinical research is aimed at characterising the involvement of the neuromuscular junction in inherited motor neuropathies, supervised by Prof Rita Horvath and Dr Roger Whittaker. Using detailed clinical and neurophysiological assessment, 14 patients with motor neuropathies with NMJ defects have been identified, including those due to defects in mitochondrial fusion-fission, synaptic vesicle transport, calcium channels and tRNA synthetises. The involvement of the NMJ may represent a novel therapeutic target in these conditions, and currently we are exploring the effect of therapies such as pyridostigmine and salbutamol in these cases.

In addition, I am involved in new CMS gene discovery and further clinical characterization of CMS subtypes. In collaboration with researchers at Inserm, Paris, we showed that mutations in *SLC5A7*, encoding the presynaptic choline transporter, cause a novel CMS with episodic apnoea (CMS-EA). In addition, we characterized a relatively large cohort of CMS-EA patients who were referred to our laboratory from around the world, providing new insights into the long-term outcomes of these patients (McMacken *et al* J Neurol 2017).

Thomas Cope	ABN/Patrick Berthoud Charitable Trust Fellow 2015 University of Cambridge

The Physiology of Dementia: network reorganisation in progressive non-fluent aphasia as a model of neurodegeneration

My PhD fellowship, funded by the ABN and Patrick Berthoud Charitable Trust, has been very successful, and its outputs have allowed me to obtain an NIHR clinical lectureship to continue my work. I have been involved in a large number of projects, which have yielded a large number of publications, but my main personal focus has been on three studies. Firstly, I conducted a magnetoencephalography study in non-fluent variant Primary Progressive Aphasia, which led to new insights into the way in which the brain makes predictions, especially for language. This work was published in *Nature Communications*. I have also conducted some follow-up work, rescanning the same patients after a two-year interval. This work is in preparation. Secondly, I combined data from positron emission tomography with a 'tau' tracer and resting-state functional MRI in Alzheimer's Disease and Progressive Supranuclear Palsy to examine the causes and consequences of tau accumulation in these diseases. This work was published in *Brain*, where widespread media coverage led to it being the most read-online paper ever published in that journal (273,832 HTML paper reads, 3,806 PDF downloads at time of writing). My oral presentation of this work at the ABN conference 2018 was awarded the Charles Symonds prize. Thirdly, in the final months of my fellowship I am conducting a 7-tesla fMRI study of language processing in non-fluent variant Primary Progressive Aphasia.

James Varley	ABN/Guarantors of Brain Fellow 2015 John Radcliffe Hospital, Oxford

The phenotype, spectrum and immunological mechanisms of neuronal surface antibody mediated diseases.

The initial aim of my DPhil was to look at the role of the immune system in neurodegenerative disorders, a strand of enquiry that was conducted in my first year and led to important negative findings. This did, however, necessitate a shift in the focus for the remainder my studies. During this time, I also contributed to Professor Irani's clinic, gaining exposure to patients with antibody-mediated neurological conditions. I became fascinated by these patients and pivoted towards working with them. This began with learning the literature, leading to two first author reviews and a clinical study, phenotyping the movement disorder in NMDAR-antibody patients, recently published in JNNP.

My second year comprised a combined clinico-immunological study of CASPR2-antibody patients. I collected a substantial cohort, with detailed clinical phenotyping and biological samples for further study. I developed a cell culture system to ask a wide variety of pertinent biological questions, a key result of which was underlining the importance of T cell help in the production of CASPR2 antibodies. The human leukocyte antigen (HLA), presents peptide-antigen to T cells, leading to their expansion and propagation of the immune response. Concomitantly we discovered a novel HLA association in patients with CASPR2 antibodies and this was recently published in Brain. The discovery of this HLA association, in combination with my previous work on in vitro lymphocyte culture models has meant I am uniquely placed to advance this work significantly and quickly, knowing the patients clinically and from a research perspective. To this end I am using the last few months of my fellowship to explore the T cell biology of these patients, with exciting results so far.

Nazia Karsan	ABN/Guarantors of Brain Fellow 2015 Kings College, London.

Investigating the premonitory stage of triggered migraine attacks using functional magnetic resonance imaging (fMRI)

This study aimed to investigate areas of brain activation during the premonitory phase of nitroglycerin (NTG) triggered attacks compared to baseline. The study has now closed to recruitment and I have obtained NTG-triggered premonitory and headache phenotypic data for 53 subjects. I have imaging data for the baseline-premonitory and baseline-headache comparisons for 25 subjects and have analysed most of the acquired data, which has now been written up for my PhD thesis and is also being prepared for publication of papers.

We have produced exciting results confirming increased regional cerebral blood flow in areas of interest in the premonitory stage of migraine, including the hypothalamus, midbrain and limbic areas. We have also provided supportive findings for the role of the thalamus, midbrain and pons during migraine headache. This study involves the largest cohort of subjects to date in the literature to be exposed to nitroglycerin on serial visits, with a view to phenotyping premonitory symptoms and headache and looking at the reproducibility of these phenotypes across serial exposures to nitroglycerin. We have evidence for moderate agreement in symptom reporting and headache laterality of triggered attacks in comparison to spontaneous attacks, as well as agreement for many symptoms across different episodes of nitroglycerin triggering. In addition, we have been able to provide some quantitative evidence for alterations in alertness and fatigue that patients commonly report in the lead up to a migraine compared to baseline using validated questionnaires.

As a result of the findings of this study, going forwards, I hope to be able to look at the effects of intravenous aspirin and subcutaneous sumatriptan as effective migraine abortive agents on the areas of brain activation seen during pain, as well as any other changes that these agents may induce, to attempt to assess how these painkillers work in migraine and to attempt to correlate the brain findings after headache resolution with clinical symptoms that can persist once pain has resolved.

Thomas Massey	ABN/Patrick Berthoud Charitable Trust Fellow 2016 Cardiff University

Disease-modifiers in Huntington's disease

Huntington's Disease (HD) is a life-shortening autosomal dominant neurodegenerative disease characterised by chorea, psychiatric disturbance, and dementia. It is caused by a CAG repeat expansion in the *HTT* gene. Previous work has implicated DNA repair processes in triggering CAG repeat expansion in striatal neurons, thereby accelerating onset of HD.

We have used exome sequencing in 500 HD patients with particularly early or late onset disease to show that there are variations in the CAG repeat sequence associated with early or late onset disease. In addition, there are multiple other trans-acting variants that are linked to altered disease onset. Many of these are in DNA repair pathways.

In addition, we have been developing a cell model of HD with 109 CAG repeats. We have shown that this repeat is unstable in cell culture and it therefore provides a good platform for testing our variants of interest. We have engineered an isogenic control line (with 20 CAG repeats) and are introducing our DNA repair variants using CRISPR/Cas9 techniques. Cells will be assayed for repeat instability and various downstream phenotypes including DNA damage and repair, mitochondrial and lysosomal function, and synapse formation.

Anne-Catherine Huys	ABN/Patrick Berthoud Charitable Trust Fellow 2016 Institute of Neurology, London

Attention and functional movement disorders: its role in symptom generation and sense of agency

Functional (psychogenic) movement disorders are involuntary, abnormal movements,

such as tremor or paralysis, that are illogical in terms of classical neurology. Intriguingly, they typically manifest when patients pay attention to them and disappear with distraction. We hypothesise that misdirected attention brings about these abnormal, involuntary movements. Instead of focusing on the goal, on the desired outcome, patients direct their attention onto the movement itself, onto "how" to perform it, thereby hampering its automatic execution. The results so far show that functional tremor improves when patients are distracted, when they move quickly, and when they perform a movement that appears to be of no importance. The next step is an fMRI study which will evaluate the effects of different attentional foci on brain activation. The idea is to show that commonly found abnormal activation patterns might in fact be caused by abnormal attentional foci. If misdirected attention is implicated in functional movement disorders, changing its focus would offer a simple and effective treatment strategy.

James Hrastelj	ABN/Guarantors of Brain Fellow 2016 Cardiff University

Gene expression regulation in Multiple Sclerosis susceptibility and severity

The aims of my PhD are:

1. To identify genes that are regulated by the MS genetic risk variants and so provide a more accurate picture of the genetic basis of MS.
2. To identify genetic variants that associate with MS disease severity.

Aim 1: I have completed sample collection from over 100 patients. I have sorted CSF and peripheral blood cells by FACS (to isolate CD4* and $CD8^{+}$ T-cells) and extracted RNA and DNA. I have commenced cDNA library preparation and sequencing. Bioinformatic pipelines have been optimised for differential gene expression and QTL analysis and I have gained substantial training in bioinformatics skills and statistics. I am currently optimising my skills to perform TWAS (transcriptome-wide association study). Which will allow me to correlate gene expression with genotype.

Aim 2: I have completed a GWAS of time to EDSS 6 in a pilot cohort of 509 patients with MS. Through building a collaboration with Prof George Davey-Smith's and Prof Yoav Ben-Shlomo's groups at Bristol University, I have been able to genotype a further 1149 patients and am currently repeating the GWAS on the larger cohort and meta-analysis.

Mark Ellul	**Association of British Neurologists Fellow 2016** **University of Liverpool**

Improving the diagnosis of encephalitis through examining whole proteome and host gene expression patterns.

Encephalitis is often associated with an acute infection or an autoimmune process, but in up to two thirds of cases the cause is unknown. In my fellowship, supervised by Prof. Tom Solomon, I am exploring whether the diagnosis of encephalitis can be improved by using novel approaches to examine the host response.

Through the multicentre Brain Infections UK network, we have recruited patients with infectious and autoimmune encephalitis, and with encephalitis of unknown cause. Following diagnostic testing, I have used mass spectrometry and NMR spectroscopy in 90 patients to examine whole proteome and metabolite profiles in the cerebrospinal fluid (CSF) of patients with infectious and autoimmune encephalitis, along with disease controls. In parallel, I have used human gene microarray to explore host gene expression patterns in RNA-stabilised blood samples.

Currently, I am working with the Computational Biology Facility at the University of Liverpool to analyse and integrate these data. This will allow the determination of the best markers to distinguish infectious from autoimmune encephalitis, which can be applied to our cohort of samples from encephalitis of unknown cause. Through pathway analysis we will also gain new insights into encephalitis pathogenesis.

Stephen Keddie	**ABN/Guarantors of Brain Fellow 2017** **Institute of Neurology, London**

Investigating the pathological mechanisms underlying the neuropathy in POEMS syndrome

With the help of the ABN RaDAR scheme, I have compiled a database of the clinical features, investigation results and treatment of 85 POEMS patients, the largest reported cohort in Europe, and am currently submitting a paper on the natural history of POEMS syndrome including prognosticating factors and treatment outcomes. I have set up a biobank of inflammatory neuropathy patients' serum at the ION, including the POEMS cohort for research use. We now have over 1500 samples stored from a range of conditions.

I have received training in commonly used neuroimmunological laboratory techniques, and am currently setting up a multiplex ELISA to be used in meso-scale discovery for peripheral nerve neurofilaments. These are hypothesised to be useful clinical biomarkers in determining axonal vs demyelinating disease, disease severity +/- prognosis.

I am also attending the John Radcliff hospital and learning how to produce HiPSC derived sensory neurones in myelinating co-culture, which will be a useful technique for the final stage of my research project.

Looking forward, the next steps are to use the meso-scale discovery system to examine 36 common serum cytokines which we suspect may be implicated in POEMS serum, providing further insights into the pathogenesis, then performing mass spec for biomarker discovery into other unknown potentially pathogenic molecules before utilising the HiPSC system to investigate the effect of such molecules on a peripheral nerve in system.

Robert Hurford	ABN/Patrick Berthoud Charitable Trust Fellow 2017 University of Oxford

Utility of second-line investigations in TIA and non-disabling ischaemic stroke at older ages: clinical and health economic considerations

I have been actively involved in ongoing collection of data in the Oxford Vascular Study, which will contribute to the datasets on which my research is based. I have also started a number of projects which will form my thesis. These are:

1. Analysis of the long-term predictive value of diffusion-weighted MRI for risk of recurrent stroke. This work has been submitted as an article to *Neurology* and is under peer-review.
2. An age stratified analysis of the burden on intracranial stenosis in minor stroke and TIA patients. This work has been presented as a conference poster and I am currently updating the cohort.
3. Assessing the utility of MRI in the clinic settling to identify stroke mimics. I am currently establishing this project which will contribute to the discussion on clinic funding and resource allocation.
4. Updating the work on the use of bubble-TCD to detect patent foramen ovale in older minor stroke and clinic patients. This will include an economic evaluations which will be important for future clinical trials in this area.
5. Updating and analysing work on the predictors and prognosis of cerebral microbleeds in older ages.

Evan Edmond	ABN/Dunhill Medical Trust 2018 University of Oxford

Biomarkers and Modulation of Cortical Hyperexcitability in ALS

Amyotrophic lateral sclerosis (ALS) is a fatal condition involving degeneration of the motor system of the brain and spinal cord. At least 5000 people in the UK live with ALS, and many more bear the physical and emotional burden of their care. The average time from first symptoms to death is 3 years. Around 10% of all cases of ALS are caused by a specific genetic mutation. New medications, including revolutionary genetic treatments for ALS, are being actively developed. To show that they are effective, sensitive markers of disease activity (**biomarkers**) are urgently needed.

The motor output of the brain is over-active in ALS, referred to as cortical hyperexcitability. I will use advanced MRI scanning techniques as a source of biomarkers for cortical hyperexcitability. I will also attempt to reduce the brain's motor excitability in ALS patients using a technique called non-invasive brain stimulation.

I will study a group of affected people carrying the abnormal genetic code, and a group with the same gene who have not yet developed the disease. By comparing these groups, I hope to identify the earliest disease changes. Future treatments might then target the disease before a person is aware of weakness. Sensitive biomarkers for those already affected by ALS will help to make clinical trials faster and cheaper, accelerating the prospects for better treatments.

Iain McGurgan	ABN/Stroke Association/Sobell Foundation 2018 University of Oxford

Blood pressure and cerebral artery pulsatility in small vessel disease-related TIA and ischaemic stroke

Stroke is the second leading cause of death worldwide, and high blood pressure (BP) is the most important treatable factor that increases a person's risk of suffering a stroke. Stiffness of the blood vessels supplying the brain, possibly due to long-standing raised BP, is also likely to be a factor that increases stroke risk. Such increased stiffness results in the blood flow through these vessels being more pulsatile than usual, and this pulsatility can be assessed by an ultrasound scan. This research is focused on assessing the relationship between this pulsatility and the risk of stroke in patients who have already had a stroke or "mini-stroke" in the past, and in particular to see if this relationship can be explained by raised BP alone. The Oxford Vascular Study (OXVASC) recruits all patients with stroke or "mini-stroke" from a single population, and shortly after such an event, participants undergo multiple investigations including an ultrasound assessment of pulsatility. They are provided with a home monitor that sends results wirelessly to our unit and facilitates detailed measurement of BP, and are followed up at regular intervals to assess for possible recurrent events. The OXVASC study represents an ideal opportunity to investigate the risk of stroke associated with BP and arterial stiffness, and this will allow us to better assess patients' risk and identify possible new treatments for reducing arterial stiffness and stroke risk.

Jeremy Johnson	ABN/Guarantors of Brain 2018 University College London

Hearing impairment in dementia: defining deficits and predicting impact

Scope. Hearing impairment has been linked to clinical deterioration in dementia, with immense implications for public health and potentially opportunities for treatment. However, important questions remain: are hearing changes in dementia due primarily to deafness or altered brain processing of sounds? How does this relate to symptoms and daily life impact in different diseases? How does hearing impairment affect disease course and brain damage? My Fellowship aims to: i) assess and compare different aspects of hearing in patients with Alzheimer's disease and primary progressive aphasia, a major dementia of middle life that profoundly affects processing of speech and other sounds; ii) establish how hearing changes relate to clinical symptoms, disability and care burden; iii) assess whether hearing impairment drives disease course, clinically and in the brain Methods. I will use a new, comprehensive test protocol to assess hearing and auditory brain functions systematically and over time in patients versus healthy older people. Associated brain changes will be assessed using MRI scanning. New hearing measures will be compared with standard hearing tests and measures of dementia diagnosis and impact.

Outcomes and timeframe. Within the lifetime of my Fellowship, this work will generate new tools and markers that define and predict the clinical and brain impact of hearing impairment in major dementias, and how this affects the daily lives of patients and caregivers. Over the next five to ten years, my findings will inform future clinical trials and interventions for improving communication and auditory environments in people with dementia.

Sam Shribman	ABN/Guarantors of Brain 2018 University College London

Biomarker discovery for neurological Wilson's disease in preparation for novel therapies

Wilson's disease (WD) is an inherited movement disorder that causes abnormal copper accumulation in the brain and/or liver. Current treatment involves copper-binding medication to remove excess copper from the body and is required lifelong. Some patients respond well to this treatment but others deteriorate despite treatment or develop debilitating side effects. New treatment approaches aiming to fix the underlying gene defect are in the early stages of development however our inability to monitor disease activity in the brain will limit our ability to test these therapies in a clinical trial. An exact role for magnetic resonance imaging (MRI), cerebrospinal fluid tests or other measures of brain damage, commonly used in other neurological disorders, is unclear.

In this study we aim to identify new approaches to monitoring neurological involvement in WD in order to prepare for clinical trials of new treatments. We will perform clinical assessments in combination with novel MRI techniques, blood tests and urine tests in 30 WD patients with neurological disease and 10 WD patients with liver disease (and without neurological involvement). We will then repeat this for each patient after 12-18 months to assess for any improvement or deterioration. We will perform lumbar punctures to sample the cerebrospinal fluid in a subset of patients.

Through identifying which novel MRI techniques, blood tests and cerebrospinal fluid tests measure disease activity in the brain we aim to enable trials for novel WD therapies within ten years and refine current management within the next five years.

Bo Sun	ABN/Patrick Berthoud Charitable Trust Clinical Research Training Fellow 2018 University of Oxford

Investigating T-Lymphocyte Function across Neuronal Surface Antibody associated Diseases

An increasingly common group of autoimmune diseases of the brain and nervous system are now recognised to be caused by antibodies. Antibodies are produced by a population of white blood cells called B-cells and, normally, play an important role in the body's ability to fight infection. However sometimes the immune system becomes confused and attacks our own body in a process termed 'autoimmunity'.

My research aims to explore and understand why the immune system attacks our own body in neurological diseases caused by antibodies. I will be focusing on a group of white blood cells called T-cells, which regulate the production of the B-cells producing self-attacking antibodies. If we can identify the reasons why these immune safety nets fail, we can then explore ways in which to manipulate them to stop the disease process. Taking samples from patients with varying degrees of disease severity, I will systematically isolate subgroups of T-cells and directly assess whether they alter autoantibody production by B-cells. This will provide valuable information into how T-cells fail to stop disease-causing B-cells. It will also identify cell subsets that could be targeted to ameliorate these diseases. This is a viable therapeutic aim, as drugs already exist to target these cell types and could be translated to this cohort within 3 years. By working in a group with a very active clinical programme, I will also learn to assess and treat patients with these illnesses.

Further information

ABN Fellowship process 2019

- October 2018: Opened for applications
- 18 November 2018: 25 applications received
- Nov—mid January 2019 Review process
- February 2019 Shortlist confirmed
- 20 March 2019 Interviews

Since the fellowship scheme was launched in 2009 the ABN has worked with a range of funding partners including individual patient charities seeking to support disease specific neurological research projects (MSA Trust, the Stroke Association, Multiple Sclerosis Society, Encephalitis Society , Parkinson's UK) as well as neurological charitable bodies keen to award fellowships on a disease agnostic basis (Guarantors of Brain, Patrick Berthoud Charitable Trust).

To learn more about the ABN Clinical Research Fellowship Scheme, please contact us via:

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ABN fellows' poster session, ABN Birmingham Meeting 2018