Association of British Neurologists

Clinical Research Training Fellowship 2015

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

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

My research will focus on two conditions. 1) Cauda Equina Syndrome (CES) describes damage to the nerves in the lower back which supply bladder, bowels, sexual function and the legs usually from slipped discs in the spine and 2) Chronic Idiopathic Urinary Retention including Fowler's syndrome where the person is unable to urinate and often requires catheters or surgery although the cause remains uncertain.

CES is as common as multiple sclerosis and is diagnosed using an MRI scan of the spine. However about 50% of people presenting with the symptoms of CES have MRI scans which do not explain their symptoms, 'scan negative' patients. These patients are typically not given an explanation and are baffled by their disabling symptoms. I will carry out the first large clinical study focusing on neglected 'scan negative' CES patients to investigate why patients have weak legs and bladder problems when there is no abnormality on the tests. I will study patients with chronic urinary retention in a similar way. We think some patients from both groups may have a functional neurological disorder which currently goes undetected but could be usefully diagnosed and treated with treatment like physiotherapy. Some other patients may have nerve root damage which is not picked up on MRI scanning and would require a different approach. Our key goal is to increase knowledge, awareness and treatment of these disorders thus improving quality of life.

Thomas Cope	ABN/Patrick Berthoud Fellow 2015 Cambridge

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

There is a long history of research on the thinking difficulties that occur in different types of dementia. Recently there have also been exciting discoveries about what is happening to brain cells as they become damaged by dementia. However, less is known about how to connect the changes in brain cells to decline in mental abilities such as language and memory.

I will concentrate on a condition called progressive non-fluent aphasia (PNFA), which is a type of frontotemporal dementia. This is an ideal 'model' to study disease because we know a lot about the brain networks for hearing and language that are damaged by this particular type of dementia. I will use two different advanced types of brain scanning. This will allow me to combine their advantages to measure what is going wrong in the way that groups of cells communicate with each other in the brain.
This work, studying the way that the brain is connected in PNFA patients, will tell researchers and doctors developing new treatments for dementia how changes within cells can lead to the difficulties experienced by patients. This will:

- help study the earliest stages of disease when reorganisation and compensation in the brain networks means that people have relatively mild symptoms

- allow more sensitive assessment of the effectiveness of potential new drugs
- allow them to improve animal, laboratory and computer models of dementia
- improve the information we are able to give to patients about why their disease causes them particular problems
- potentially identify new targets for drugs

Additionally, this work will be of use to scientists who are interested in how the brain normally processes language, and how it makes predictions.

Grace McMacken	Guarantors of Brain/ABN Fellow 2015 Newcastle

Adrenergic Signalling at the Neuromuscular Junction and Congenital Myasthenic Syndromes

The body's sympathetic nervous system, its "fight or flight" response, can be modified by drugs for many medical purposes; in heart disease, high blood pressure and asthma for example. Congenital myasthenic syndromes (CMS) are a group of genetic diseases in which affected individuals experience muscle weakness, which is usually apparent at birth or in early childhood. Affected individuals may have severe disabilities, as well as weakness in muscles needed to breathe or swallow. Drugs acting on the sympathetic nervous system have been shown to be helpful for some patients with CMS with improvement of muscle strength and function for walking and breathing. However, it is not clear how these drugs work nor why they only work for certain types of CMS. In addition, the use of these drugs can be inhibited as patients often experience "fight or flight" side effects such as anxiety or accelerated heart beat.

In order to understand how these drugs work, I will study the precise effects of these drugs on cell and animal models. In doing so we will gain understanding of which individuals with muscle weakness should be given these drugs. If we can explain how these drugs act on neuromuscular junctions we may also be able to help many other conditions in which muscle weakness or fatigue is a symptom. This research will also aid development of new therapies that can treat muscle weakness without activating the body's fight or flight response, and therefore reduce the side-effects of these potentially life-saving treatments.

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

Investigating brain representation of premonitory symptoms in migraine using functional magnetic resonance imaging

I am trying to study how the brain represents the symptoms that many encounter before the start of a migraine headache (the premonitory symptoms), as well as the pain itself. Premonitory symptoms can include thirst, fatigue, neck stiffness, cravings and yawning. I am assessing the brain representation of these symptoms using a technique called Functional Magnetic Resonance Imaging (fMRI), by scanning migraine brains throughout an attack, from the premonitory symptoms through the headache to post-treatment with aspirin, after triggering an attack using a drug called nitroglycerin. The study is being conducted so that I and the participants do not know which treatment subjects are receiving (double-blinded). On some study visits, participants may not receive an active drug trigger or drug treatment (placebo-controlled).

I am interested in seeing how the areas of brain activity change during different phases of the attack, from the very early stages in the absence of pain through the headache to the post-treatment recovery phase. I am using intravenous aspirin as this is a known painkiller which does not work on blood vessels or blood flow.

I hope that this study enables understanding of the mechanisms behind the early symptomatically diverse phase in migraine, and for the first time, allows brain imaging throughout an entire attack. Assessing imaging changes in response to treatment, and

correlation of these changes with subjective pain experience and other symptomatology may enable understanding of how effective painkillers work, and allow future therapeutic development.

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

Neuronal-surface directed antibodies in parkinsonian syndromes.

Antibodies are designed by the body's immune system to protect against infection. However, clearing the infection, sometimes they bind to the body's own proteins. When this is a brain protein, an autoimmune brain disease can result. Recently, we identified patients with symptoms similar to Parkinson's disease (PD) with brain-reactive autoantibodies. We would like to ask whether these antibodies are also found in patients with PD and related disorders.

PD is the second most common degenerative brain disease, with an aging population it is set to become even more common. No disease-modifying treatments currently exist.

We will collaborate with the Oxford Parkinson's Disease centre to test blood and spinal fluid samples from their bank of patients with PD. We will apply contemporary techniques, developed in Oxford, to detect autoantibodies which specifically target the outside of brain cells in patients with PD. This is important as only antibodies which target proteins on the outside of cells can access their targets in living patients. Importantly, these antibodies with disease-modifying potential can be removed from patients with existing immunotherapies.

By correlating our findings with clinical information, we can determine whether autoantibodies are present at disease onset, if they predict a different disease severity and if they affect the course of their disease. The presence of autoantibodies may offer a disease-modifying treatment for patients, help us understand which patients to treat more intensively from onset, and act as a marker to give patients much more information about their disease progression.