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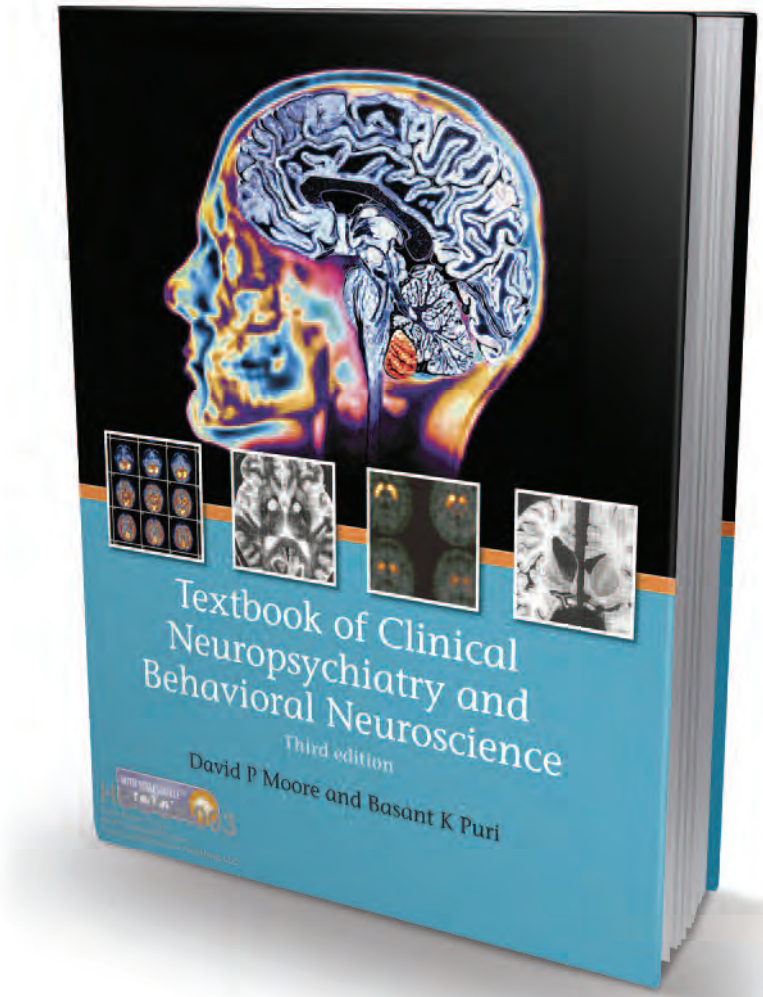

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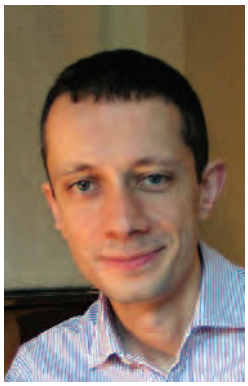

Mike Zandi, Editor.

In this first issue of 2014, Camilla Clark and Jason Warren from the Dementia Research Centre, UCL review the neurology of humour in the healthy and diseased brain. They explain the functional imaging and electrophysiological evidence for humour's subdivision into separable neural correlates, and show us how the study of the appreciation of humour can provide an opportunity to examine a range of diseases of the brain. Michael Parkinson, Fion Bremner and Paola Giunti, from UCL, write a comprehensive review on Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS), which is increasingly recognised as an important cause of genetic ataxia, and not as rare as had been thought. The characteristic retinal features seen on optical coherence tomography are described by Fion Bremner. Alex Leff, from the Institute of Neurology and Institute of Cognitive Neurology, UCL, reviews the innovative advances in rehabilitiation for language and vision recovery after stroke, including web based therapies, and his article is introduced by David Werring on page 26. Anish Bahra introduces our headache article, written by Philip Holland, from King's, and Shazia Afridi from Guy's and St Thomas' Hospitals, which provides a clear review of the latest evidence for the pathophysiology of the symptoms of migraine, focusing on abnormal sensory processing mechanisms.

We have two articles on Parkinson's Disease. James Shine and Simon Lewis, from Sydney, write a clear overview of their model of the mechanisms underlying freezing of gait in Parkinson's Disease, and Andrew Larner, from the Walton Centre for Neurology and Neurosurgery, dissects the few earliest descriptions of what may have been Parkinson's disease before the publication of *An Essay on the Shaking Palsy* in 1817. Angelos Kolias and colleagues from the British Neurosurgical Trainees Association (BNTA) describe their development of collaborative trainee-driven research networks in neurosurgery and the studies already underway. We have our usual conference, book and journal reviews, and hope you continue to enjoy ACNR into 2014.

Mike Zandi, Editor.
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Juliet Ashton Appointed as First Ever National Commissioning Nurse for Epilepsy

The first ever 'national' commissioning nurse for epilepsy has been appointed. As Sapphire Nurse Consultant for Epilepsy Commissioning, Juliet Ashton will be providing expert advice and support to Clinical Commissioning Groups. The aim of this is to improve local services and outcomes for people with epilepsy.

The role is the first of its kind for neurology. It is the brain child of voluntary organisations, Neurological Commissioning Support and Epilepsy Action. Epilepsy Society and Epilepsy Action are providing the funding.

Juliet has more than 25 years' experience in neurology nursing, including specialist nursing roles in multiple sclerosis, acquired brain injury and Parkinson's.

2013 Linacre Medal winner

Miratul Muqit has been awarded the 2013 Linacre Medal and Prize Lecture of the Royal College of Physicians. The award recognises recent advances Dr Muqit and his group have made in the molecular mechanisms underlying Parkinson's disease. Dr Muqit is a Wellcome Trust Senior Clinical Fellow at the MRC Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee and a Consultant Neurologist at Ninewells Hospital. His research aims to uncover how mutations in rare genes lead to neurodegeneration in Parkinson's and exploit this knowledge to develop novel ideas for therapy and diagnosis.

Alzheimer's Research UK grants Bath scientist funds for new dementia study

$1 million has been awarded to Imperial College to set up a Stroke Centre of Research and Training Excellence in Doha, Qatar. The money will not only lead to the creation of the first such centre in the Middle East but also will establish a highly characterised DNA biobank for haemorrhagic stroke. This award comes on the back of an existing $1million grant last year to establish the largest ischaemic stroke DNA repository in this region of the world.

The PI for both awards, Pankaj Sharma, who leads the Imperial College Cerebrovascular Research Unit (ICCRU) said he was "delighted with both grants which allow us, for the first time, to study the mechanisms that cause stroke in Middle Eastern and Asian populations and allow us to compare and contrast these mechanisms with those from Caucasian ancestry. Ethnic minority stroke has been grossly under investigated and this highly characterised biobank will be an important resource for scientists from across the globe for years to come." The Qatari Stroke Research Centre will also be a single and central source for research and training in stroke in Qatar. Pankaj Sharma is to be appointed its Director.

To feature your awards news here, Email Anna@acnr.co.uk

ERRATUM

We apologise for the incorrect numbering of the issues in Volume 13.
Issue number 3 was omitted, so this last issue in the volume is number 7, not number 6.
Normal numbering will resume with the next issue being Volume 14, number 1, March/April 2014. Apologies for any confusion this causes.

New Insights into the Pathophysiology of SUDEP – Results from the MORTEMUS Study

Reviewer: Dr Aidan Neligan, UCL Institute of Neurology, Queen Square, London, UK.

Sudden unexplained death in epilepsy (SUDEP) is the most common epilepsy-related cause of non-accidental death in adults with refractory epilepsy. It is estimated that the incidence is approximately four deaths per 1000 patient-years which translates into a 12% cumulative risk over 40 years for people with uncontrolled childhood-onset epilepsy. It is well-recognised that the incidence of SUDEP is higher in more severe epilepsy and in people with generalised seizures. It is also more likely to occur at night with nocturnal supervision suggested to have a protective effect. Whilst SUDEP is believed to be a post-ictal event, with the few documented cases of witnessed of SUDEP occurring in the aftermath of a generalised convulsive seizure, the exact pathophysiology and risk factors for SUDEP are poorly understood.

Philippe Ryvlin and colleagues carried out a retrospective survey of 147 epilepsy-monitoring units in Europe, Israel, New Zealand and Australia (the MORTality in Epilepsy Monitoring Unit Study (MORTEMUS)) between 1st of January 2008 and the 29th December 2009. In total 29 cardiorespiratory arrests were reported, of which 16 cases were classified as eight definite (SUDEP for which post-mortem examination failed to reveal a cause) and eight possible (SUDEP for which post-mortem examination was not available, with no other suspected cause) SUDEP. There were nine cases of near SUDEP (whereby patients survived resuscitation for more than one hour after the cardiorespiratory arrest) and four cases of deaths from other causes.

The 29 events were reported by 27 different units from 11 countries, with all non-monitored SUDEP and fatal near SUDEP occurring at night in a unit where nocturnal staff numbers were at a level comparable to a standard neurological ward. In all but one case of monitored SUDEP, the event occurred between 19:30 and 06:00. Cardiorespiratory resuscitation (CPR) was performed in 11 of the 16 cases of SUDEP and all cases of fatal near SUDEP with an average delay greater than 10 minutes after the initial apnoeic episode. In contrast CPR was initiated within three minutes of all cases of near fatal SUDEP, six of which occurred during the daytime.

In all assessable cases a seizure occurred immediately before the cardiorespiratory arrest, which was a generalised tonic clonic seizure (GTCS) in all SUDEP cases and seven of the nine near SUDEP cases. Tapering or cessation of anti-epileptic drugs (AEDs) (in order to capture a seizure) occurred in nine cases of GTSC-induced cardiorespiratory arrest, none of whom had a GTCS in the preceding three months. Respiratory distress was observed in almost all cases of SUDEP prior to terminal arrest underlining the compulsory need for the use of pulse oximetry alarm systems on all epilepsy monitoring units. The risk of definite or probable SUDEP per 10,000 video EEGs was 1.2 (0.6-2.1) in adults; 2.1 (1.0-3.8) in those undergoing pre-surgical evaluation compared to 0.2 (0.0-1.2) undergoing vEEG for other reasons.

Several conclusions can be inferred from this study: 1) The majority of cases of SUDEP occur at night mandating improved levels of nocturnal supervision on epilepsy monitoring units 2) All cases of observed SUDEP occurred in the aftermath of a convulsive seizure 3) Tapering or cessation of AEDs is a clear risk factor for SUDEP 4) Breathing difficulties are a prominent feature in the sequence of events preceding cardiorespiratory arrest in all cases of SUDEP. The routine use of pulse oximetry monitoring systems should be mandatory on all epilepsy monitoring units.

Ryvlin P, Nashef L, Lhatoo SD et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013;12:966-77.

Long-Term Cognitive Impairment After Critical Illness

Reviewer: Sian K Alexander, Addenbrooke's Hospital, Hills Road, Cambridge, UK.

Cognitive impairment is often seen in patients following admission to critical care units, and anecdotally acknowledged to be common amongst physicians. However, studies of the incidence and causes of this cognitive impairment have been lacking, and where performed have been generally small in size and limited in scope. In this paper, Pandharipande et al describe a robust multi-centre study of 821 patients enrolled at the time of ICU admission. They assess pre-morbid cognition using a quantitated informant questionnaire, measure duration of delirium using research-trained observers and quantify doses of major classes of centrally-acting drugs (including benzodiazepines, propofol and other analgesic and sedative medications). Outcome measures of global cognitive performance (using the Repeatable Battery for the Assessment of Neuropsychological Status, RBANS), and executive function specifically, were assessed at three and twelve months. Patients with severe cognitive impairment were excluded from the study, and only 6% of the studied cohort had pre-existing cognitive impairment.

Twelve months after ICU admission, 34% of patients had cognitive impairment akin to that of moderate traumatic brain injury (TBI), with 24% of these patients having cognitive impairment two standard deviations below the mean, equivalent to mild Alzheimer's disease.

Observed length of delirium was directly correlated with long-term cognitive impairment, which will be unsurprising to many. The relationship between delirium in the context of acute illness and long-term cognitive impairment remains an area of active investigation. It is unclear whether a set of risk factors predispose a patient to both, or whether the specific toxic insults in delirium, and associated response of neurohormones and cytokines, mediate neuronal pathophysiology with longer-term sequelae. A more surprising finding was that cognitive outcome was not related to exposure to sedative and analgesic medication, contrary to my intuitive hypothesis. Importantly, young patients (aged 49 years or younger) were not exempt from the risk of cognitive impairment; similar rates were seen in young and older patients alike.

This study provides important information on the frequency of cognitive impairment in the critical-care setting and does well to achieve follow-up in this cohort at twelve months. The relationship between critical illness and long-term cognitive impairment is an important subject for research, not least because it is one that acutely affects rehabilitation in patients and the perception of recovery for patients' families. This study provides important information on the frequency of cognitive impairment in the critical-care setting and does well to achieve follow-up in this cohort at twelve months. Nevertheless, further work to evaluate the profile of cognitive impairment over longer periods of time remains an important area to address: do patients experience progressive impairments akin to those with sporadic Alzheimer's disease? Or is this a static or even reversible phenomenon? This information is important to guide rehabilitation strategy and counselling of patients and families. Finally, although this study did not identify any protective strategies for the prevention of cognitive impairment, this would be an interesting avenue for further research.

Pandharipande PP, Girard TD, Jackson JC et al (BRAIN-ICU Study Investigators). Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369:1306-16.

Hands up if You're Better

Reviewer: Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals NHS Foundation Trust.

The measurement and quantification of improvement is fundamental to the process of rehabilitation. Ensuring that specific interventions and approaches work as opposed to "seeming to" work is important in meeting patient's needs. Or is it?

This study looks at the changes in upper limb function that can follow a stroke and compares quantified improvements on standardised scales with patient perceptions of improvement.

Because upper limb function is complex

and multi-dimensional, there is no single scale that can adequately capture impairment and change. There is a difficulty, therefore, in knowing how well our attempts at measuring improvement or response to therapeutic interventions actually relate to an individuals own view of their impairments and consequent disabilities.

The "objective" scale used as a comparator, here, is the Action Research Arm test (ARAT), which evaluates common upper limb movements that form part of everyday functioning, but in an abstract setting. This was set against the "subjective" Motor Activity Log (MAL) and the Stroke Impairment Scale (SIS). These are both self-report scales that measure perceived ability in a variety of specific functional activities.

The exclusion criteria around upper limb baseline function, cognitive and communication impairments meant that of 200 potential participants only 39 were able to participate. This challenge of recruitment will be familiar to anyone who has attempted upper limb functional trials.

When comparing the objective and subjective measures of improvement, there was significant matching for outcomes between the ARAT and the MAL but not the SIS. This means that for the latter scale there is a mismatch in how well patients perceived they have progressed and how much things have actually changed.

Interestingly, the two main factors that predicted this mismatch were level of education and mood. A lower level of education and better mood scores were both predictive of a greater match between the objective and subjective scales. While intuitively, one would expect a lower mood to associate with poorer self-image and perception of progress, the connection between educational level and mismatch is a little harder to conceptualise. Perhaps this discrepancy may arise because of different expectations or even exposure to other (not always reliable) information around recovery from non-clinical sources. Either way it is, perhaps, important to consider self-reported and subjective measures of change as meaningful outcomes for the individual.

Van Delden AL, Peper CL, Beek PJ et al. Match and Mismatch between Objective and Subjective Improvements in Upper Limb Function after Stroke. Disability and Rehabilitation. 2013;35:1961-67.

PD Psychosis: A New Drug on the Block

Reviewer: Dr Gemma Cummins, Van Geest Centre for Brain Repair, Cambridge University, UK.

Psychosis, comprising of hallucinations and delusions, affects more than half of patients with Parkinson's disease, especially later in the course of the disease. It can be a major source of patient and caregiver stress, and frequently leads to hospital admissions, and earlier nursing home placement. Pharmacological approaches to managing psychosis in Parkinson's disease can be disappointing, and sometimes come at the cost of deterioration in motor disability. Whilst quetiapine is frequently used in everyday practice, double blind placebo controlled trials have demonstrated safety but not efficacy. Similarly, data on the effectiveness of cholinesterase inhibitors is limited. The best evidence to date is for clozapine, an atypical antipsychotic which has a favourable side effect profile in terms of having minimal impact on motor function. However, it is infrequently prescribed as a first line treatment due to safety concerns and haematological monitoring requirements. Thus, there is a clear clinical gap for new therapeutic agents able to confer antipsychotic benefit in Parkinson's disease without harmful side effects.

A recent well-designed study published in the Lancet demonstrated that pimavanserin, a selective serotonin 5-HT2A inverse agonist, may be able to address this unmet need. In a six week, double-blind study, 199 patients with Parkinson's disease psychosis were randomly assigned to receive pimavanserin 40mgs once daily or matched placebo. Patients were assessed at baseline and days 15, 29 and 43 using the PD-adapted scale for positive symptoms (SAPS-PD), which is a nine-item scale rating symptoms like delusions and hallucinations. Pimavanserin treated patients had clinically significant improvements on this scale, and tolerated the medication well without experiencing sedation or worsening motor scores on the UPDRS. Treatment benefit was independent of age and cognitive status.

Outcomes were independently assessed by raters, investigators and carers enabling us to have much more confidence in the results. On the back of these study outcomes, licensing applications are now to start in Europe and the US, with plans to also trial this drug in Alzheimer's disease.

Cummings J, Isaacson S, Mills R et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2013 Oct 31.S0140-6736.

Neurodegeneration: Paving a Pathway Through Protein

Reviewer: Jemeen Sreedharan, Dept of Neurobiology/ Neurology, University of Massachusetts Medical School, Worcester, USA.

Going into neurodegeneration research may be considered by some to be academic suicide. Indeed, we have failed to develop effective therapies for these progressive diseases, despite our growing knowledge of the genetic causes and improved clinical and pathological phenotyping. Thus, it was with incredible excitement that the work of the Malluci lab at the MRC Toxicology Unit in Leicester was widely publicised by the media, including BBC television (Moreno et al 2013).

Moreno et al used a transgenic mouse over-expressing mouse wild-type prion protein (PrPC). This mouse does not get ill. However, after inoculating the brain with PrPSc extract (i.e. PrP with the pathological beta pleated conformation) the animal develops progressive behavioural changes and motor impairment culminating in death just 12 weeks after inoculation. Classical PrPSc inclusions, spongiform cortical changes and neurodegeneration are seen, mimicking human spongiform encephalopathies such as CJD.

In work published in Nature in 2012 the Malluci lab showed that a critical pathway was active in these mice: the Unfolded Protein Response (UPR). The UPR is thought to be one mechanism by which a cell deals with accumulating misfolded proteins, which are a hallmark of neurodegenerative diseases. It is activated by a molecular sensor (BiP) in the endoplasmic reticulum followed by a phosphorylation cascade involving PERK and then eiF2-alpha. The outcome is a temporary shutdown of protein synthesis. In the PrP mice activation of the UPR resulted in a dramatic reduction in synaptic protein synthesis, synapse loss and neuronal death. Strikingly, genetically inhibiting the UPR pathway using lentiviral RNA interference prevented this catastrophic neural degeneration (Moreno et al 2012).

The breakthrough in the current paper from the same lab is that an orally bioavailable agent, a highly specific PERK inhibitor called GSK2606414, was used to globally inhibit the UPR throughout the mouse brain with dramatic effect. Mice treated before symptom onset never developed disease and there was no neurodegeneration, despite ongoing accumulation of misfolded PrP. Importantly for us as clinicians, animals treated after disease onset also responded with a stabilisation of their phenotype.

This result is astounding in its magnitude, suggesting that such a destructive process as spongiform encephalopathy could be treated with a pill. However, Malluci is mindful to point out that PERK inhibition does lead to unwanted effects in her PrP mice, including weight loss and glucose intolerance. Nonetheless, it has not escaped her attention that the UPR is activated in the brains of patients with ALS, Alzheimer's disease and Parkinson's disease and it is exciting to speculate that PERK inhibition may thus have therapeutic potential in the broader context of neurodegeneration. It may be that a careful balance between UPR activation and inhibition may be necessary to allow a neuron to deal with cellular stress without culminating in irreversible synaptic loss. Further compound screening, testing and trials are clearly urgently warranted.

Moreno JA, Halliday M, Molloy C et al. Oral treatment targeting the unfolded protein response prevents neurodegeneration and clinical disease in prion-infected mice. Sci Transl Med. 2013 Oct 9;5(206):206ra138.

Moreno JA, Radford H, Peretti D et al. Sustained translational repression by eIF2α-P mediates prion neurodegeneration. Nature. 2012 May 6;485:507-11.

The Neurology of Humour

Dr Camilla Neergaard Clark

is a Clinical Research Fellow doing a PhD at the Dementia Research Centre at the National Hospital, Queen Square. She did her medical training at Gonville & Caius College, Cambridge and University College London. Her particular research interest is sensory processing in frontotemporal dementia.

Dr Jason Donald Warren

is a Wellcome Senior Clinical Fellow and Reader in Neurology at the Dementia Research Centre, UCL and jointly runs the Specialist Cognitive Clinic at the National Hospital, Queen Square. His research investigates disordered information processing in neurodegenerative disease using the paradigm of complex sound with neuropsychological, neurophysiological and neuroimaging techniques.

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Summary

- Functional imaging in the normal brain has implicated distributed cortical and subcortical networks in processing different aspects of humour perception and comprehension with separable cognitive, affective and social dimensions
- Impaired appreciation of humour is a feature of diverse developmental and acquired brain disorders
- Humour may present a useful model for studying certain complex behavioural functions of high clinical relevance: these include the resolution of ambiguity and incongruity, mentalising and empathy

A neurologist, a neurosurgeon and a psychiatrist walk into a bar.
The barman says, 'Is this some kind of joke?'

A sense of humour is among our most cherished attributes. It eases the daily grind, promotes amity with our fellows and may even salve our hurts[1] or confer reproductive success.[2] Laughter might be 'the shortest distance between two people', as averred by Victor Borge; avowedly humourless societies tend to disintegrate (think of Nazi Germany) and humour is feared by tyrants of all persuasions. In its more refined forms it is held up as a mark of discernment, but there can be very few of us who have not, from time to time, been reduced to fits of helpless mirth even in highly unsuitable situations. This underlines the extraordinary range and power of humour in its many genres. Despite its ubiquity as a phenomenon, the peculiarities of humour are often closely bound to time and place; the jokes of Euripides and Shakespeare have travelled less well than their tragedies and tastes in humour are heavily socially and culturally sanctioned.[3] On the other hand, certain humour motifs may be truly universal: from an evolutionary perspective, laughter is probably older than language[4] and the destabilising properties of fruit peel were probably already drawing uncharitable sniggers among our cave-dwelling forebears. Though it is not clear that other animals possess humour, it is perhaps relevant that analogues of laughter and smiling in our primate relatives signal aggression or threat.[5]

In addition to its social and existential virtues, humour is of considerable interest as a cognitive neuropsychological phenomenon. Jokes typically entail the opposition of apparently incongruous elements that must be resolved in a surprising way.[6] These operations entail a number of cognitive processing stages and components. The process of resolution requiring the integration of conflicting alternatives is a model of frontal lobe function,[7] while the emotional payoff suggests an analogy with other phenomena (such as music) that link psychological expectancies with the brain mechanisms of reward.[8] However, the neurobiological basis of humour remains largely obscure and the effects of brain disease on humour processing are poorly understood. Neurologists have taken an interest in the more extreme outward manifestations (like pathological affect and fou rire prodromique)[9] while largely ignoring the cognitive machinery behind them. Here we argue that this is a wasted opportunity, using examples in which alterations of humour are integral to neurological disease. We do not, however, wish to minimise the challenges inherent in attempting to study the neurology of humour.[10,11,12] There is presently no standard, widely accepted cognitive model of humour processing, nor indeed any agreed terminology of the processes involved.[10] Caution is therefore required in interpreting the published literature and this is compounded by the diversity of stimuli and paradigms that have been used to assess humour processing in health and disease.[11,12] Furthermore, as is the case for all complex, multi-component cognitive processes, functional neuroimaging studies of humour (which delineate all brain areas involved in the relevant process) must be reconciled with clinical lesion studies (which identify areas critical for the process). In functional imaging work it is not always clear which contrasts should be employed to isolate specific components of humour processing and most imaging modalities lack the temporal resolution to capture the temporal staging of these components (this typically requires electrophysiological techniques).

In this review we highlight the many gaps in our current understanding of the neurology of humour and propose a framework for the systematic clinical analysis of humour cognition. Our focus here is on the brain mechanisms that process humour and the disorders that affect humour processing, rather than pathological affect and abnormal laughter, which are already well reviewed.[13]

Humour and the healthy brain

What happens in the brain when we 'get' a joke? Functional imaging studies in the healthy brain using stimuli as diverse as one-liners, sight gags, captionless cartoons, comic strips, Seinfeld, The Simpsons and stand-up comedy videos have implicated distributed cortical and subcortical networks in processing different aspects of humour perception and comprehension with separable cognitive, affective and social dimensions of the brain's response. The temporo-parietal junction is engaged in the cognitive analysis of potentially humorous stimuli:[14] this is consistent with a proposed role for this region in bringing stored expectations online[7] and for processing socially relevant information more generally.[15] This may be particularly pertinent to the basic humour associated with physical comedy (slapstick), which relies on the violation of physical or social norms. More widespread brain regions

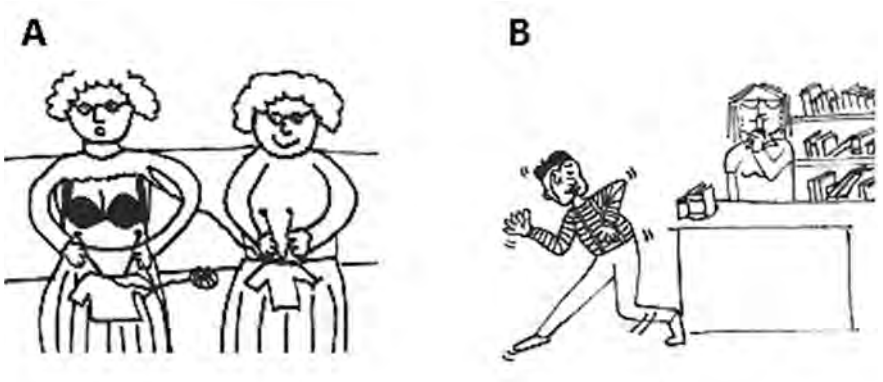

Figure 1: Examples of customised humour stimuli for neuropsychological testing of cognitively impaired patients. These nonverbal cartoons do not require linguistic processing and have been created by one of the authors (C.N.C.) to control for perceptual characteristics such as form, complexity, colour and surface affective cues (e.g., facial expressions such as smiling). The cartoons shown represent two general categories of humour motivated by current cognitive models (see Table 1): A humour reliant on violation of physical norms (slapstick – an unravelling blouse); B humour based on juxtaposition of incongruous elements requiring resolution to a surprising conclusion (the mime artist being hushed in a library). After norming in healthy age-matched individuals of similar cultural background (and in the context of appropriate control stimuli), tasks based on such stimuli could include; to decide whether or not a joke is intended, to explain the joke or to rate its funniness.

including posterior inferior temporal, inferior frontal and premotor cortices, limbic structures such as the insula and amygdala and subcortical structures including nucleus accumbens, putamen, thalamus and cerebellum are more specifically involved in detecting and appreciating incongruity and accompanying emotions of surprise and delight.[7,12,16,17] While these processes are generally intimately intertwined and difficult to separate using imaging paradigms,[18] they are dissociable; humorous intent can be recognised even when it does not provoke amusement. The onset of laughter has been taken to signal the dawning of amusement, associated with insula and amygdala activation;[7] while degree of amusement (funny contrasted with unfunny jokes) has been correlated with activation in ventral prefrontal, anterior cingulate, superior and mid temporal cortices and limbic and dopaminergic reward networks including ventral striatum and nucleus accumbens.[12,16,19] Electrophysiological techniques may allow dissection of the temporal dynamics of joke comprehension.[11]

There is some evidence for separable neural correlates of different kinds of humour. Puns engage components of a phonological processing network including the left inferior frontal gyrus whereas semantic jokes engage regions including the posterior temporal lobe which are involved in semantic integration.[12] Pictorial cartoons recruit areas mediating visual imagery[19] whereas those requiring inference on mental states particularly engage brain regions concerned with mentalising or 'theory of mind'.[14] The process of incongruity resolution associated with sarcasm detection activates brain networks engaged in language processing and mentalising.[20] While the brain basis for idiosyncratic tastes in humour is likely to remain obscure, responses may be modulated by gender[21] and personality.[22] Individual variation in sense of humour (ability to grasp one-liners) has been correlated with electrophysiological markers including lateralised frontal evoked potentials that may index frame-shifting and surprise.[11]

Brain disorders and humour

Various brain disorders have been linked to disturbed understanding or appreciation of humour. Aside from their clinical relevance, such disturbances can (as with other complex neuropsychological functions) potentially reveal underlying critical brain substrates and cognitive architecture. However, much early work on the neurology of humour draws on a very broad anatomical distinction between the right and left cerebral hemispheres.[23,24] Damage involving the non-dominant hemisphere (particularly the frontal cortex and anterior temporal lobe) often degrades the appreciation of humour;[10,23] in these patients, amusement dissociates from comprehension of jokes, perhaps reflecting a more general deficit in linking cognitive with appropriate emotional responses. Some patients with right hemisphere damage find humour in intrinsically humourless situations.[23] Damage involving right frontal polar cortex impairs appreciation of more sophisticated jokes while leaving responses to slapstick scenarios largely unscathed,[10] perhaps reflecting an inability to resolve incongruity in novel contexts. It is our clinical impression that patients with frontotemporal dementia chiefly involving the right hemisphere have somewhat similar difficulties; particularly in the context of mesio-orbital frontal involvement, such patients may exhibit reduced comprehension of sarcasm[25] and frequent prankish joking and punning (Witzelsucht)[26] though the onset of the disorder may be signalled by a more subtle predilection for comic strips, slapstick or scatological jokes (a coarsening of comedic tastes that may have parallels in the culinary or musical realms). More specifically verbal jokes appeared to rely on the ability to set shift and verbal abstraction whereas the performance in cartoons was more reliant on attention to details and the ability to visually search the scene.[10]

Patients with focal damage restricted to a particular cerebral hemisphere show characteristic profiles of deficits for particular components of humour processing.[24] Whereas patients with right hemisphere damage may be unable to discriminate between punchlines and non sequitur endings to jokes, those with left hemisphere damage tend to prefer coherent but unsurprising (and unfunny) endings. Individuals with agenesis of the corpus callosum may also have particular difficulty with narrative jokes, perhaps because these depend on inter-hemispheric integration of linguistic and non-literal metaphorical dimensions.[27] Right hemisphere damage seems more likely to be associated with impaired ability to mentalise (theory of mind), while left hemisphere damage is more likely to affect the comprehension of humour that does not rely on mental inferences.[28] A mentalising defect is also likely to contribute to degraded humour processing in frontotemporal dementia.[25]

Impaired appreciation of humour is a feature of diverse developmental and acquired disorders with more diffuse brain dysfunction, including autism spectrum disorders,[29] schizophrenia,[30] amyotrophic lateral sclerosis,[31,32] traumatic brain injury,[33] and Tourette's syndrome.[34] Orbitofrontal cortex dysfunction may be a common theme linking these disorders with cases of focal brain damage and network disintegration in frontotemporal dementia. Certain disorders may produce specific cognitive deficits that impact on humour processing. The difficulty shown by patients with schizophrenia in interpreting sarcasm may at least partly reflect pitch processing difficulties[35] while impaired mentalising in social phobia or Asperger's syndrome impairs understanding of humour that depends on theory of mind, but not visual jokes or puns.[29] There have been few functional neuroimaging studies of humour processing in brain disease; in one fMRI study with cartoon stimuli, individuals with cataplexy compared with healthy controls had heightened activation of subcortical reward circuitry, but in addition, increased engagement of 'inhibitory' circuitry in right inferior frontal gyrus, suggesting an intriguing disease model for the common experience of struggling to regain composure when we are 'weak' with laughter.[36]

In Table 1, we present a simplified framework for assessing humour cognition that summarises functional neuroimaging evidence concerning the brain basis of humour with proposed clinical associations requiring substantiation in further work.

Future directions

Observations such as these in the healthy and damaged brain should encourage neurologists to enquire more systematically about their patients' humour sensibilities and for cognitive scientists to develop frameworks that can reconcile lesion and functional neuroimaging work. It is clear that humour, as an aspect of brain function, is multi-dimensional and highly distributed. Admittedly no single cognitive model is ever likely to subsume the double entendres of Benny Hill, the acerbic social commentary of Peter Cook or Woody Allen, the sparkling wordplay of Wilde and Moliere, the

Table 1: A framework for assessing humour cognition, based on published functional neuroimaging and clinical evidence

Components of humour processing	Functional neuroanatomical associations in healthy brain	Diseases predicted to affect process
Detection of potential joke, e.g. based on norm violation (slapstick, other)	Bilateral temporo-parietal junction, superior frontal gyrus; right posterior middle temporal gyrus, left anterior medial prefrontal cortex	Focal lesions of left cerebral hemisphere, especially involving temporo-parietal junction
Processing of incongruity	Right frontal pole, right posterior middle temporal gyrus, left posterior inferior temporal gyrus	Focal lesions of right cerebral hemisphere
Inference of mental states (theory of mind, mentalising)	Anteromedial prefrontal cortex	Autism, schizophrenia, social anxiety, behavioural variant frontotemporal dementia
Affective response to joke	Insular cortex, ventromedial prefrontal cortex; subcortical network including amygdala, nucleus accumbens, ventral striatum	Focal lesions of right hemisphere and frontotemporal dementia, especially involving limbic structures
Processing of joke categories		
Puns	Left superior temporal gyrus, left inferior frontal gyrus	Diseases affecting language network, especially phonological processing
Sarcasm	Left temporal pole, superior temporal sulcus, medial prefrontal cortex, inferior frontal gyrus	Behavioural variant frontotemporal dementia, other disease processes involving anterior temporal and medial prefrontal cortex

whimsical meanderings of Peanuts. Nevertheless, humour may present a useful model for studying certain complex behavioural functions of high clinical relevance: these include the resolution of ambiguity and incongruity, mentalising and the exercise of empathy;[18] and the putative 'lexicon' of jokes (particularly slapstick scenarios) that may be laid down in early childhood.[37] These different dimensions of humour processing might be probed by customised stimuli that control for potentially confounding surface characteristics (for example, Figure 1). More broadly, if humour serves to debug inferential errors in our comprehension of the world,[1] it might turn out to have a key role in the maintenance of cognitive well-being: perhaps the enduring appeal of Rabelais, the Pythons and Dali's Aphrodisiac Telephone reflect such neural housekeeping by the absurd and the surreal.

If it seems ironic to have two neurologists write on humour, perhaps a more compelling lead lies with literature, which is replete with melancholy clowns and the wisdom of fools. We hope the neuroscientific study of humour will help us to a better understanding of our patients and the predicaments they face, which do, after all, encompass some of the more grim and bitter ironies of medical practice. ◆

REFERENCES

1. Hurley MM, Dennett DC, Reginald BA. *Inside Jokes: using humor to reverse-engineer the mind.* Cambridge, Massachusetts: MIT Press; 2011.
2. Bressler ER, Balshine S. *The influence of humor on desirability.* Evol Hum Behav 2005;27:29-39.
3. Holmes J, Marra M. *Humour as a discursive boundary marker in social interaction.* In: Duszak A, editor. *Us and Others: Social Identities Across Languages, Discourses and Cultures.* Amsterdam: John Benjamins Publishing Company; 2002.
4. Hayworth D. *The social origins and functions of laughter.* Psychological Review 1928;35:367-84.
5. De Waal FB. *Darwin's legacy and the study of primate visual communication.* Ann N Y Acad Sci 2003;1000:7-31.
6. Suls J. *A two-stage model for the appreciation of jokes and cartoons: an information-processing analysis.* Goldstein PE, McGhee JH, editors. New York: Academic Press; 1972. 81–100 p.
7. Moran JM, Wig GS, Adams RB, Jr., Janata P, Kelley WM. *Neural correlates of humor detection and appreciation.* Neuroimage 2004;21:1055-60.
8. Lehne M, Rohrmeier M, Koelsch S. *Functional neuroimaging of tension: A study with music.* Soc Cogn Affect Neurosci 2013.
9. Fere MC. *Le fou rire prodromique.* Rev Neurol 1903;11:353-8.
10. Shammi P, Stuss DT. *Humour appreciation: a role of the right frontal lobe.* Brain 1999;122(Pt 4):657-66.
11. Coulson S, Kutas M. *Getting it: human event-related brain response to jokes in good and poor comprehenders.* Neurosci Lett 2001;316:71-4.
12. Goel V, Dolan RJ. *The functional anatomy of humor: segregating cognitive and affective components.* Nat Neurosci 2001;4:237-8.
13. Lauterbach EC, Cummings JL, Kuppuswamy PS. *Toward a more precise, clinically-informed pathophysiology of pathological laughing and crying.* Neurosci Biobehav Rev 2013;37:1893-916.
14. Samson AC, Zysset S, Huber O. *Cognitive humor processing: different logical mechanisms in nonverbal cartoons--an fMRI study.* Soc Neurosci 2008;3:125-40.
15. Schurz M, Aichhorn M, Martin A, Perner J. *Common brain areas engaged in false belief reasoning and visual perspective taking: a meta-analysis of functional brain imaging studies.* Front Hum Neurosci 2013;7:712.
16. Mobbs D, Greicius MD, Abdel-Azim E, Menon V, Reiss AL. *Humor modulates the mesolimbic reward centers.* Neuron 2003;40:1041-8.
17. Wild B, Rodden FA, Rapp A, Erb M, Grodd W, Ruch W. *Humor and smiling: cortical regions selective for cognitive, affective, and volitional components.* Neurology 2006;66:887-93.
18. Bartolo A, Benuzzi F, Nocetti L, Baraldi P, Nichelli P. *Humor comprehension and appreciation: an FMRI study.* J Cogn Neurosci 2006;18:1789-98.
19. Watson KK, Matthews BJ, Allman JM. *Brain activation during sight gags and language-dependent humor.* Cereb Cortex 2007;17:314-24.
20. Uchiyama H, Seki A, Kageyama H, Saito DN, Koeda T, Ohno K, Sadato N. *Neural substrates of sarcasm: a functional magnetic-resonance imaging study.* Brain Res 2006;1124:100-10.
21. Azim E, Mobbs D, Jo B, Menon V, Reiss AL. *Sex differences in brain activation elicited by humor.* Proc Natl Acad Sci U S A 2005;102:16496-501.
22. Mobbs D, Hagan CC, Azim E, Menon V, Reiss AL. *Personality predicts activity in reward and emotional regions associated with humor.* Proc Natl Acad Sci U S A 2005;102:16502-6.
23. Gardner H, Ling PK, Flamm L, Silverman J. *Comprehension and appreciation of humorous material following brain damage.* Brain 1975;98:399-412.
24. Bihrle AM, Brownell HH, Powelson JA, Gardner H. *Comprehension of humorous and nonhumorous materials by left and right brain-damaged patients.* Brain Cogn 1986;5:399-411.
25. Kipps CM, Nestor PJ, Acosta-Cabronero J, Arnold R, Hodges JR. *Understanding social dysfunction in the behavioural variant of frontotemporal dementia: the role of emotion and sarcasm processing.* Brain 2009;132:592-603.
26. Lishman WA. *Organic Psychiatry: The Psychological Consequences of Cerebral Disorder.* 3rd ed. United Kingdom: Blackwell Publishing; 2003.
27. Brown WS, Paul LK, Symington M, Dietrich R. *Comprehension of humor in primary agenesis of the corpus callosum.* Neuropsychologia 2005;43:906-16.
28. Gallagher HL, Happe F, Brunswick N, Fletcher PC, Frith U, Frith CD. *Reading the mind in cartoons and stories: an fMRI study of 'theory of mind' in verbal and nonverbal tasks.* Neuropsychologia 2000;38:11-21.
29. Samson AC, Hegenloh M. *Stimulus characteristics affect humor processing in individuals with Asperger syndrome.* J Autism Dev Disord 2010;40:438-47.
30. Corcoran R, Cahill C, Frith CD. *The appreciation of visual jokes in people with schizophrenia: a study of 'mentalizing' ability.* Schizophr Res 1997;24:319-27.
31. Girardi A, Macpherson SE, Abrahams S. *Deficits in emotional and social cognition in amyotrophic lateral sclerosis.* Neuropsychology 2011;25:53-65.
32. Staios M, Fisher F, Lindell AK, Ong B, Howe J, Reardon K. *Exploring sarcasm detection in amyotrophic lateral sclerosis using ecologically valid measures.* Front Hum Neurosci 2013;7:178.
33. Braun CM, Lussier F, Baribeau JM, Ethier M. *Does severe traumatic closed head injury impair sense of humour?* Brain Inj 1989;3:345-54.
34. Eddy CM, Mitchell IJ, Beck SR, Cavanna AE, Rickards H. *Social reasoning in Tourette syndrome.* Cogn Neuropsychiatry 2011:1-22.
35. Kantrowitz JT, Hoptman MJ, Leitman DI, Silipo G, Javitt DC. *The 5% difference: early sensory processing predicts sarcasm perception in schizophrenia and schizo-affective disorder.* Psychol Med 2013:1-12.
36. Reiss AL, Hoeft F, Tenforde AS, Chen W, Mobbs D, Mignot EJ. *Anomalous hypothalamic responses to humor in cataplexy.* PLoS One 2008;3:e2225.
37. Goel V, Dolan RJ. *Social regulation of affective experience of humor.* J Cogn Neurosci 2007;19:1574-80.

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Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

Summary

- ARSACS is a rare autosomal recessive disorder characterised clinically by cerebellar ataxia, spasticity, pyramidal signs, peripheral neuropathy and skeletal foot abnormalities
- It is caused by mutations in the SACS gene which encodes the 520kDa protein sacsin
- The availability of the genetic test has extended the clinical spectrum to include examples without spasticity or ataxia
- Retinal examination shows retinal striations on fundoscopy and thickening of the retinal nerve fibre layer on ocular coherence tomography (OCT) in the majority of the cases
- Neurophysiological studies show an early demyelinating sensorimotor neuropathy with progressive axonal degeneration
- MR imaging shows superior vermian cerebellar atrophy, thinning of the cervical spinal cord and pontine linear hypointensities

ARSACS is a rare and disabling, slowly progressive neurodegenerative disorder characterised by cerebellar ataxia, spasticity, pyramidal signs, peripheral neuropathy, skeletal foot abnormalities and thickening of the retinal nerve fibre layer (RNFL) visible on fundoscopy and by ocular coherence tomography (OCT). The condition was first considered to be confined at relatively high frequency to the descendants of founder populations in the Charlevoix and Saguenay-Lac Saint Jean regions of North-Eastern Québec, but the discovery of the causative SACS gene has permitted its identification throughout the world and has extended the diversity of mutations known, and the spectrum of clinical features described. ARSACS is now recognised as one of the important causes of autosomal recessive ataxia. In this review, we summarise the clinical, genetic and pathophysiological features of this condition, and the investigations used in its diagnosis.

History and origins

Québec was one of the first regions of North America to be colonised by Europeans and the majority of French Canadians living in Québec Province today are thought to descend from these original founders. As a result, a number of rare neurogenetic disorders show increased prevalence or local variants in this region, including Friedreich's ataxia (FRDA), and other hereditary ataxias, spastic parapareses and neuropathies.[1] Québec City was founded in 1608 under the rule of the French crown and between 1665 and 1725, around forty families migrated from there to the isolated mountainous region of Charlevoix on the north shore of the Saint Lawrence River. Between 1838 and 1855, further families moved from here to the more distant Saguenay and Lac Saint Jean regions to the north. It is estimated that the carrier frequency of SACS mutations is 1/22 in these regions.

The clinical syndrome of ARSACS was first described in 1978 in these populations,[2] and this community of more than 300 affected individuals remains the most numerous and the most extensively studied. The clinical phenotype was remarkably homogeneous, probably because more than 92% of individuals shared the same mutation, and more than 96% shared one of two mutations.[3] The causative gene was first described in 2000[4] enabling the subsequent identification of cases in Europe, North Africa, Turkey, Japan and Brazil[5] with considerable phenotypic heterogeneity, so that now neither spasticity nor ataxia must be regarded as an obligate feature of the condition.[6]

Genetics and sacsin protein function

The causative gene on chromosome 13q12.12 is named SACS and was originally thought to contain a single giant exon[4] (see Figure 1). A further 8 coding exons and a tenth non-coding exon have subsequently been identified upstream of this, forming a 13,737bp open reading frame.[7] More than 100 different pathogenic mutations have now been described,[3,8] largely missense, nonsense, frameshift and splice-site mutations spread over 6 of the 10 exons, but still primarily in the giant exon 10.[3] Large deletions have also been described causing atypical features such as late onset or

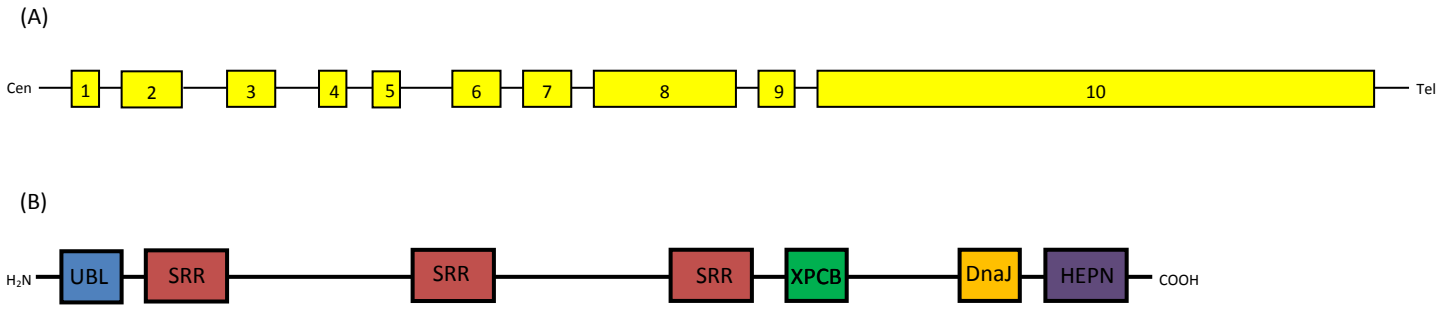

Figure 1: (A) Primary structure of SACS gene showing the 10 exons. Mutations have thus far been described in exons 4, 6, 7, 8, 9 but largely in the giant exon 10. (B) Domain organisation of sacsin protein. UBL, ubiquitin-like domain; SSR, sacsin repeat region; XPCB, xeroderma pigmentosum complementation group C binding domain; DnaJ, J-domain; HEPN, higher eukaryote and prokaryote nucleotide binding domain.

prominent hearing loss. These have included an intragenic deletion of exons 3-5,[8] deletion of the whole gene[9] and deletion of SACS and the contiguous gene SGCG causing concomitant limb girdle muscular dystrophy type 2c.[10]

The gene encodes a 4,579 amino acid 520kDa protein called sacsin (see Figure 1) whose true function is currently not fully understood[11] but may have a protective effect against mutant ataxin-1.[12] Sacsin is most highly expressed in cerebellar Purkinje cells; thalamic, midbrain, precerebellar and brainstem nuclei; and large pyramidal forebrain neurones.[12] Within cells, it is localised to the cytoplasm and mitochondria, and may have a role in the regulation of mitochondrial dynamics, leading to mitochondrial mislocalisation and dysfunction.[11]

Histopathology

Nerve biopsies most consistently show a marked decrement in large myelinated fibres. More variably, axonal degeneration with condensation of the axoplasm, increased collagen pockets and accumulation of mitochondria and vesicular bodies is seen, sometimes with regenerative axonal sprouting. Thinning of the myelin sheaths with rare onion bulbs may also be observed.[13-15] Taken together, these findings suggest an axonal neuropathy associated with some demyelinating features. Muscle biopsies are typical of neurogenic atrophy.

Two post-mortem examinations of patients with ARSACS have been published.[16] The first in a young patient, showed a grossly atrophied superior cerebellar vermis especially in the anterior structures (central lobule and culmen). No changes were seen in the dentate nucleus and inferior olives. The molecular and granular cell layers were thinned with practically absent Purkinje cells. The pyramids, lateral and anterior corticospinal tracts and posterior spinocerebellar tracts all showed significant loss of myelin staining, particularly the lateral corticospinal tracts. The corticospinal changes were more marked in the upper cord, whereas the spinocerebellar changes were more marked caudally. The second, in an older patient, showed similar findings although to a more pronounced degree. Swollen thalamic and cerebellar cortical neurones were seen, suggestive of a storage disorder. Most of these cells showed dense, lipofuscin-like granules within lysosomes, although testing of an extensive panel of lysosomal enzymes was normal. Interestingly, lipofuscin deposits have also been seen in the skin biopsy of a patient with ARSACS performed to exclude Lafora body disease.[17] Peripheral nerve and muscle biopsies have not shown lipofuscin deposits. The significance of this finding therefore remains unclear.

Clinical aspects

Much of the clinical knowledge of ARSACS is based on the relatively homogeneous Québecois cases. However, subsequently identified cases from elsewhere have demonstrated a genetic and clinical variability which continues to extend the phenotypic description of this condition. In the Québecois cases, unsteadiness was noted from beginning to walk (12-18 months old) which was rarely delayed.[16,18] 80% initially presented because of walking difficulties and a tendency to fall. At first presentation, approximately 60% were found to have limb ataxia, 80% showed some pyramidal involvement and 50% had both pyramidal and cerebellar involvement. There was no clinical evidence of neuropathy at presentation in the form of pes cavus or intrinsic hand muscle wasting.[19] There is some evidence that age at onset may be a little later in non-Québecois cases, particularly in Japanese and Tunisian cases.[20] In a series of 17 Belgian patients, 29% had onset at or after age 20 with one as late as 40.[8] There is no male-female preponderance.

Thus, limb and gait ataxia are early signs followed by spasticity, which is more prominent in the lower limbs. Spasticity and ataxia affect speech, which is often slightly slurred in childhood and can become explosive in adulthood. Dysphagia is usually mild or absent.[18,21] Plantar reactions are frequently upgoing from childhood. Eye movements show horizontal bidirectional nystagmus, saccadic alterations of smooth ocular pursuit and saccadic dysmetria.[18] Supranuclear gaze palsy has been described in one case.[17] In the Québecois cases, by the age of 10 more than 90% showed both pyramidal and cerebellar involvement.[19] Muscle cramps may be a troublesome feature. Progression of symptoms is slow. In the Québecois cases, only 4% used a wheelchair before the age of 18.[19] Mean age to being wheelchair-bound was around 40 (range 17-58) and to death around 50 (range 21-72).[18]

From childhood, deep tendon reflexes are frequently increased, but by adulthood, may diminish or become absent due to progressive neuropathy. Ankle jerks are commonly absent whilst knee jerks may be hyperreflexic but patients may have a very mixed and asymmetric picture. Sensory deficits usually appear later and progressively into adulthood, involving vibrational sense more than proprioception and cutaneous sensation. Distal amyotrophy also appears progressively later in the condition.[18] The combination of early spasticity and progressive neuropathy commonly causes skeletal abnormalities of the foot including pes cavus, talipes equinus or varus, and hammer or clawed toes. Unlike FRDA, spinal scoliosis is not a prominent feature[18] but has been described in Tunisian[14] and Italian[21] series. Straight dorsal spine has been described in a Spanish series.[22] In the hands, swan-neck deformity of the fingers and claw hands have been described[2,15] with dystonia sometimes causing abnormal posturing of the hands and neck.[23]

Cognition is generally preserved particularly on tests of verbal function, but visuospatial handling may be diminished and deteriorate with time.[16] Cognitive impairment may be a more prominent feature amongst non-Québecois patients, with intellectual impairment and dementia described in patients from Japan, Italy and Turkey.[15] Although cerebellar eye signs may cause visual disruption, optic nerve and retinal function are not generally affected with normal acuity, fields and colour vision, despite the presence of thickened retinal nerve fibres (see below).[18] Hearing loss is not generally found but may be more prominent amongst cases involving SACS gene deletions.[9,21,24]

Bladder and bowel symptoms are not well-studied in ARSACS although urinary urge incontinence has been most commonly described.[2,6,18,21,23] Faecal incontinence and constipation may also be a problem in patients with long disease duration.[18] Co-existent epilepsy has been described in a minority of cases and it remains unclear whether this is a definite association.[17,23] It appears more common in the Québecois cases, occurring in more than 15% in one series.[19] Frequent

abnormal electroencephalographic features have also been described (see below).

Currently no clinical diagnostic criteria exist for ARSACS. The descriptive clinical features published by Bouchard, et al[16,18] have come closest to this, although may be more representative of the Québecois cases.

Clinical Features of ARSACS
(modified from Bouchard, et al[16,18])

Onset
- Unsteadiness at gait initiation

Progressive signs
- Mostly spastic ataxia of the four limbs
- Slurred and dysrythmic speech
- Discrete to severe distal amyotrophy
- Absent ankle jerks after 25 years of age

Early non-progressive signs
- Increased deep tendon reflexes
- Bilateral abnormal plantar response
- Marked saccadic alteration of ocular pursuit
- At funduscopy: prominent retinal nerve fibres radiating from the disc and embedding retinal vessels

Positive diagnostic tests
- CT or MRI: atrophy of the superior vermis; progressive atrophy of the cerebellar hemispheres and of the cervical spinal cord.
- NCS: axonal neuropathy with absent sensory action potentials and low motor conduction velocities.

Imaging

The predominant radiological manifestations of ARSACS on MRI and CT are marked atrophy of the superior cerebellar vermis with consequent enlargement of the supravermian cisterns and cisterna magna[8,15,21,22] (see Figure 2). Posterior fossa arachnoid cysts are also sometimes reported.[6] While such prominent cerebellar atrophy is uncommon in FRDA, these findings are also seen in other causes of spinocerebellar ataxia (SCA). More specific appear to be the paramedian, bilaterally symmetrical, parallel, linear hypointensities in the pons on T2 and T2-FLAIR MRI sequences[22,25] which some have called 'pontine tigroid hypointensities'.[26] Associated with these may be bilateral T2-FLAIR hyperintensities of the lateral pons at the level of the middle cerebellar peduncles (MCPs).[6] The hypo- and hyper-intensities may extend into the MCPs.[27] The pons generally may be bulky[21] and the MCPs thickened.[6,21,22] The pontine striations have not been reported in other causes of ataxia or spastic paraparesis, making them useful in distinguishing ARSACS from these conditions when present. Diffusion tensor imaging (DTI) has shed some light on the underlying nature of these changes and the cause of symptoms in ARSACS, with hyperplastic pontocerebellar fibres at the same level as thin and abnormally placed pyramidal tracts, suggesting that the former may be compressing the latter.[21,22]

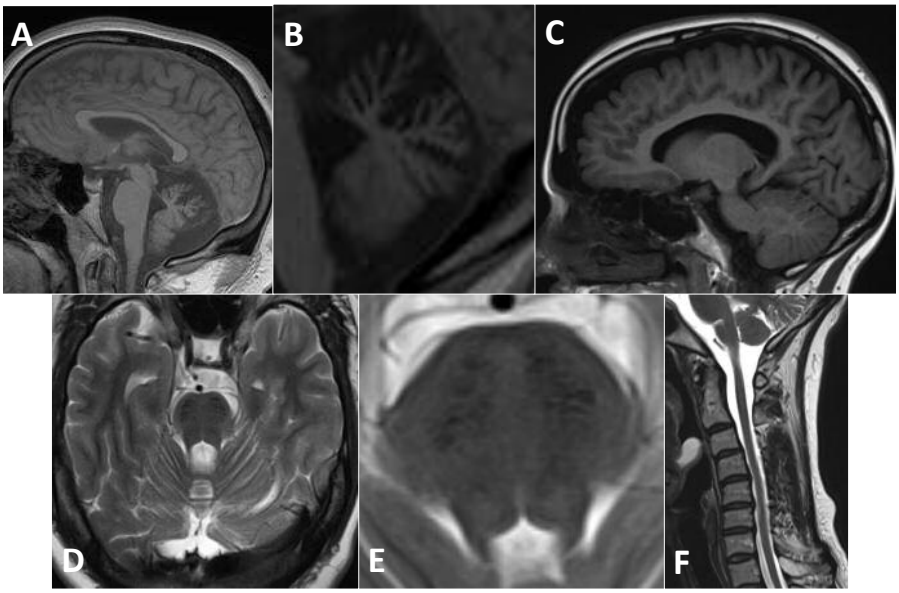

Figure 2: A) Sagittal T1 MRI showing superior vermian atrophy and corpus callosal thinning ; B) Sagittal T1 MRI showing superior vermian atrophy ; C) Sagittal T1 MRI showing generalized cerebral volume loss, most preponderant in the parietal lobe ; D) Axial T1 MRI showing pontine hypointensities ; E) Axial T2 MRI showing pontine hypointensities ; F) Sagittal T2 MRI showing thinning of the cervical spinal cord

Atrophy of the superior cerebellar peduncles (SCPs), medulla, cervical and thoracic cords has also been observed,[18,21] although again not consistently particularly in non-Québecois cases.[27] More widespread cerebral atrophy, particularly bilaterally in the parietal lobes,[6] may be seen later in the course of the condition but is not as prominent as the cerebellar or cervical atrophy.[8,16] Thinning of the corpus callosum and a rim of T2 hyperintensity around the thalami have also variably been reported.[6,21] No white matter abnormalities have been seen in either brain or spine,[15,18] except in one atypical case in which the explanation was felt to be concomitant multiple sclerosis.[26] Single photon emission computed tomography (SPECT) has shown decreased blood flow in the superior cerebellar vermis.[28]

Thus the salient imaging features of ARSACS are prominent early superior vermian cerebellar atrophy, thinning of the predominantly cervical spinal cord and pontine linear hypointensities.

Neurophysiological studies

Nerve conduction studies show increased distal motor latency and decreased conduction velocities which are more pronounced in the lower limbs than the upper limbs. Typical median nerve conduction velocities are 29-44ms^{-1} and peroneal nerve 17-35ms^{-1}. This appears to distinguish ARSACS from FRDA in which motor conduction velocities are usually preserved. Motor conduction slowing appears early in life with progressive degeneration which may make compound motor action potentials impossible to detect at the feet by middle age. Sensory nerve conduction is usually of low amplitude or unrecordable, especially in the lower limbs.[13,14,18,22] Electromyography shows fibrillations, occasional fasciculations, increased polyphasic action potentials and decreased or absent recruitment, indicating chronic denervation of distal muscles early in the disease process.[18,22] Sympathetic skin responses are normal. Somatosensory evoked potentials show a dispersed and delayed cortical response indicating slowed central sensory conduction. Brainstem and visual evoked potentials show increased latencies even in the absence of auditory or visual symptoms.[18,22] Electroretinography is normal.[21,29] Transcranial magnetic stimulation also shows marked delay in the central pathways.[18] Thus, neurophysiological studies suggest an early demyelinating sensorimotor neuropathy with progressive axonal degeneration, and involvement of the central sensory and motor pathways.

Electronystagmography most commonly shows horizontal gaze-evoked nystagmus and impairment of smooth ocular pursuit. There is also impairment of optokinetic nystagmus and defective fixation suppression of caloric nystagmus. Saccades are dysmetric but saccadic velocities are normal.[18]

Electroencephalography (EEG) reveals abnormalities in 40-60% of patients although frank epilepsy is much less commonly reported.[18,21] These abnormalities are non-specific findings indicating involvement of cortical and subcortical structures similar to those reported in FRDA.

Retinal changes

Thickening of the retinal nerve fibre layer (RNFL) is the characteristic retinal change visible on funduscopy in ARSACS (see Figure 3). This appears as prominent streaks

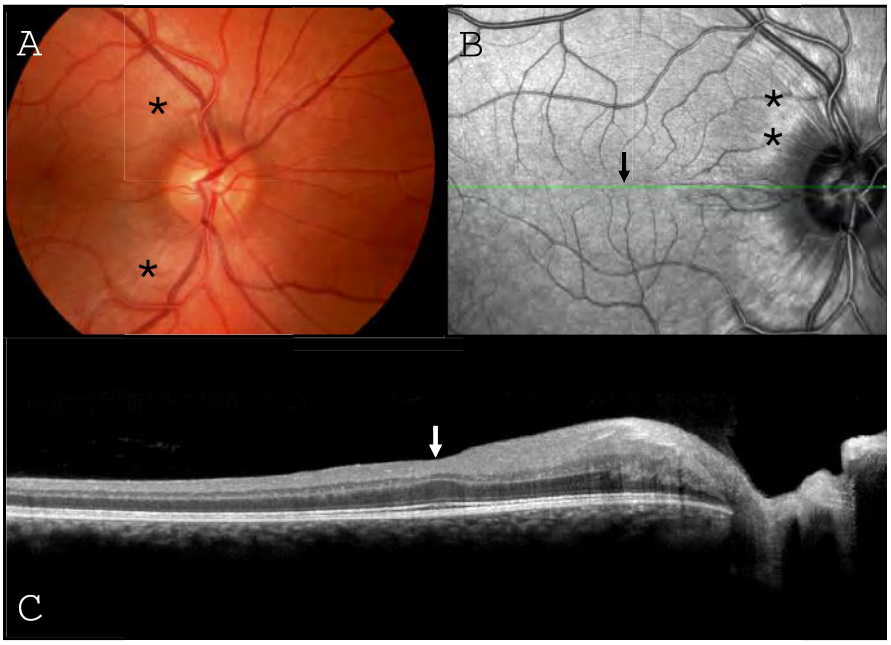

Figure 3: Retinal appearance of patient with ARSACS, (A) in colour and (B) red-free image. The optic disc is normal but there is visible thickening of the RNFL in all quadrants; in some places this has obscured the normally sharp edges of the retinal vessels (asterisks). (C) OCT scan along green line in image (B) confirms thickening of both ganglion cell and nerve fibre layers; these layers extend across the fovea (arrowed), a cyto-architectural appearance not seen in normal eyes.

emanating in all directions from the optic disc, most striking in the papillomacular bundle and nasal to the disc (where such striations are rarely visible in healthy people). The retinal vessels, which normally lie on the surface of the nerve fibre layer, may be 'buried' within this thickened layer obscuring their normally crisp margins.[2] These retinal striations are often described in the literature as composed of myelinated[18] or hypermyelinated[15,21] retinal fibres, although their exact nature remains unknown as no histopathological studies of the eyes in ARSACS have yet been published. Indeed, it is likely that 'myelinated fibres' is a misnomer; myelin in the retina is rare, but when present appears opaque and is associated with a corresponding area of visual field loss, whereas the retinal striations in ARSACS are translucent and not associated with any loss of sight.[29-33]

However, these retinal changes are not consistently observed on funduscopy, particularly in non-Québecois cases of ARSACS. A more sensitive method of detecting them appears to be ocular coherence tomography (OCT). This technique and its uses in neurological disease have previously been reviewed in this journal.[34] In ARSACS, OCT shows thickening of the RNFL in all sectors around the disc, with average peripapillary thicknesses of between 119 and 220μm.[22,29-33] In the macula, RNFL thickening extends over the fovea and can obscure the foveal pit.[31] RNFL thickening is not seen in the context of any other chronic progressive neurodegenerative diseases, only in cases of optic disc swelling associated with intracranial hypertension, optic neuritis or other local pathologies affecting the optic nerve head. Some cases of retinitis pigmentosa have shown thickening of the RNFL although with heavily disrupted outer retinal layers. It is therefore important to interpret the OCT results alongside the clinical history and fundoscopic findings.

Differential diagnosis

FRDA is the commonest cause of autosomal recessive cerebellar ataxia and the chief condition in the differential diagnosis of ARSACS. Retained or brisk reflexes and spasticity are rarely features of FRDA except in atypical late-onset cases known as Friedreich's ataxia with retained reflexes (FARR).[35] Cerebellar atrophy is more pronounced in ARSACS. A striking feature which distinguishes ARSACS from FRDA and other mitochondrial disorders, is the absence of extraneurological features such as diabetes, cardiomyopathy and scoliosis. The electrocardiogram in ARSACS is typically normal, as compared to the frequent existence of repolarisation abnormalities in FRDA. Although mitral valve prolapse was described in the original cases of ARSACS,[2] this finding has not been replicated in subsequent studies of families outside Québec.

Ataxia with oculomotor apraxia (AOA) may be distinguished from ARSACS because of the presence of oculomotor apraxia, dystonia, chorea and the absence of pyramidal features. AOA type 1 is associated with low levels of serum albumin and elevated levels of low density lipoproteins (LDLs), whilst AOA type 2 shows elevated levels of α-fetoprotein (AFP). Ataxia telangiectasia has many features in common with AOA together with cutaneous and scleral telangiectasiae, diabetes, immunodeficiency and sensitivity to radiation causing tumours.[19]

Late-onset Alexander's disease may have onset in adolescence and have a presentation similar to ARSACS. Cerebellar atrophy is less prominent and there may be periventricular white matter changes on MRI which are not seen in ARSACS. Cerebrotendinous xanthomatosis has onset in infancy but is often associated with diarrhoea, cataracts and tendon xanthomata, and is identifiable because of elevated serum cholestanol and urinary bile alcohols. Of the hereditary spastic parapareses (HSPs), HSP7 may be one of the most common to be complicated by ataxia, although onset is generally in adulthood. HSP 11, 15, 20, 21 and 27 may also present with ataxia, although often show distinguishing features.[36,37] In the spinocerebellar ataxias (SCAs), cerebellar ataxia generally predominates and inheritance is autosomal dominant. Amongst these, SCA1 and SCA3 (Machado-Joseph disease) are the most common which can present with a spastic paraparesis, however in both of these conditions, age at onset is in adulthood.[38,39]

If neuropathy dominates the clinical picture over spasticity and ataxia, Charcot-Marie-Tooth (CMT) disease may be considered.[6] A number of other rare causes of ataxia or spastic paraparesis may need to be considered including spastic ataxia types 1 to 5 (SPAX1-5), abetalipoproteinaemia, ataxia with vitamin E deficiency (AVED), ataxia with coenzyme Q10 deficiency, Niemann-Pick disease type C, Refsum's disease and autosomal recessive cerebellar ataxia type 2 (ARCA2), for which genetic or metabolic tests are available.[40]

Once acquired causes of spastic ataxia have been excluded, the combination of age at onset, suspected mode of inheritance, associated clinical, neuroimaging, neurophysiological and other features should guide genetic testing. In the future, next generation[41] and whole exome sequencing will allow parallel testing of multiple suspected genes, although it will remain vital to interpret the results in terms of pre-existing suspicions from careful clinical phenotyping.

Conclusions

The triad of early-onset ataxia, spasticity and axonal-demyelinating neuropathy, together with sporadic or autosomal recessive inheritance, prominent superior cerebellar and cervical atrophy on MRI and no extraneurological features, should provoke the suspicion of ARSACS. Many formes frustes will continue to be described as genetic techniques permit the identification of more cases. The presence of pontine linear hypointensities on MRI and thickened retinal nerve fibres on OCT, appear to be sensitive markers of ARSACS. All suspected cases should therefore undergo these two tests. Cellular and animal models, and molecular biological techniques are beginning to elucidate the underlying pathophysiology of this condition which may permit the first interventional trials. ◆

REFERENCES

1. Dupré N, Bouchard JP, Brais B, Rouleau GA. *Hereditary ataxia, spastic paraparesis and neuropathy in the French-Canadian population.* Can J Neurol Sci 2006;33(2):149-57.
2. Bouchard JP, Barbeau A, Bouchard R, Bouchard RW. *Autosomal recessive spastic ataxia of Charlevoix-Saguenay.* Can J Neurol Sci 1978;5(1):61-9.
3. Thiffault I, Dicaire MJ, Tetreault M, et al. *Diversity of ARSACS mutations in French-Canadians.* Can J Neurol Sci 2013;40(1):61-6.
4. Engert JC, Berube P, Mercier J, et al. *ARSACS, a spastic ataxia common in northeastern Quebec, is caused by mutations in a new gene encoding an 11.5-kb ORF.* Nat Gen 2000;24(2):120-5.
5. Bouhlal Y, Amouri R, El Euch-Fayeche G, Hentati F. *Autosomal recessive spastic ataxia of Charlevoix-Saguenay: an overview.* Parkinsonism Rel Dis 2011;17(6):418-22.
6. Synofzik M, Soehn AS, Gburek-Augustat J, et al. *Autosomal recessive spastic ataxia of Charlevoix Saguenay (ARSACS): expanding the genetic, clinical and imaging spectrum.* Orphanet J Rare Dis 2013;8:41.
7. Ouyang Y, Takiyama Y, Sakoe K, et al. *Sacsin-related ataxia (ARSACS): expanding the genotype upstream from the gigantic exon.* Neurol 2006;66(7):1103-4.
8. Baets J, Deconinck T, Smets K, et al. *Mutations in SACS cause atypical and late-onset forms of ARSACS.* Neurol 2010;75(13):1181-8.
9. Breckpot J, Takiyama Y, Thienpont B, et al. *A novel genomic disorder: a deletion of the SACS gene leading to spastic ataxia of Charlevoix-Saguenay.* Eur J Hum Gen 2008;16(9):1050-4.
10. McMillan HJ, Carter MT, Jacob PJ, et al. *Homozygous contiguous gene deletion of 13q12 causing LGMD2C and ARSACS in the same patient.* Muscle Nerve 2009;39(3):396-9.
11. Girard M, Lariviere R, Parfitt DA, et al. *Mitochondrial dysfunction and Purkinje cell loss in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS).* Proc Nat Acad Sci USA 2012;109(5):1661-6.
12. Parfitt DA, Michael GJ, Vermeulen EG, et al. *The ataxia protein sacsin is a functional co-chaperone that protects against polyglutamine-expanded ataxin-1.* Hum Mol Gen 2009;18(9):1556-65.
13. Peyronnard JM, Charron L, Barbeau A. *The Neuropathology of Charlevoix-Saguenay Ataxia: An Electrophysiological and Pathological Study.* Can J Neurol Sci 1979;6(2):199-203.
14. El Euch-Fayache G, Lalani I, Amouri R, et al. *Phenotypic features and genetic findings in sacsin-related autosomal recessive ataxia in Tunisia.* Arch Neurol 2003;60(7):982-8.
15. Takiyama Y. *Autosomal recessive spastic ataxia of Charlevoix-Saguenay.* Neuropath 2006;26(4):368-75.
16. Bouchard JP, Richter A, Mathieu J, et al. *Autosomal recessive spastic ataxia of Charlevoix-Saguenay.* Neuromusc Dis 1998;8(7):474-9.
17. Stevens JC, Murphy SM, Davagnanam I, et al. *The ARSACS phenotype can include supranuclear gaze palsy and skin lipofuscin deposits.* J Neurol Neurosurg Psychiatry 2013;84(1):114-6.
18. Bouchard JP. *Recessive spastic ataxia of Charlevoix-Saguenay.* Handbook Clin Neurol 1991;16(60):451-9.
19. Duquette A, Brais B, Bouchard JP, Mathieu J. *Clinical presentation and early evolution of spastic ataxia of Charlevoix-Saguenay.* Mov Dis 2013 Aug 2. doi: 10.1002/mds.25604. [Epub ahead of print]
20. Takiyama Y. *Sacsinopathies: sacsin-related ataxia.* Cerebellum 2007;6(4):353-9.
21. Prodi E, Grisoli M, Panzeri M, et al. *Supratentorial and pontine MRI abnormalities characterize recessive spastic ataxia of Charlevoix-Saguenay. A comprehensive study of an Italian series.* Eur J Neurol 2013;20(1):138-46.
22. Gazulla J, Benavente I, Vela AC, et al. *New findings in the ataxia of Charlevoix-Saguenay.* Journal of neurology 2012;259(5):869-78.
23. Vermeer S, Meijer RP, Pijl BJ, et al. *ARSACS in the Dutch population: a frequent cause of early-onset cerebellar ataxia.* Neurogenetics 2008;9(3):207-14.
24. Terracciano A, Casali C, Grieco GS, et al. *An inherited large-scale rearrangement in SACS associated with spastic ataxia and hearing loss.* Neurogenetics 2009;10(2):151-5.
25. Martin MH, Bouchard JP, Sylvain M, St-Onge O, Truchon S. *Autosomal recessive spastic ataxia of Charlevoix-Saguenay: a report of MR imaging in 5 patients.* Am J Neuroradiol 2007;28(8):1606-8.
26. Terracciano A, Foulds NC, Ditchfield A, et al. *Pseudodominant inheritance of spastic ataxia of Charlevoix-Saguenay.* Neurol 2010;74(14):1152-4.
27. Shimazaki H, Takiyama Y, Honda J, et al. *Middle cerebellar peduncles and Pontine T2 hypointensities in ARSACS.* J Neuroimaging 2013;23(1):82-5.
28. Shimazaki H, Sakoe K, Niijima K, Nakano I, Takiyama Y. *An unusual case of a spasticity-lacking phenotype with a novel SACS mutation.* J Neurol Sci 2007;255(1-2):87-9.
29. Desserre J, Devos D, Sautiere BG, et al. *Thickening of peripapillar retinal fibers for the diagnosis of autosomal recessive spastic ataxia of Charlevoix-Saguenay.* Cerebellum 2011;10(4):758-62.
30. Garcia-Martin E, Pablo LE, Gazulla J, et al. *Retinal nerve fibre layer thickness in ARSACS: myelination or hypertrophy?* Br J Ophthalmol 2013;97(2):238-41.
31. Nethisinghe S, Clayton L, Vermeer S, et al. *Retinal Imaging in Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay.* Neuro-Ophthalmol 2011;35(4):197-201.
32. Pablo LE, Garcia-Martin E, Gazulla J, et al. *Retinal nerve fiber hypertrophy in ataxia of Charlevoix-Saguenay patients.* Mol Vis 2011;17:1871-6.
33. Vingolo EM, Di Fabio R, Salvatore S, et al. *Myelinated retinal fibers in autosomal recessive spastic ataxia of Charlevoix-Saguenay.* Eur J Neurol 2011;18(9):1187-90.
34. Raftopoulos R, Trip A. *The Application of Optical Coherence Tomography (OCT) in Neurological Disease.* ACNR 2012;12(2):30-3.
35. Parkinson MH, Boesch S, Nachbauer W, Mariotti C, Giunti P. *Clinical features of Friedreich's ataxia: classical and atypical phenotypes.* J Neurochem 2013;126:103-17.
36. de Bot ST, Willemsen MAAP, Vermeer S, et al. *Reviewing the genetic causes of spastic-ataxias.* Neurol 2012;79(14):1507-14.
37. Salinas S, Proukakis C, Crosby A, Warner TT. *Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms.* Lancet Neurol 2008;7(12):1127-38.
38. Giunti P, Sweeney MG, Spadaro M, et al. *The trinucleotide repeat expansion on chromosome 6p (SCA1) in autosomal dominant cerebellar ataxias.* Brain 1994;117(4):645-9.
39. Giunti P, Sweeney MG, Harding AE. *Detection of the Machado-Joseph disease/spinocerebellar ataxia three trinucleotide repeat expansion in families with autosomal dominant motor disorders, including the Drew family of Walworth.* Brain 1995;118(5):1077-85.
40. Anheim M, Tranchant C, Koenig M. *The Autosomal Recessive Cerebellar Ataxias.* New Engl J Med 2012;366(7):636-46.
41. Németh AH, Kwasniewska AC, Lise S, et al. *Next generation sequencing for molecular diagnosis of neurological disorders using ataxias as a model.* Brain 2013;136(10):3106-18.

Advances in our Understanding of the Brain Mechanisms of Freezing of Gait in Parkinson's Disease

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Freezing of gait (FOG) is a devastating symptom that affects the majority of patients with advanced Parkinson's disease (PD). It typically manifests as a sudden inability to move the lower limbs despite the intention to walk.[1] However, the phenomenon is not limited to gait and individuals with PD have been shown to suffer from freezing in other movements, such as handwriting, brushing teeth and even speech. The pathophysiology underlying freezing is not well understood but a number of recent research approaches have led to insights that offer the prospect of new avenues for therapeutic intervention and management.

Due to the obvious problems associated with the neuroimaging of gait disorders, the investigation of the neural basis of FOG has been problematic. Although potentially very informative, studies usually suffer from limits in temporal precision (such as Positron Emission Tomography) or are required to provide challenging links between imaging results and behaviour (such as tasks that measure brain activity while subjects watch a first-person perspective video of an actor walking). To combat these issues, a novel Virtual Reality (VR) paradigm in which subjects navigate a non-immersive, yet realistic three-dimensional environment using footpedals to control their 'walking' has been developed.[2] The VR task requires bipedal motor activity whilst processing cognitive and environmental information. Importantly, the task can successfully and safely elicit motor freezing in susceptible individuals and performance on the VR task has been correlated with self-reported FOG symptoms[2] and more recently, with the severity of actual recorded episodes of FOG.[3]

This validated VR technology can also be combined safely with fMRI to provide unique insights into the pathophysiological mechanism of freezing. A recently published study has provided evidence that freezing behaviour in the VR task is associated with hyper-activity within cortical regions subserving cognitive operations but with concomitant decreases in the activity within the striatum, a key region within the basal ganglia nuclei.[4] A subsequent study has demonstrated that these cortical and subcortical regions show functional decoupling at the network level.[5] That is, the cortical and subcortical structures communicate well during effective navigation of the VR task, however when a subject shows evidence of a breakdown in the normal footstep pattern, their corticostriatal networks show a similar breakdown in effective communication. Together, these imaging studies provide convincing evidence that the dynamic process of freezing is due to paroxysmal breakdowns in communication between large-scale networks within the brain.

The results from these fMRI studies are also supported by recent evidence obtained from an ambulatory electroencephalography (EEG) study in which the electrophysiological correlates of brain activity have been measured whilst patients with FOG navigated a standardised clinical walking assessment (timed up-and-go). After strict correction for movement-related artefacts, it has been shown that episodes of freezing were associated with an increase in theta band power (~3-7Hz) over the central and frontal regions, which broadly map to motor execution and planning regions of the brain, respectively. In addition, there was a transition in the degree of synchrony between different regions in the theta frequency over the temporal evolution of a freezing episode, further supporting the notion that FOG is due to impaired functional coupling between distant brain regions.

Using these objective insights has led to a revised framework[6] that extends a previously proposed model of freezing behaviour,[7] in which freezing behaviour was conceptualised as occurring secondary to transient increases in GABAergic neuronal activity within the output structures of the basal ganglia (such as the globus pallidus internus), which ultimately manifests as an overwhelming inhibition of the key targets of the basal ganglia, such as the anterior thalamus and the brainstem structures controlling gait.[7] Although the previous model made specific predictions regarding the likely behavioural predictors of freezing behaviour, the recent insights gained from the aforementioned neuroimaging and neurophysiological studies have helped to clarify the role of impaired corticostriatal coupling in the pathophysiological manifestation of FOG. For example, there is now evidence to suggest that impairments in neural coupling may precede freezing, providing a potential therapeutic avenue[5].

In addition, the neuroimaging studies above have also provided clues that help to link the impaired corticostriatal coupling to the final manifestation of freezing, which is most likely related to increased firing within the output structures of the basal ganglia. These results implicate dysfunction within the 'hyper-direct' pathway of the basal ganglia, which links regions of the medial frontal cortex (such as the pre-supplementary motor area or pSMA) with the subthalamic nucleus of the basal ganglia.[8] Through its connection to the pSMA, the STN is able to bypass the striatum and directly drive an increase in inhibitory GABAergic output from

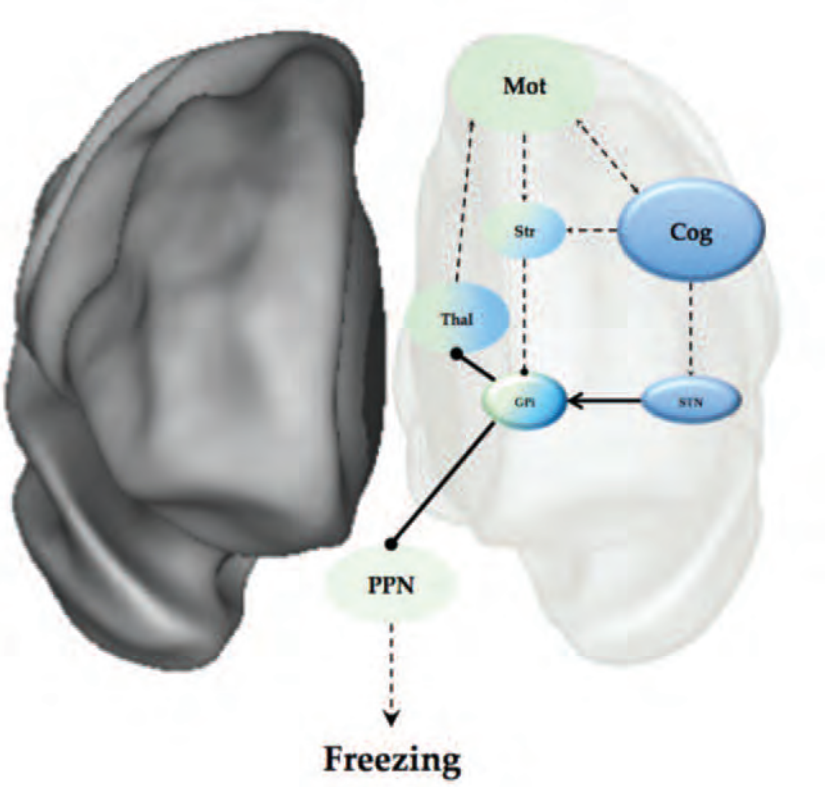

Figure 1 – Graphical depiction of the updated model of freezing behaviour. Increases in response conflict lead to functional decoupling between large-scale networks responsible for Motor (Mot) and Cognitive (Cog) operations. In addition, the cortical regions within these networks also become decoupled from their striatal targets, leading to an increase in the GABAergic outflow from the globus pallidus internus (GPi). The increased response conflict also leads to increased firing within the subthalamic nucleus (STN), perhaps due to a lack of functional communication with the Cog network. Together, these neural changes manifest as overwhelming inhibitory outflow onto the anterior thalamus (Thal) and the pedunculopontine nucleus (PPN), leading to decreased corticothalamic and brainstem activity, respectively, ultimately manifesting as freezing.

the output structures of the basal ganglia, such as the internal segment of the globus pallidus (GPi). Increased activity in the GPi, which is a member of the direct pathway of the basal ganglia, leads to an increase in the rate of inhibitory output onto the brainstem and thalamic structures that control the output of effective motor behaviours[7] (see Figure 1). Importantly, the STN has been shown to increase its firing rate during periods of response conflict,[9] suggesting that transient increases in STN firing may represent the pathophysiological link between impaired corticostriatal coupling during periods of increased response conflict, leading to an increase in the inhibitory output of the basal ganglia.[7] This overwhelming inhibition of the brainstem structures controlling gait, such as the PPN, would impair motor initiation due to the PPNs efferent connectivity with the central pattern generators in the spinal cord controlling gait.[10]

These proposed roles of the STN are well supported by both behavioural[11] and neuroimaging evidence.[12] For example, the STN has been consistently implicated in set-shifting behaviour,[13] which has been shown to be impaired in patients with freezing.[14] Furthermore, the role of the STN in freezing is aligned with the previously described functional neuroimaging studies that showed evidence that the globus pallidus and the STN enter into a low energy oscillatory state during freezing behaviour.[4,5]

These new insights into the pathophysiological mechanism of freezing behaviour suggest a number of exciting directions for future studies. For instance, the VR task could be combined with direct cellular recordings during deep brain stimulation surgery to test the hypothetical prediction that freezing is associated with increased firing within the STN. In addition, the combination of these insights with the temporal predictive capacity of EEG could also potentially inform future therapeutics, perhaps utilising specific neurophysiological signatures to 'tune' a closed loop deep brain stimulation feedback system[15] that might even offer the potential of aborting freezing episodes. ◆

REFERENCES

1. Giladi N, Kao R, Fahn S. *Freezing phenomenon in patients with parkinsonian syndromes.* Mov Disord. 1997;12(3):302-5.
2. Naismith SL, Lewis SJG. *A novel paradigm for modelling freezing of gait in Parkinson's disease.* J Clin Neurosci. 2010;17(8):984-7.
3. Shine JM, Matar E, Bolitho SJ, Dilda V, Morris TR. *Modeling freezing of gait in Parkinson's disease with a virtual reality paradigm.* Gait Posture. 2012;38(1):104-8.
4. Shine JM, Matar E, Ward PB, Bolitho SJ, Gilat M, Pearson M, et al. *Exploring the cortical and subcortical functional magnetic resonance imaging changes associated with freezing in Parkinson's disease.* Brain. 2013;136(Pt 4):1204-15.
5. Shine JM, Matar E, Ward PB, Frank MJ, Moustafa AA, Pearson M, et al. *Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia.* Brain. EPub ahead of Print.
6. Shine JM, Moustafa AA, Matar E, Frank MJ, Lewis SJG. (2013). *The role of frontostriatal impairment in freezing of gait in Parkinson's disease.* Front Syst Neurosci. 7:61.
7. Lewis SJG, Barker RA. *A pathophysiological model of freezing of gait in Parkinson's disease.* Parkinsonism Relat Disord. 2009;15(5):333-8.
8. Aron AR, Robbins TW, Poldrack RA. *Inhibition and the right inferior frontal cortex.* Trends Cogn Sci. 2004;8(4):170-7.
9. Cavanagh JF, Wiecki TV, Cohen MX, Figueroa CM, Samanta J, Sherman SJ, et al. *Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold.* Nature Neurosci. 2011;14(11):1462-7.
10. Lemon RN. *Descending pathways in motor control.* Annu Rev Neurosci. 2008;31:195-218.
11. Frank MJ. *Hold your horses: A dynamic computational role for the subthalamic nucleus in decision making.* Neural Networks. 2006;19(8):1120-36.
12. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. *Triangulating a Cognitive Control Network Using Diffusion-Weighted Magnetic Resonance Imaging (MRI) and Functional MRI.* J Neurosci. 2007;27(14):3743-52.
13. Block AE, Dhanji H, Thompson-Tardif SF, Floresco SB. *Thalamic-prefrontal cortical-ventral striatal circuitry mediates dissociable components of strategy set shifting.* Cereb Cortex. 2007;17(7):1625-36.
14. Shine JM, Naismith SL, Palavra NC, Lewis SJG, Moore ST, Dilda V, et al. *Attentional set-shifting deficits correlate with the severity of freezing of gait in Parkinson's disease.* Parkinsonism Relat Disord. 2012;19(3):388-90.
15. Rosin B, Slovik M, Mitelman R, Rivlin-Etzion M, Haber SN, Israel Z, et al. *Closed-loop deep brain stimulation is superior in ameliorating parkinsonism.* Neuron. 2011;72(2):370-84.

transient increases in subthalamic nucleus firing may represent the pathophysiological link between impaired corticostriatal coupling during periods of increased response conflict and an increase in the inhibitory output of the basal ganglia

Introduction to the ACNR Headache Series

Headache is the most common neurological disorder seen in neurology outpatient clinics and in an emergency setting. Headache is associated with low mortality but high morbidity, largely affecting the working population. Yet medical attention and with it resources are instinctively driven towards the few with fatal outcome. In 2013, *ACNR* published the first part of this Headache series addressing these very issues – Secondary Headache (Bahra) and at the other end of the spectrum, Chronic Daily Headache (Katsarava and Obermann), where the burden of economic disability lies.

In 2014 the series will move on to look at the less common headache disorders, such as the Trigeminal Autonomic Cephalalgias, the prevalent but under-diagnosed Migraine with Vestibular aura, management of Headache in Pregnancy and Current Advances in Treatment options. Key to insightful management is a progressive understanding of central nervous system mechanisms in generating headache disorders. In the current issue Phil Holland and Shazia Afridi explain the complexities of an inherently dysfunctional pain network as demonstrated from both pre-clincial and clinical studies.

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Migraine Pathophysiology

Summary

- Migraine is a disabling neurovascular disorder
- Key diencephalic and brainstem nuclei play critical roles in the pathophysiology of migraine
- Functional imaging has revealed the dorsal pons is activated during migraine and the hypothalamus in the premonitory phase

Migraine is among the most common neurological disorders affecting humans, which is ranked 7th most disabling by the WHO. The underlying pathophysiology will be discussed herein; however the readers are also directed towards recent reviews exploring novel genetic susceptibility loci and therapeutic targets.[1,2] It is now widely accepted that migraine is a disease of the brain with the pain component reliant on activation and disrupted modulation of the trigeminovascular system (Figure 1).[3]

The anatomy of the trigeminovascular system

The trigeminovascular system originates in the dense plexus of nociceptors which innervate the cranial vasculature and dura matter, the central projections of which travel via the trigeminal ganglion (TG) and synapse on second order neurons in the dorsal horn giving rise to the trigeminal cervical complex (TCC). Activation of these sensory afferents results in the release of a number of neuropeptides, in both humans and animals, which have actions on the cerebrovasculature and spinal cord. The TCC has direct ascending connections with areas of the brainstem (locus coeruleus (LC) and periaqueductal grey (PAG)), thalamus and hypothalamus via the trigeminothalamic and trigeminohypothalamic tracts en route to cortical structures. In addition to the ascending projections there is also a reflex connection from the TCC to the parasympathetic system via the superior salivatory nucleus (SuS) and sphenopalantine ganglion (SPG). This connection results in cranial autonomic features, which are seen in approximately 30-40% of migraineurs, are diagnostic for cluster headache and, currently a target of neurostimulation and proposed action of oxygen,[4] and efferent connections from the facial and cervical dermatomes (via cervical ganglia, CG).

Migraine is a disorder of dysfunctional central sensory processing

A combination of seminal preclinical and brain imaging studies have highlighted the importance of key pontine, brainstem and diencephalic structures involved in the pain neuroaxis in migraine.

Thalamus

The trigeminothalamic tract terminates in multiple thalamic nuclei, which are activated in migraine, SUNCT and cluster headache, and are involved in the parallel processing of nociceptive information, en route to cortical areas.[4] Trigeminovascular activation in experimental models activates specific nuclei which have been shown to be possible sites of action for anti-

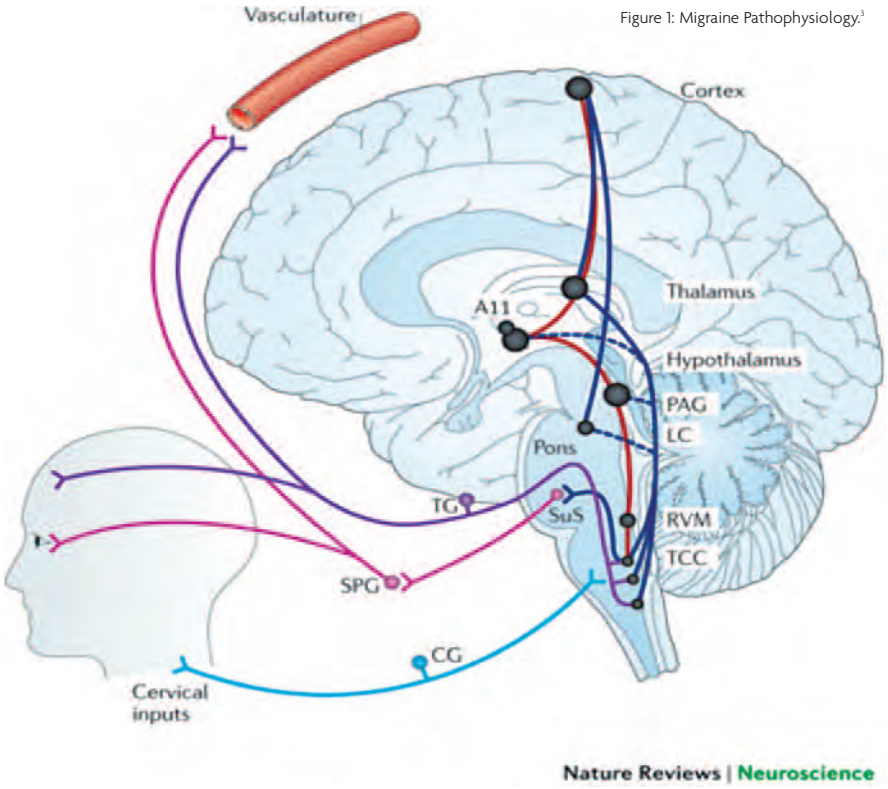


Figure 1: Migraine Pathophysiology.[3]

migraine therapeutics including the triptans. Moreover, sensitisation of thalamic neurons has been implicated in the spread of cutaneous allodynia and where convergent inputs from light sensitive ganglion cells exist, photophobia.[5]

Trigeminovascular modulation

It is now widely accepted that disruption of normal pain modulatory tone plays a critical role in primary headaches (Figure 1). The hypothalamus has a critical role in the pain neuroaxis and a multitude of functions, which may underlie certain migraine premonitory symptoms. The hypothalamus (and the associated A11 nuclei) has clear projections to the TCC and is activated during headache disorders[6] and trigeminovascular stimulation. Recently the hypothalamic orexinergic[7] and dopaminergic[8] pathways have gained attention for their role in trigeminovascular modulation and associated symptoms, with a dual orexin receptor antagonist currently undergoing phase 2 clinical trials.

Activation of the trigeminovascular system results in neuronal activation in numerous pontine and brainstem regions including the LC and PAG.[9-13] Stimulation of these nuclei can result in altered cerebral blood flow and inhibition of trigeminal neuronal activity, while pharmacological modulation can result in inhibition or facilitation of trigeminovascular nociceptive processing.[14] Interestingly the brainstem has been implicated in the generation of central sensitisation, with a likely role in disease chronification.

While we have not discussed the role of cortical spreading depression (CSD) here, we refer the reader to an excellent recent review[15] and imaging data below regarding the occurrence of CSD like events in humans, thought to underlie the aura of migraine.

Imaging Insights into the pathophysiology of migraine

migraine is considered to be a neurovascular disorder. It is thought that any vascular changes are a consequence rather than a cause. MRA has revealed an absence of extracranial artery dilatation during spontaneous migraine attacks in 19 subjects with unilateral headache.[16] There was slight intracranial dilatation (10%) on the pain side but this was not altered by sumatriptan administration.

Premonitory phase

Many migraineurs experience premonitory symptoms such as yawning, thirst, neck stiffness or polyuria up to three days prior to the headache.[17] A PET study of eight subjects used glyceryl trinitrate (GTN), a known migraine trigger[18], to study the premonitory phase.[12] Hypothalamic activation was found in the early premonitory phase. The authors postulate that hypothalamic and ventral tegmental involvement would explain yawning related to dopaminergic mechanisms; frequent urination and thirst may relate to reduced vasopressin and mood changes through hypothalamic connections with the limbic system. Hypothalamic activation has been noted in only one previous study during migraine (within four hours of onset) although this study did not look at the premonitory phase specifically[6].

Imaging aura

In a BOLD fMRI study signal intensities increased in the red nucleus, substantia nigra and occipital cortex when aura was triggered using a checker-board stimulus.[10] The onset of headache or visual change was preceded by suppression of initial activation. No clear evidence of ischaemia was noted in this study.

In a more detailed study involving five attacks of migraine with aura, two induced by exercise and three spontaneous, an initial focal increase in BOLD signal (thought to reflect vasodilatation) developed within the extrastriate visual cortex.[19] This signal then propagated contiguously at a rate of 3.5 ± 1.1 mm/min over the occipital cortex, congruent with the retinotopy of the visual percept (Figure 2). The BOLD signal then diminished, possibly reflecting vasoconstriction. The spreading phenomenon did not cross prominent sulci and were restricted to the hemisphere corresponding to the aura.

Headache

The first PET study detailing regional activation during migraine without aura involved nine subjects scanned within six hours of onset of migraine. Brainstem activation was revealed during the migraine and persisted after sumatriptan administration had relieved the pain.[13] The resolution of the PET camera used was not high enough to identify specific nuclei, but the dorsal midbrain, which contains the dorsal raphe nucleus and PAG, was thought to be involved.

Brainstem activation was also demonstrated in a study of five subjects with spontaneous migraine.[20] Two had typical migraine aura prior to the onset of the headache. Activation was seen in the dorsal pons and

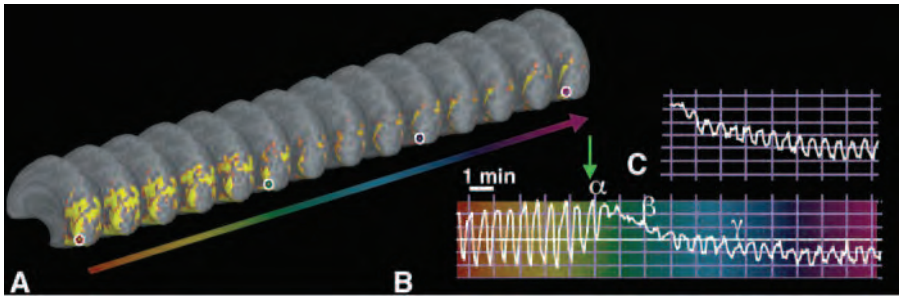


Figure 2: (A) A series of anatomical images, including BOLD activity on "inflated" cortical hemispheres. Time-dependent BOLD activity changes from a single region of interest in VI, acquired before and during episodes of either or induced (B) or spontaneous (C) visual aura.

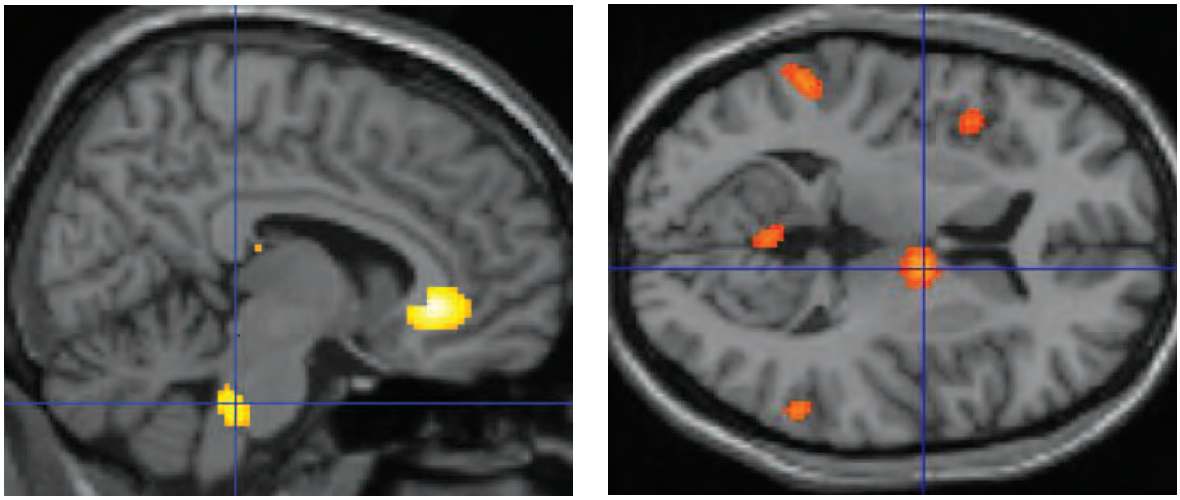


Figure 3: Activation in brainstem (a-left) and thalamus (b-right) during migraine.[9,20]

thalamus (Figure 3) but also in areas which form part of the pain matrix: right anterior cingulate, posterior cingulate, cerebellum, insula, prefrontal cortex and temporal lobes.

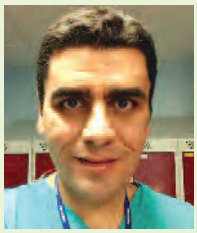
The largest PET study, to date, involved 24 migraineurs (with and without aura) and eight healthy controls[9] and investigated laterality. The migraineurs were divided into three groups according to the site of their headache: right, left or bilateral. Migraine was induced using a GTN infusion. Brainstem activation was seen in the dorsal pons during the migraine state versus the pain-free state when comparing migraineurs to controls. When each group was analysed separately to investigate laterality it was found that the dorsal pontine activation was ipsilateral in the right-sided and left-sided groups and bilateral in the bilateral headache group with a left-sided preponderance.

The demonstration of key brainstem and diencephalic involvement in migraine and its experimental models, which form integral parts of the descending pain modulatory networks (Figure 1), highlights their critical role in primary headache disorders. They are ideally located to modulate the trigeminovascular system, cerebrovasculature, cortical activity, and the integration of external stimuli. Thus it is likely that dysregulation of these central nervous system networks underlie not just the migraine attack, but also the array of associated symptoms. ◆

REFERENCES

1. Ferrari MD. *Headache: the changing migraine brain.* Lancet neurology. 2013;12:6-8.
2. Goadsby PJ. *Therapeutic prospects for migraine: Can paradise be regained?* Annals of neurology. 2013;74:423-34.
3. Akerman S, Holland PR, Goadsby PJ. *Diencephalic and brainstem mechanisms in migraine.* Nature reviews. 2011;12:570-84.
4. Akerman S, Holland PR, Lasalandra MP, Goadsby PJ. *Oxygen inhibits neuronal activation in the trigeminocervical complex after stimulation of trigeminal autonomic reflex, but not during direct dural activation of trigeminal afferents.* Headache. 2009;49:1131-43.
5. Noseda R, Burstein R. *Migraine pathophysiology: Anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain.* Pain. 2013;154S1:S44-S53.
6. Denuelle M, Fabre N, Payoux P et al. *Hypothalamic activation in spontaneous migraine attacks.* Headache. 2007;47:1418-26.
7. Holland P, Goadsby PJ. *The hypothalamic orexinergic system: pain and primary headaches.* Headache. 2007;47:951-62.
8. Charbit AR, Akerman S, Holland PR, Goadsby PJ. *Neurons of the dopaminergic/calcitonin gene-related peptide A11 cell group modulate neuronal firing in the trigeminocervical complex: an electrophysiological and immunohistochemical study.* J Neurosci. 2009;29:12532-41.
9. Afridi SK, Matharu MS, Lee L et al. *A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate.* Brain. 2005;128:932-9.
10. Cao Y, Aurora SK, Nagesh V et al. *Functional MRI-BOLD of brainstem structures during visually triggered migraine.* Neurology. 2002;59:72-8.
11. Hoskin KL, Bulmer DC, Lasalandra M et al. *Fos expression in the midbrain periaqueductal grey after trigeminovascular stimulation.* Journal of anatomy. 2001;198:29-35.
12. Maniyar FH, Sprenger T, Monteith T et al. *Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks.* Brain. 2013.
13. Weiller C, May A, Limmroth V et al. *Brain stem activation in spontaneous human migraine attacks.* Nature medicine. 1995;1:658-60.
14. Akerman S, Holland PR, Lasalandra MP, Goadsby PJ. *Endocannabinoids in the brainstem modulate dural trigeminovascular nociceptive traffic via CB1 and "triptan" receptors: implications in migraine.* J Neurosci. 2013;33:14869-77.
15. Charles AC, Baca SM. *Cortical spreading depression and migraine.* Nat Rev Neurol. 2013;9:637-44.
16. Amin FM, Asghar MS, Hougaard A et al. *Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross-sectional study.* Lancet neurology. 2013;12:454-61.
17. Giffin NJ, Ruggiero L, Lipton RB et al. *Premonitory symptoms in migraine: an electronic diary study.* Neurology. 2003;60:935-40.
18. Afridi SK, Kaube H, Goadsby PJ. *Glyceryl trinitrate triggers premonitory symptoms in migraineurs.* Pain. 2004;110:675-80.
19. Hadjikhani N, Sanchez Del Rio M, Wu O et al. *Mechanisms of migraine aura revealed by functional MRI in human visual cortex.* Proceedings of the National Academy of Sciences of the United States of America. 2001;98:4687-92.
20. Afridi SK, Giffin NJ, Kaube H et al. *A positron emission tomographic study in spontaneous migraine.* Archives of neurology. 2005;62:1270-5.

Collaborative Research Networks: the way forward for clinical neurosciences research?



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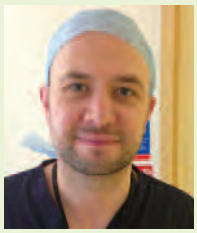

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Summary

- Over the last five years, surgical trainee research collaboratives have been established at a regional and national level throughout the UK.
- The British Neurosurgical Trainee Research Collaborative (www.bntrc.org.uk) was formed as an initiative of the British Neurosurgical Trainees Association in 2012.
- The first UK-wide, prospective, observational study of the BNTRC, which was launched in June 2013, has already become the largest multi-centre study of patients with chronic subdural haematoma worldwide.
- Establishment of such networks in other clinical neuroscience disciplines will facilitate the set-up and delivery of cross-specialty studies in clinical neurosciences.

High quality clinical research is essential for improving patient care and outcomes. A multi-centre approach to clinical research is necessary not only in order to reach the required sample size in a shorter time frame but also in order to increase the external validity of findings. Of course, the latter is associated with a greater impact on 'real-world' practice.

Recent years have seen the emergence of trainee-led research collaboratives in surgical specialties across the United Kingdom. These networks have a number of benefits, both for trainees and clinical research studies. Trainees acquire an excellent grounding in clinical research methodology and skills, while at the same time improving their CV and portfolios. Undertaking trials in close collaboration with trainees can help reach recruitment targets faster and hence may also be cost-effective.[1]

Specialties that are located in a number of acute hospitals within each region (both regional hospitals and district general hospitals) have followed a model of regional collaboratives. These regional groups can undertake regional-based studies but also collaborate in the context of national networks. The trainee-led West Midlands Research Collaborative (WMRC; www.wmresearch.org.uk) is an example of a highly successful regional network in general surgery. The WRMC, with the support of experienced senior clinicians and researchers, designed and managed all aspects of the ROSSINI randomised trial from the outset to its conclusion. The ROSSINI trial, that was run by trainees 'from the ground' in the 21 participating sites, is a landmark study as it managed to secure funding from the NIHR Research for Patient Benefit (NIHR RfPB) programme and completed recruitment ahead of schedule.[2] In addition, the National General Surgical Research Collaborative recently published the Multicentre Appendicectomy Audit, that included 3326 consecutive patients from 95 centres during two months.[3]

Disciplines that are located in large regional hospitals (such as neurosurgery, cardiothoracic surgery, paediatric surgery etc) have adopted a model of national rather than regional networks. The British Neurosurgical Trainee Research Collaborative (BNTRC; www.bntrc.org.uk) was formed as an initiative of the British Neurosurgical Trainees

Association (BNTA; the representative body for neurosurgical trainees in the UK and Ireland) in 2012. During the BNTA spring general meeting (Aberdeen, April 2012), the proposal for establishing the BNTRC received unanimous support. Three study proposals were submitted during an open call from June to July 2012; this process culminated in a launch meeting that was attended by trainees from 21 different units, as well as by numerous consultants and senior academics at the Royal College of Surgeons of England in October 2012.[4]

The first UK-wide, prospective, observational study of the BNTRC was launched in June 2013: the National Audit of Chronic Subdural Haematoma. Prior to launching the audit, a collaborative process, overseen by the Academic Committee of the Society of British Neurological Surgeons (SBNS), led to the development of the first set of national audit standards for chronic subdural haematoma (CSDH) on the basis of best available evidence.[5] An electronic data collection module was also developed within the Outcome Registry Intervention and Operation Network (ORION) secure online platform. The vast majority of adult UK neurosurgical units have signed up to the audit, which has already become the largest multi-centre prospective study of patients with CSDH worldwide. Two randomised multi-centre trials and a further prospective cohort study are currently in development. The academic, structural, and logistical support provided by the SBNS, the Royal College of Surgeons of England, and the UK Neurosurgical Research Network (UKNRN) has also played an important role in the early success of the BNTRC.

We recognise that trainee involvement in research is not in itself something new. However, never before have trainees worked together across the UK in delivering high-quality clinical research.[6] A session focused on national trainee-led collaboratives during the National Research Collaborative Meeting (Friday 6 December 2013, Royal College of Surgeons of England; www.nationalresearch.org.uk) showcased the development of national collaboratives in all surgical specialties and anaesthesia.

Trainee-led research networks are likely to have a more pronounced impact on surgical specialties where research has traditionally taken a back seat in daily clinical practice. However, we believe that the momentum gathered can now be transferred to non-surgical specialties closely allied to their respective surgical counterparts. Therefore, we are very keen to share the experience we have gained so far with neuroscience disciplines -such as Neurology and Stroke medicine- in order to facilitate the development of trainee networks with a view to ultimately rolling out cross-specialty studies in clinical neurosciences. ◆

REFERENCES

1. Kolias AG, Cowie CJ, Tarnaris A, Hutchinson PJ, Brennan PM. *Proposal for a British neurosurgical trainee research collaborative.* Br J Neurosurg 2012;26:434-5.
2. Pinkney TD, Calvert M, Bartlett DC, Gheorghe A, Redman V, Dowswell G, Hawkins W, Mak T, Youssef H, Richardson C, Hornby S, Magill L, Haslop R, Wilson S, Morton D; West Midlands Research Collaborative; ROSSINI Trial Investigators. *Impact of wound edge protection devices on surgical site infection after laparotomy: multicentre randomised controlled trial (ROSSINI Trial).* BMJ 2013;347:f4305.
3. National Surgical Research Collaborative. *Multicentre observational study of performance variation in provision and outcome of emergency appendicectomy.* Br J Surg 2013;100:1240-52.
4. Kolias AG, Jones TL, Cowie CJ, Coulter IC, Afshari FT, Tarnaris A, Nelson RJ, Gray WP, Hutchinson PJ, Brennan PM; UK Neurosurgical Research Network; British Neurosurgical Trainee Research Collaborative. *A report from the inaugural meeting of the British Neurosurgical Trainee Research Collaborative held in the Royal College of Surgeons of England, 19 October 2012.* Br J Neurosurg 2013;27:307-10.
5. Coulter IC, Kolias AG, Marcus HJ, Ahmed AI, Alli S, Al-Mahfoudh R, Borg A, Cowie CJ, Hill CS, Joannides AJ, Jones TL, Kailaya-Vasan A, Livermore JL, Narayanamurthy H, Ngoga D, Shapey J, Tarnaris A, Gregson BA, Gray WP, Nelson RJ, Hutchinson PJ, Brennan PM; UK Neurosurgical Research Network, British Neurosurgical Trainee Research Collaborative. *Proposal for a prospective multi- centre audit of chronic subdural haematoma management in the United Kingdom and Ireland.* Br J Neurosurg 2013 [Epub ahead of print].
6. Bhangu A, Kolias AG, Pinkney T, Hall NJ, Fitzgerald JE. *Surgical research collaboratives in the UK.* Lancet 2013;382:1091-2.

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History of Neurology: Parkinson's Disease Before James Parkinson

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Introduction

Every neurologist knows that James Parkinson (1755-1824) published *An Essay on the Shaking Palsy* in 1817. In this work Parkinson described six personally observed cases, although three were only seen in passing, what Professor Andrew Lees has evocatively termed "street watch methodology", an experience which may be familiar to many neurologists even today. The eponym of Parkinson's disease was promoted later in the nineteenth century (1877) by Jean-Martin Charcot.[1]

A question long asked is whether Parkinson was describing a new disease in 1817, or whether he was simply the first to crystallise the clinical gestalt which we now recognise as "Parkinson's disease" (PD).

Parkinson and his pamphlet

Like authors before and since, Parkinson attempted a review of the previous literature in his account of the shaking palsy, mentioning the works of authors dating from classical antiquity (Galen) up until the eighteenth century (e.g. Gerard van Swieten, Hieronymus David Gaubius, William Cullen). Two authors whose works seem to have been of particular significance to Parkinson were Sylvius and Boissier de Sauvages.

Franciscus Sylvius de la Boë (1614-1672) was a Dutch physician and scientist who made a distinction between "those tremors which are produced by attempts at voluntary motion, and those which occur whilst the body is at rest"; the latter he termed *Tremor coactus*. This distinction still forms an important component of clinical history taking in the assessment of tremor disorders. Galen and van Swieten had also distinguished between rest and action tremor.[2]

François Boissier de Sauvages de la Croix (1706-1767) was a French physician and botanist. His interest for Parkinson was his description of *Scerotyrbe festinans*, the phenomenon whereby "Patients, whilst wishing to walk in the ordinary mode, are forced to run". Festination or festinant gait is a reflection of the postural instability which is one of the cardinal features of PD.

Whether these authors were describing PD is not clear, since they each mentioned only one aspect of the clinical phenotype. In recent years, an account by the Hungarian physician Ferenc Pápai Páriz (1649-1716) has been identified, the *Pax corporis* of 1690, in which all four cardinal signs of PD are described.[3] Parkinson does not reference this work, and it would seem highly unlikely that he knew of it, since it was written in Hungarian.

Parkinson's disease before Parkinson?

Appeal to the historical record may help to answer the question as to whether cases conforming to Parkinson's description occurred before his pamphlet. In this context it should be remembered that "shaking palsy" might have been used in ways other than that denoted by Parkinson. For example, Parkinson's almost exact contemporary Caleb Hillier Parry (1755-1822), based in rural Bath rather than cosmopolitan and industrial London, described in 1815 the "shaking palsy" in which the "head and limbs shake, more especially on any muscular exertion", a description perhaps more suggestive of essential tremor than Parkinson's disease.[4]

The surgeon and anatomist John Hunter (1728-1793) has been suggested to have described a case of PD in his Croonian Lecture of 1776:

> "Lord L-'s hands are almost perpetually in motion, ... When he is asleep his hands etc are perfectly at rest, but when he wakes, in a little time they begin to move."[5]

The French painter Nicolas Poussin (1594-1665) was from 1650 troubled with worsening tremor. A sophisticated tremor analysis of lines in selected of his works produced between the 1620s and 1660s has concluded that they show a progressive decrease in movement velocity, which would be consistent with a diagnosis of PD.[6]

Leonardo da Vinci (1452-1517) may also have described a case of PD. In a manuscript now in Windsor Castle he wrote:

> " ... in paralytics... who move their trembling limbs such as the head or the hands without permission of the soul; which soul with all its power cannot prevent these limbs from trembling."[5]

Calne and colleagues suggest that the reference to "paralytics" indicates a difficulty with voluntary movement[5] which might now be interpreted as hypokinesia.

Non-medical narratives

Non-medical narratives may sometimes contain descriptions of clinical disorders. There are several examples of novels which feature characters with PD, most published in recent years.[7,8] Charles Dickens (1812-1870) may have described progressive supranuclear palsy in 1857, over a century before the definitive clinical account of Steele, Richardson and Olszewski (1964).[9] Dickens may also have described Parkinson's disease in his characterisation of Frederick Dorrit in the novel *Little Dorrit* (1857). He "stooped a good deal", turned round in a "slow, stiff, stooping manner", and spoke with a "weak and quavering voice", which might be indicative of the typical posture of PD and, possibly, the hypophonic voice.[10]

William Shakespeare (1564-1616) is credited by one influential literary critic, Howard Bloom, with the "invention of the human",[11] so it is perhaps not

surprising that his plays and poetry are claimed to describe various clinical disorders including paralysis, stroke, sleep disturbances, epilepsy, dementia, and the neurology of syphilis.[12] Claims for PD have also been made,[13] for example in this quote from *Troilus and Cressida* (I:ii:172-5), wherein Ulysses is describing the ageing Achilles:

> And then, forsooth, the faint defects of age
> Must be the scene of mirth; to cough and spit
> And with a palsy fumbling on his gorget,
> Shake in and out the rivet.

The gorget is a piece of armour protecting the throat.

Conclusion

There are occasional accounts dating prior to 1817, in both medical and literary sources, which are suggestive of PD. The relative paucity of these reports has been ascribed to the fact that the disease typically occurs in those aged greater than the prevailing life expectancy of earlier historical periods, and that the symptoms were not easily distinguished from "normal senescence".[5] This echoes Parkinson's own comments in 1817 to the effect that remedies were seldom sought for the symptoms and signs he was describing, which may also explain why three of his cases were seen only in passing on the street. ◆

REFERENCES

1. Parkinson J. *An Essay on the Shaking Palsy 1817.* Chichester: Wiley-Blackwell, 2010.
2. Koehler PJ, Keyser A. *Tremor in Latin texts of Dutch physicians: 16th-18th centuries.* Mov Disord 1997;12:798-806.
3. Bereczki D. *The description of all four cardinal signs of Parkinson's disease in a Hungarian medical text published in 1690.* Parkinsonism Relat Disord 2010;16:290-3.
4. Larner AJ. *Neurological contributions of Caleb Hillier Parry.* Adv Clin Neurosci Rehabil 2004;4(3):38-9.
5. Calne DB, Dubini A, Stern G. *Did Leonardo describe Parkinson's disease?* N Engl J Med 1989;320:594.
6. Haggard P, Rodgers S. *The movement disorder of Nicolas Poussin.* Mov Disord 2000;15:328-34.
7. Haan J. *Protagonists with Parkinson's disease.* In: Bogousslavsky J, Dieguez S (eds.). *Literary medicine: brain disease and doctors in novels, theater, and film* (Frontiers of Neurology and Neuroscience Volume 31). Basel: Karger, 2013:178-87.
8. Van der Brugger H, Widdershaven G. *Being a Parkinson's patient: Immobile and unpredictably whimsical. Literature and existential analysis.* Medicine Health Care and Philosophy 2004;7:289-301.
9. Larner AJ. *Did Charles Dickens describe progressive supranuclear palsy in 1857?* Mov Disord 2002;17:832-3.
10. Larner AJ. *Charles Dickens qua neurologist.* Adv Clin Neurosci Rehabil 2002;2(1):22.
11. Bloom H. *Shakespeare: the invention of the human.* London: Fourth Estate, 1999.
12. Fogan L. *The neurology in Shakespeare.* Arch Neurol 1989;46:922-4.

UKABIF LAUNCHES MANIFESTO TO IMPROVE SERVICES FOR CHILDREN AND YOUNG PEOPLE WITH ACQUIRED BRAIN INJURY

"There is a general lack of understanding about the effects of Acquired Brain Injury (ABI) in children and young people, and a lack of awareness that over time ABI is a developing disability. Current care planning and service provision is woefully inadequate" said Professor Michael Barnes, Chair of the United Kingdom Acquired Brain Injury Forum (UKABIF) at the November launch of the UKABIF Manifesto 'Life After Brain Injury? A Way Forward'.

The charity is calling for a National Audit of brain injury incidence and rehabilitation not only for children and young people, but also for adults. As Professor Barnes pointed out: "How can you plan rehabilitation services if you don't have accurate data about the incidence and prevalence of ABI?".

This is the second Manifesto to be launched by UKABIF as part of its Campaign to highlight the need for improvements in the provision of services for people with ABI. The Manifesto outlines the importance of considering ABI as a chronic health condition with associated ongoing symptoms and emphasises that current care planning and service provision is inadequate. Education services also play a crucial role in the care pathway but personnel have limited knowledge of ABI. In addition practical, easy access to information is required for children, young people, their families and all professionals involved in their care and support.

Speaking at the launch Maureen Le Marinel, President of UNISON, Britain's biggest trade union with members in the public services and the essential utilities, talked about Katie, her niece, who was knocked down by a car and suffered an ABI. "UNISON is supporting the UKABIF Campaign because I've seen at first hand just how devastating an ABI in a young person can be. Although our NHS was brilliant there was a lack of information, service integration and co-ordination. And although the whole family is pivotal in the rehabilitation of the child they are often not considered such a key part of the process".

Lord Ramsbotham, Chair of the Criminal Justice and Acquired Brain Injury Interest Group, commented that there can be major consequences if children and young people are not monitored long-term – a study published in 2010 highlighted that almost 50% of young male offenders had a traumatic brain injury at some stage in their lives; a significantly higher prevalence than that expected in society as a whole. "ABI must be managed early to avoid long-term disability and monitored long-term for problems arising post-injury" said Lord Ramsbotham.

"ABI is a leading cause of death and disability" concluded Professor Barnes. "Our Manifesto presents four key recommendations which we hope health professionals, purchasers and providers of services will support and implement. By working together we can improve services and ensure the best possible outcomes."

Introduction to the ACNR Stroke Series

In the second article in the ACNR stroke series, we are delighted to have an article by Alex Leff on recovery of language and vision, key challenges in stroke rehabilitation where new insights into mechanisms have developed rapidly in recent years, with the beginnings of evidence-based treatments. Alex has been a pioneer in these fields, especially in translating new understanding of reading problems after stroke into web-based solutions for both treatment delivery and data collection. In this clear and succinct summary, he outlines the latest advances and challenges for the future.

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The Future of Stroke Rehabilitation:

recovery of language and vision

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Leff AP, ACNR 2014;V13(7):26-8

Language

Normal language function is usually dependent on an intact left-hemisphere; however, the current neuroscientific evidence suggests that individual language functions are supported by a network of nodes and connections.[1] For instance, naming is subserved by an extensive network that is vulnerable to damage at many of its nodes which is why most aphasic patients suffer from anomia. Acquired language impairment (dysarthria or aphasia) is the second commonest major symptom caused by stroke, with an estimate prevalence of 250,000 in the UK.

Evidence base for speech therapy for aphasia

Despite occasional high profile papers that appear to show that speech and language therapy (SALT) is no better than non-specialist interventions,[2] the evidence for the overall effectiveness of SALT is pretty clear, even Cochrane agrees: "We identified 39 trials involving 2518 randomised participants that were suitable for inclusion in this review. Overall, the review shows evidence from randomised trials to suggest there may be a benefit from speech and language therapy but there was insufficient evidence to indicate the best approach to delivering speech and language therapy.[3]"

Bhogal's meta-analysis treated the data in an interesting way, segregating positive from negative SALT studies and asking what the systematic differences between them were.[4] The answer was compelling: positive studies delivered ~100 hours of therapy, while patients in negative studies clocked-up only 45 hours of therapy. Unfortunately, the average out-patient NHS dose is 8-12 hours in total.[5]

Future for SALT

Given what we know about the total dose required and the lack of SALT time, computer-based or web-based therapies are probably the most promising way to deliver enough dose of appropriate SALT to aphasic patients. There are many e-therapy devices or programmes available with over 50 software programs and over 40 apps: http://www.aphasia-softwarefinder.org/. Unfortunately, almost none have been subject to a clinical trial.

Quite a large range of drug therapies have been trialed in aphasia. Well-designed studies (placebo-controlled, double-blind) have been carried out that show significant improvements when L-dopa, memantine or donepezil are used. In studies where the drug was paired with behavioural therapy, the SALT effect sizes average at a fairly consistent 0.3 while the drug effects can be substantially higher than this but are patchy by comparison.[6]

Another promising adjuvant is transcranial direct current stimulation (tDCS). In this technique a small current is passed through the brain using a battery and scalp electrodes. Because the current is continuous, there is no sensory stimulation to the scalp making this an easy technique to double-blind. It is not yet clear which regime to use (strength of current, exact placement of leads, activation of left, right or both hemispheres)[7] but if tDCS effects on language follow in the foot-steps of motor system research, then modest gains of about a third, compared with the effect of practice alone, can be expected.

Exactly when therapy should be delivered is still an open question. "As soon as possible" seems an obvious answer but the jury is still out on the effects of high-intensity speech therapy in the acute phase. It is important to remember that with survival rates increasing (current five-year survival is now at 82% in the UK[8]), the vast majority of aphasics are in the chronic phase, where NHS therapy resources are scant. Importantly, in terms of years post-stroke, there appears to be no upper limit beyond which patients cannot improve if they have access to targeted therapy.[9]

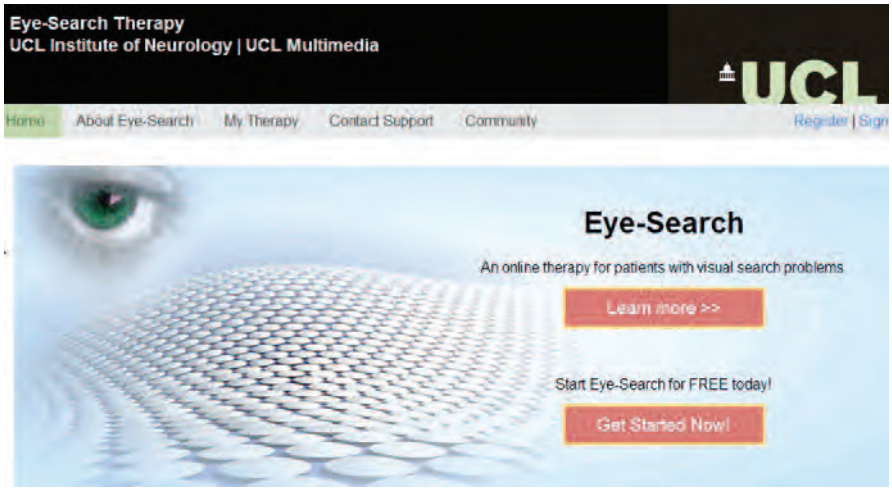


Figure 1: Screenshot of the free-to-use, web-based therapy app Eye-Search for patients with hemianopia and visual search problems. Patients sign an online consent form and their data is streamed to a secure server so that the effectiveness of the therapy can be scientifically assessed. The site is hosted by UCL and funded by The Stroke Association.

Vision

The many interventions for hemianopia can be classified into three main groups: visual restitution, eye movement therapy (a strategy-based therapy) and visual aids. The difference between the last two categories is that strategy-based therapies transfer gains to function outside the periods of therapy, whereas aids improve function while being used but have no effect on behaviour once removed (wearing glasses improves your visual acuity, but not when you take them off).

Hemianopia is very common with stroke alone responsible for ~15,000 new cases per year in the UK. Unlike in the language or motor system where therapy induced gains can be seen years or even decades after stroke, visual field defects rarely improve six months after the onset.[10] Hemianopias that encroach on central vision (the majority) affect a whole host of activities of daily living.[11]

Evidence base for hemianopia therapies

There are two main types of visual restitution therapies and each comes with its own patented hardware. One aims to improving high-acuity, conscious vision at the borders of the field defect, NovaVision VRT (visual restoration therapy); while the other, Neuro-Eye therapy, improves vision deep into the impaired field. Both rely on mass practice of detecting stimuli. There has been much controversy over whether NovaVision VRT really is effective, and, if so, by what mechanism. The main issue has been that any visual field gains have only been seen using the visual field test that is bundled with the therapy package. This is a problem as the visual field test relies on the same stimuli that are used in the training or therapy part of the programme. Obviously, if vision is really being restored, it shouldn't matter what method is being used to test visual field gains. The prevailing view is that the training results in more efficient eye movements into the damaged field and not genuine field expansion. Patients themselves care much less about the mechanism of action than dueling scientists, and there is good evidence that the therapy does improve visual function.

Neuro-Eye therapy is less controversial as the stimuli (Gabor patches) are presented deep into the blind field and probably rely on sparse, non-V1 pathways by which visual stimuli can be processed but do not always reach conscious perception (the definition of blindsight). Practice effects are retinotopic, that is, performance gains are only seen in those parts of the visual field where stimuli were shown although this requires thousands to tens-of-thousands of trials. The question is: how useful is blindsight? It is certainly better than nothing and may help reduce patients colliding with objects, but there have been no studies addressing the impact of this training regime on activities of daily living.

The most convincing and consistent evidence for improving visual function comes from studies that retrain eye movements. This involves mass practice using stimuli that provoke a specific type of eye movement. Unlike the visual restitution therapies these have a clear carry-over effect onto untrained stimuli. There are over 10 published studies in this area and a recent Cochrane review of the more rigorous ones concluded that, "There is limited evidence which supports the use of compensatory scanning training for patients with visual field defects."[12] A further study published since then very nicely demonstrates the specificity of these techniques.[13] Using a randomised, cross-over design of reading therapy and visual exploration training, the results showed that the training-related improvements in reading and visual exploration were specific and task dependent; the combined effect size was 0.47 for visual search and 0.28 for reading. Interestingly, the cross-over therapy had no effect (positive or negative) on the other task; that is, when undergoing the second therapy block, gains made from the first block remained stable. While the specificity was no great surprise (although this was the first study to explicitly test this) it is good news that there was no interference.

There are two, free-to-use, web-based therapies for patients with hemianopia for patients with either: 1) hemianopic alexia: www.read-right.ucl.ac.uk; or, 2) problems with visual search: www.eyesearch.ucl.ac.uk (Figure 1). Both contain testing and therapy materials and are designed for home use by patients. Evidence for the efficacy of the Read-Right diagnostic and therapy tools has been published [14,15].

Prism adaptation for hemianopia, which can be successfully used to improve navigation within the environment,[16] is anecdotally poorly tolerated by patients as any gains in one part of the visual field are at the expense of losses to another; also, the prisms required are very different to those used to correct double vision and there are very few NHS providers.

'Higher' visual function (pure alexia, neglect)

The evidence for therapeutic interventions in more complex perceptual disorders (pure alexia, prosopagnosia, simultanagnosia) is sporadic and weak and it is difficult to make any recommendations for specific therapies, although cross-modal therapy for pure alexia looks promising.[17] Spatial neglect or inattention is more common and has a stronger evidence base although the presumed efficacy for the main therapy (prism adaptation) has been questioned in a well conducted review.[18] Drug therapies have also been tried, with a recent study showing a small (10%) but significant improvement in table-top tests of selective attention when transdermal rotigotine, a dopamine agonist, was compared against placebo.[19]

Summary

The therapeutic landscape for patients with language and/or visual impairments post-stroke is improving rapidly. There are many completed and ongoing small-scale trials of adjuncts that aim to improve the efficiency of rehabilitation: pharmacological and brain stimulation techniques. Rehabilitation of adult cognition can be viewed as a form of learning or re-learning and as such, whatever the role of exciting new adjuncts, requires a certain amount of brute-force in terms of practice-based learning. The most pertinent issue now is not whether these therapies work but how best to deliver them in a high enough dose so that patients can make meaningful gains? Self-supporting internet-based therapies seem the ideal solution for many specific therapy programmes. ◆

REFERENCES

1. Price, CJ. *The anatomy of language: a review of 100 fMRI studies published in 2009.* Ann N Y Acad Sci 2010;1191:62-88.
2. Bowen, A, Hesketh, A, Patchick, E, Young, A, Davies, L, Vail, A, et al. *Effectiveness of enhanced communication therapy in the first four months after stroke for aphasia and dysarthria: a randomised controlled trial.* BMJ 2012;345:e4407.
3. Brady, MC, Kelly, H, Godwin, J, & Enderby, P. *Speech and language therapy for aphasia following stroke.* Cochrane Database of Systematic Reviews 2012(5).
4. Bhogal, SK, Teasell, R, & Speechley, M. *Intensity of aphasia therapy, impact on recovery.* Stroke 2003;34(4):987-93.
5. Code, & Heron, C. *Services for aphasia, other acquired adult neurogenic communication and swallowing disorders in the United Kingdom, 2000.* Disabil Rehabil 2003;25(21):1231-7.
6. Seniow, J, Litwin, M, Litwin, T, Lesniak, M, & Czlonkowska, A. *New approach to the rehabilitation of post-stroke focal cognitive syndrome: effect of levodopa combined with speech and language therapy on functional recovery from aphasia.* J Neurol Sci 2009;283(1-2):214-8.
7. Crinion, J. *Shocking speech.* Aphasiology 2012;26(9):1077-81.
8. Lee, S, Shafe, AC, & Cowie, MR. *UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database.* BMJ Open 2011;1(2):e000269.
9. Moss, A, & Nicholas, M. *Language rehabilitation in chronic aphasia and time postonset: a review of single-subject data.* Stroke 2006;37(12):3043-51.
10. Zhang, X, Kedar, S, Lynn, MJ, Newman, NJ, & Biousse, V. *Natural history of homonymous hemianopia.* Neurology 2006;66(6):901-5.
11. Warren, M. *Pilot study on activities of daily living limitations in adults with hemianopsia.* Am J Occup Ther 2009;63(5):626-33.
12. Pollock, A, Hazelton, C, Henderson, CA, Angilley, J, Dhillon, B, Langhorne, P, et al. *Interventions for visual field defects in patients with stroke.* Cochrane Database of Systematic Reviews 2011(10).
13. Schuett, S, Heywood, CA, Kentridge, RW, Dauner, R, & Zihl, J. *Rehabilitation of reading and visual exploration in visual field disorders: transfer or specificity?* Brain 2012;135(Pt 3):912-21.
14. Koiava, N, Ong, YH, Brown, MM, Acheson, J, Plant, GT, & Leff, AP. *A 'web app' for diagnosing hemianopia.* J Neurol Neurosurg Psychiatry 2012.
15. Ong, YH, Brown, MM, Robinson, P, Plant, GT, Husain, M, & Leff, AP. *Read-Right: a "web app" that improves reading speeds in patients with hemianopia.* J Neurol 2012.
16. Bowers, AR, Keeney, K, & Peli, E. *Community-based trial of a peripheral prism visual field expansion device for hemianopia.* Arch Ophthalmol 2008;126(5):657-64.
17. Woodhead, ZVJ, Penny, W, Barnes, GR, Crewes, H, Wise, RJS, Price, CJ, et al. *Reading therapy strengthens top-down connectivity in patients with pure alexia.* Brain 2013 (in press).
18. Barrett, AM, Goedert, KM, & Basso, JC. *Prism adaptation for spatial neglect after stroke: translational practice gaps.* Nature Reviews Neurology 2012;8(10):567-77.
19. Gorgoraptis, N, Mah, YH, Machner, B, Singh-Curry, V, Malhotra, P, Hadji-Michael, M, et al. *The effects of the dopamine agonist rotigotine on hemispatial neglect following stroke.* Brain 2012;135:2478-91.

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th February, 2014

February

Dementias 2014
13-14 February, 2014; London, UK
Call Jackie on 020 7501 6762,
www.mahealthcareevents.co.uk

Deep Brain Stimulation Masterclass Roadshows
27 February, 2014 – Evening; Birmingham
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

BNPA 27th Annual General Meeting
27-28 February, 2014; London, UK
Register at www.bnpa.org.uk or
T. 0560 348 3951,
E. admin@bnpa.org.uk or
jashmenall@yahoo.com

Positive Steps in PD
28 Feb – 1st March, 2014; Birmingham, UK
Emily Ball, T. 01932 379897,
www.positivestepsinpd.com

March

1st Liverpool MS Study Weekend
15-16 March, 2014: Liverpool
www.liverpoolmscourse.org.uk
E. lucie@medivents.co.uk

Deep Brain Stimulation Masterclass Roadshows
20 March, 2014 – Evening; Oxford, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

NEUROLOGY 2014: Leading edge neurology for the practising clinician
26-28 March, 2014; London, UK
www.ucl.ac.uk/ion/education/courses/other/neurology or E. Jean Reynolds, jean.reynolds@ucl.ac.uk
T. 020 344 84460

International Brain Injury Symposium: 'How to navigate through the rehabilitation pathway' (Day 1)
'Changes and challenges in Disorders of Consciousness' (Day 2)
March 27 – 28, 2014; London, UK
E. institute@rhn.org.uk
www.rhn.org.uk/bisymposium

April

Deep Brain Stimulation Masterclass Roadshows
3 April, 2014 – Evening; Bristol, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

8th World Congress of Neurorehabilitation (WCNR 2014)
8-12 April, 2014; Istanbul, Turkey
For more information see www.wcnr2014.org, or
E. traceymole@wfnr.co.uk

Brain Repair Centre Spring School
9-11 April, 2014; Cambridge, UK
www.brc.cam.ac.uk E. skt37@cam.ac.uk

Deep Brain Stimulation Masterclass Roadshows
24 April,2014 – Evening; Sheffield, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

May

Deep Brain Stimulation Masterclass Roadshows
8 May, 2014 – Evening; Manchester, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact info@redpublish.co.uk

ABN Annual Meeting
7-9 May, 2014; Cardiff, UK
E. info@theabn.org
Telephone: 020 7405 4060

4th Essential Stroke Imaging Course
10 May, 2014; Liverpool, UK
Contact Kath Tyler,
T. 07799 723 925
Email:essentialcourses@hotmail.com

14th Annual Pain Therapeutics Conference
19-20 May, 2014; London, UK
See www.pain-therapeutics.co.uk or contact
Fateja Begum on +44 (0)20 7827 6184,
E. fbegam@smi-online.co.uk

Primary Care & Public Health 2014
21-22 May 2014; Birmingham, UK
T. 0151 709 8979,
E. info@sterlingevents.co.uk

June

Parkinson's Classic Masterclass 25c
Module 1 - 3-5 June, 2014; Bristol, UK
For further information contact info@redpublish.co.uk

Deep Brain Stimulation Masterclass Roadshows
30 June, 2014 - evening; North London
www.redpublish.co.uk/courses/other-courses/
For further information contact info@redpublish.co.uk

July

ISMRM Workshop on: Function MRI: Emerging Techniques & New Interpretations
July, 2014; Charleston, SC, USA
www.ISMRM.org
T. +1 510 841 1899

Deep Brain Stimulation Masterclass Roadshows
1 July, 2014 - 1.30 /5.30pm; South London, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact info@redpublish.co.uk

September

Parkinson's Registrar's Masterclass 26s
17-18 September, 2014; Location TBC
http://www.redpublish.co.uk/courses/
E. info@redpublish.co.uk

Deep Brain Stimulation Masterclass Roadshows
TBC Sept/Oct, 2014 – Evening; Newcastle, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact info@redpublish.co.uk

ABN Autumn Meeting
30 September-1 November, 2014; Stratford, UK
E. info@theabn.org
T. 020 7405 4060

November

Parkinson's Classic Masterclass 25c
Module 2-27 November, 2014; Location TBC
For further information contact info@redpublish.co.uk

Translating Science into Practice Third UK Conference on Huntington's Disease

Conference details: 14th November, 2013; Stoke on Trent,UK. ***Report by:*** Dr George El-Nimr, Consultant Neuropsychiatrist, Clinical Tutor and Clinical Lead for Neuropsychiatry and Old Age Psychiatry Services, North Staffordshire Combined Healthcare NHS Trust.

Recent years have witnessed significant international efforts in supporting Huntington's Disease (HD) research that would indeed offer considerable hope for future generations. Nevertheless, our patients, families and clinicians are yet to experience how accumulating evidence would influence care standards and service developments in a consistent manner.

Following on from the success of our previous HD national educational events, our Third UK national conference was aimed at exploring how science can be translated into practice. While scientists should have a vital role, HD history does clearly highlight that having our patients and families in the driving seat would be instrumental.

The programme of the day flowed well with a great mix of keynote presentations and workshop sessions. Presentations and videos were made available for delegates after the event. Feedback from the day was extremely positive and very encouraging for the planned Fourth UK National Conference on HD.

Following an introduction from Dr George El-Nimr, the conference organiser, Ms Fiona Myers, Chief Executive of North Staffordshire Combined Healthcare NHS Trust welcomed all the speakers, delegates and sponsors. Ms Myers also highlighted the holistic multidisciplinary HD services that are offered by the Trust together with various educational, research and other HD-related academic activities.

Mr Charles Sabine, TV journalist, who facilitated the day, gave a talk on HD through the prism of the media. Mr Sabine talked about the stigma that was attached to HD throughout its history. However, the revolution in communications and the expansion in potential outlets for dramatic interpretations of the complex emotions and relationships have given the global HD community an opportunity to transform its image. A carer from the local service then gave an overview of the care-giving challenges.

Katie Dale, an actress and an author, discussed how HD has been portrayed in literature and the inspiration for and research behind her own award winning novel "Someone Else's Life".

Following on from this, Ms Asun Martinez, Vice President of the International Huntington's Association (IHA) talked about how the organisation developed and how it plays an instrumental role in supporting HD patients, families and professionals from various countries.

Dr Edward Wild of the UCL Institute of Neurology and co-founder of HDBuzz summarised the basic science behind HD research, pointing out the top approaches being worked on.

Professor Landwehmeyer, Professor of Neurology at the University of Ulm and the Chair of Executive Committee of the European HD Network discussed ongoing international research developments and rapidly growing European and American collaboration. He also presented current opportunities and challenges in the way of finding a cure for HD.

Professor Roger Barker of the University of Cambridge presented thought-provoking research findings in relation to sleep, metabolism and cognition in HD. He discussed how these changes might be an early marker of the disease onset. This could open up new areas for research on therapy and pathogenesis.

The conference delegates were then offered a selection of workshops:

Cath Stanley, Chief Executive of the HD Association of England and Wales chaired a workshop discussing caring issues in relation to advanced HD patients. Dr Hugh Rickards, Neuropsychiatrist, and Honorary Reader at Birmingham University discussed HD services and the challenges that professionals face within the existing service arrangements. Doug Feery, barrister, facilitated a workshop on mental capacity and human rights and their relevance to HD.

In his workshop, Dr David Craufurd from the University of Manchester highlighted the importance of understanding irritability and apathy and how these can be managed. Dr Oliver Quarrell discussed the challenges in HD genetic testing for diagnostic purposes, predictive and prenatal testing.

Josephine Spring from the Royal Hospital for Neuro-disability ran a workshop where she emphasised that while gardens provide sensory stimulation, colour vision may be perceived better at the red end of the spectrum.

Dr Monica Busse of Cardiff University emphasised that an accessible "toolkit" of evidence based mobility and physical activity targeted interventions may better equip professionals to the challenge of providing support in an ever-changing landscape.

Following on from the workshops the conference closed with two lectures. Dr George El-Nimr explored six questions in relation to Neuropsychiatric problems that are commonly encountered in HD. The presentation addressed these issues from clinical management and care-giving viewpoints. It was argued that better understanding of how and why our patients present in a certain way can significantly assist clinicians in developing more effective management plans and carers in fostering more healthy coping strategies and management skills.

Dr Ken Barrett presented six stories of patients whom he thought taught him the most about HD. HD services in many ways evolved around the issues that they highlighted.

The conference was well received by a wide range of delegates and speakers, some of whom came from other countries to support this event. It was equally well received by various voluntary, statutory and private organisations that supported the conference. ◆

Key messages:

- Although currently incurable, HD has many treatable consequences.
- There are a number of under-utilised potentially effective treatments.
- Patients are great educators to clinicians.
- Families and clinicians need to appreciate the complexity of ethical and medico-legal issues in HD.
- Progress can only be made via patients, scientists and clinicians working together.
- Cure is not found but made by collaborative working.

Recent years have witnessed significant international efforts in supporting Huntington's Disease (HD) research that would indeed offer considerable hope for future generations

Proceedings of the 2nd Annual Meeting of the International Encephalitis Consortium

Conference details: 1 October, 2013; San Francisco, California, USA. ***Report by:*** Dr Philip Britton, Deptartment of Microbiology & Infectious Diseases, The Children's Hospital at Westmead, Australia and Dr Parashar Ramanuj, Virus Reference Department, Public Health England (joint first authors) and Ava Easton, Chief Executive, The Encephalitis Society.

The International Encephalitis Consortium is a collective of about 50 clinicians, scientists and lay persons from North America, Europe, Asia and Australasia that formed in 2011 with the explicit mission to advance the knowledge of the causes, diagnosis, treatment and outcome of encephalitis. Its aim is to implement actionable clinical and public health interventions based upon this knowledge and so reduce the global impact of encephalitis.

Taken literally, encephalitis means inflammation of the brain. It is a complex neurological syndrome caused by a wide variety of infections and/or the body's own immune system. It can result in death or significant damage to the brain leaving many sufferers with long-term problems such as poor mobility, problems with language or speech and seizures. It can also lead to more subtle difficulties such as fatigue, inability to concentrate and emotional problems.

Following the Consortium's first annual meeting in 2012, a consensus guideline was developed for the investigation and management of encephalitis in adults and children. This guideline has recently been published (Venkatesan A, Tunkel AR, Bloch K, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 2013;57:1114-28 http://www.ncbi.nlm.nih.gov/pubmed/23861361). The Consortium met in person for the second time in early October, 2013, in San Francisco, USA. Over the course of the meeting, a number of key themes arose around which the Consortium will build working parties and encourage further research over the next 12 months.

1. Patient led priorities:

The meeting was opened by two adult survivors of encephalitis, Becky Dennis and Bob Morris. Becky and Bob spoke with great candour and openness about the patient experience of encephalitis: the confusion and bewilderment of losing innate skills and the resultant identity crisis; the all too common experience of dismissal by clinicians; the cost and burden of rehabilitation services and the burden to families; the feelings of isolation; the benefits of meeting with other survivors and the powerful bonds created; and the hope for better treatments and outcomes for future sufferers.

Bob asserted that encephalitis remained an invisible illness to the broader public and the health system. He explained that in his experience clinicians lack awareness of investigation and management guidelines, particularly for treatment after the acute phase and many sufferers find themselves at a loss in navigating healthcare and other systems. They were concerned about the huge variability in care offered by different specialists. Most of all they emphasised the chronicity of the brain injury that results from encephalitis.

Their stories highlighted the critical importance of researchers and clinicians talking with the people they are aiming to help as 'experts by experience' so that resources and efforts can be prioritised according to their needs in meeting the challenges of encephalitis.

2. Long term outcomes:

Ava Easton, CEO of The Encephalitis Society chaired the session on long-term outcomes and described how Encephalitis has a huge impact on people, and many of the problems that survivors struggle with can be subtle and no less profound than the more visible consequences. One way to raise the importance placed on these hidden effects is to try to measure the impact of encephalitis on survivors' quality of life. Research looking at this showed that 6 months after encephalitis, even if recovery had been classified as 'good', survivors' quality of life was much worse when compared to the general population in both adults and children. The quality of life for someone who has recovered from encephalitis could also be considered worse (unpublished at the time of writing) than for someone living with a long-term illness like HIV or recovering from a brain tumour.

These results were almost identical to a survey conducted by the Encephalitis Society (www.encephalitis.info) amongst their adult members, who on average had been diagnosed with encephalitis 10 years previously, suggesting that quality of life drops sharply after encephalitis and then does not improve. The greatest determinant of a person's quality of life after encephalitis was found to be their level of disability. Dr Karen Bloch, Assistant Professor of Medicine at Vanderbilt University showed from her research that if a person survives encephalitis, recovery from the disabilities it causes can occur for up to a year after the illness, although most recovery occurs in the first six months (about a third show improvement between six and twelve

months). However Professor Tom Solomon, Chair of the Encephalitis Society Professional Panel reminded us that not all disabilities have the same impact and that encephalitis is a global illness. Physical disabilities would have a greater impact in a labour-demanding environment (such as for a farm labourer in a low income country), mental or emotional difficulties in places where there is no access to appropriate medical management and subtle or cognitive deficits in industrialised societies.

Quality of life is hugely affected by level of disability, so if we can help people to have fewer disabilities after encephalitis (for example by diagnosing encephalitis promptly, finding its cause and treating it appropriately) or reduce the disability's impact/severity (through rehabilitation) we can help people to lead fuller lives.

3. Neurocognitive rehabilitation:

An expert panel of neurologists and rehabilitation specialists was invited to the meeting by Dr Jim Sejvar to discuss what it would take to achieve the best outcomes of encephalitis survivors, particularly in the area of cognitive rehabilitation. The panel emphasised that issues of causation and pathogenesis of encephalitis was significant in as much as truly static versus ongoing injury would change the rehabilitation approach. Recent insurance provider data from California was presented that showed that expenditure on encephalitis rehabilitation was significantly out of proportion with the burden of the disease, especially when compared to stroke and other forms of traumatic brain injury. People with encephalitis accounted for 1.68% of people in community nursing facilities (compared to 0.55% for stroke survivors) and yet only $3.8mill was spent on them in 2010, compared to $33.9mill on stroke survivors. This may be because of a paucity of research both describing in detail the long-term cognitive outcomes of encephalitis and the benefits of rehabilitation and the strategies used.

Specific research questions that would help us ensure that people who suffer encephalitis receive the optimal possible outcome include:

1. how early could neuroprotective rehabilitation be commenced for encephalitis sufferers (acute, post-acute, long-term?);
2. the particular association of structure (focal vs multi-focal vs diffuse processes) and function (neurological deficits) in the context of a growing focus on neuronal networks and with the assistance of novel imaging modalities;
3. the benefits and harms of psychotropic medication in recovery;
4. applying measures of emotional functioning in outcome studies;
5. the spectrum of disciplines required for effective implementation of interventions;
6. the effect of co-morbidities on outcome such as depression and anxiety disorders.

Despite the lack of specific evidence for encephalitis, the panel described a robust literature developing around cognitive rehabilitation for sufferers of stroke and traumatic brain injury. The panel was in agreement with the Consortium that this literature should form the basis of recommendations for rehabilitation for encephalitis survivors pending the gathering of specific data for encephalitis.

4. Poorly understood syndromes/ aetiologies:

The Consortium was presented with one syndrome and two infectious aetiologies of which our current understanding is limited:

a. *Febrile Infection Related Encephalopathy with refractory Status epilepticus (FIRES):*
Dr Ariane Soldatos and Dr Carol Glaser.

FIRES is known by a number of different acronyms. It has an incidence of around 1 per million population. It presents as an explosive epileptic encephalopathy in previously well children following an uncomplicated febrile illness. It progresses to refractory status epilepticus with multi-focal seizure activity and results in severe neurological disability. The cause is unknown, and can be differentiated from viral encephalitis by the strikingly unremarkable cerebrospinal fluid (CSF) findings on microscopy and the normal neuroimaging findings in the acute phase. Of those cases consistent with the FIRES phenotype in the California Encephalitis Project (CEP-55), the median age was 5 years. There was no seasonality or clear common exposure. There was an almost universally poor therapeutic response and outcome. A National Institutes of Health pilot project is underway collecting specimens from cases of FIRES in order to determine the pathogenesis of the disorder and discover a possible underlying genetic susceptibility in patients.

b. *Human Herpes Virus-6 (HHV-6):*
Dr Kate Ward and Dr Ari Bitnun.

HHV-6 is a beta-herpesvirus that is ubiquitous with almost all children seropositive by the age of four. HHV-6 is in fact two species: HHV-6A and HHV-6B. Consensus has developed that HHV-6B is an uncommon cause of encephalitis in haematopoetic stem cell transplants, with the most well described syndrome being Post-transplant Acute Limbic Encephalitis (PALE). Whether HHV6B can cause encephalitis in immunocompetent humans and whether HHV-6A can cause encephalitis is unclear. HHV-6 is best known as the cause of Exanthem subitum or Roseola in infants and has a strong association with febrile convulsions. A problem with the diagnosis of HHV-6 is its capacity for integration into human DNA at the telomere (end of chromosomes). This occurs in 1% of the population and involves reproductive tissues so can be transmitted from parents to children. In clinical practice the characteristic of this is high levels of HHV-6 DNA in the blood that does not change with antiviral therapy. In determining the role of HHV-6 in encephalitis in future studies HHV6A should be distinguished from HHV-6B, chromosomal integration should be excluded and molecular techniques supplemented by antibody testing both in the CSF and the blood.

c. *Human Herpes Virus-7 (HHV-7):*
Dr Kate Ward and Dr Ari Bitnun.

Like HHV-6, HHV-7 is a ubiquitous beta-herpesvirus, with almost all children seropositive by the age of five. It is a poorly appreciated cause of encephalitis in children and adolescents. Data from Canada showed that HHV-7 may be implicated as a cause of 1% of paediatric encephalitis, although it must be emphasised that the majority of patients in whom HHV-7 DNA is detected in the CSF do not have serology consistent with acute infection and many will have an alternative cause identified. Future studies of HHV-7 should include molecular techniques and antibody testing both in the CSF and the blood. The children at highest risk might be those with uncommon primary infection during adolescence.

5. Conclusions:

The first meeting of the International Encephalitis Consortium resulted in a much-needed peer-reviewed guideline for the investigation and acute-phase treatment of encephalitis. It is hoped that the second meeting will lead to ways to help the long-term outcomes associated with encephalitis. It is of particular importance that patients and carers are being seen as collaborators in these efforts. The service user movement of the mid 1980s and early 1990s in HIV/AIDS helped shape the research direction in what was then a neglected specialty of medicine – sexually transmitted infections – with the resultant huge strides made in HIV care. It is hoped that a similar partnership between encephalitis experts and those with expertise in living with encephalitis will lead to such improvements in a similarly neglected area of neurology; after all how else are the experts to know what matters most to those who survive, live or care for someone with encephalitis? ◆

5th North East Epilepsy Research Meeting (NEERM V)

Conference details: 27th September, 2013; County Durham, UK. ***Report by:*** Dr Mark Baker, Institute of Neuroscience, Newcastle University & Neurology/Clinical Neurophysiology, Royal Victoria Infirmary; Dr Mark Cunningham, Institute of Neuroscience, Newcastle University and Dr Yvonne Hart, Department of Neurology, Royal Victoria Infirmary.

The fifth annual meeting of the North East Epilepsy Research Network was held recently in the serene surroundings of the 18th Century Beamish Hall. The focus of the meeting was to foster and develop the already burgeoning collaborative interactions between various basic scientists and clinicians working in the field of epilepsy in the region. The meeting, supported by the Institute of Neuroscience, Newcastle University, UCB Pharma S.A., Cyberonics, Digitimer, Eisai Ltd., Fannin, Medtronics, Nutricia and Viropharma was attended by over 70 delegates.

The first session, which was chaired by Dr Mark Baker (co-organiser), began in great style with a fascinating insight into the emerging evidence from imaging studies of cognitive dysfunction in Juvenile Myoclonic Epilepsy (JME). Presenting data from the literature and examples from his studies, Dr Rob Powell (Morriston Hospital, Swansea), revealed how structural and functional brain changes in JME may be important for assessing the severity of the epilepsy observed in this patient cohort. Continuing the theme of cognitive impairment and epilepsy Dr Tangunu Fosi (RVI, Newcastle) summarised findings from his studies with event-related potentials and MRI techniques. Dr Fosi presented data from children with West Syndrome demonstrating functional changes in temporal lobe and identifying a potential microstructural substrate for his observations.

John Osselton spent his entire academic career at Newcastle University. His contribution to the development and refinement of EEG technology is acknowledged by the universal appreciation that many neurologists, neurophysiologists and technicians, past and present, hold for his edition of the Handbook of Clinical Neurophysiology. To honour John's contributions, we dedicate an annual lecture in his memory. This year's Osselton lecture was given by Professor Matthew Walker (Queen Square/UCL) who took us on a journey describing a number of emerging treatments for epilepsy. Beginning with the writings of Hughlings Jackson, Professor Walker incorporated viruses, slime moulds and coconuts in his scientific travails. This work involved the development of novel gene therapies to alter the excitability of cortical neurons in the seizure focus. Specifically, his team conducted

lentiviral over-expression of the potassium channel Kv1.1 in neocortical pyramidal neurons. Using a model of focal epilepsy (neocortical tetanus toxin injection), both co-injection and administration of the Kv1.1 lentivirus, prevented and progressively suppressed epileptic activity, respectively. In the second portion of his lecture, Professor Walker outlined how, in collaboration with Dr Robin Williams (Royal Holloway), he has used Dictyostelium (slime mould) to screen drugs which act on the biochemical pathway that valproate also works on. The clinical use of sodium valproate is tempered by its serious side effects, crucially the drug's teratogenic action. By using the slime mould model, they have been able to identify novel antiepileptic drugs, more potent than valproate but lacking the teratogenic effect. A number of the lead compounds were identified as medium-chain fatty acids, which are found in high quantities in coconut oil. Interestingly, coconut oil is a core component of the MCT ketogenic diet, which is known to be beneficial in difficult to treat epilepsies.

Following lunch, the theme shifted to invasive and non-invasive monitoring techniques in epilepsy, with a session chaired by Dr Andrew Trevelyan (Institute of Neuroscience, Newcastle University). First up, Dr Jenny Read (Institute of Neuroscience, Newcastle University) outlined aspects of her work with visual perception and how tests of vision may reveal subtle alterations in epilepsy as well as other neuropsychiatric disease states. This is likely to be due to the importance of cortical inhibition for physiological processes such as visual perception and their primary pathological role in epilepsy. Continuing with the theme of cortical inhibition and its contribution to epilepsy, Dr Catherine Schevon (Columbia University) presented novel approaches to seizure localisation using multielectrode array (MEA) and subdural recordings in human patients. Highlighting the false localisation qualities of traditional EEG techniques, Dr Schevon demonstrated the usefulness of MEA recordings of high gamma frequencies and neuronal firing patterns in overcoming the poor surgical outcomes in non-lesional neocortical epilepsy. This session was followed by a pharmacological interlude in which Dr Ben Whalley (Reading University) outlined the effectiveness of chemical compounds found in cannabis. There is a large amount of anecdotal evidence concerning the usefulness of cannabinoids in controlling human seizures. However, this effect has to be considered in the context of the side effects associated with cannabis use. Using rodent models of epilepsy, Dr Whalley presented data on the anti-convulsant properties of cannabidivarin, a little studied chemical found in cannabis. The epileptic

animals experienced less severe seizures and lower mortality compared with animals given a placebo.The drug also had fewer side effects and was better tolerated than three of the most widely prescribed anticonvulsants.

The final session of the day, chaired by Dr Yvonne Hart (co-organiser), focused on research pertaining to epilepsy surgery. Dr Ian Schofield (Department of Clinical Neurophysiology, RVI, Newcastle) presented data on thalamic recordings undertaken during the implantation of deep brain stimulators for the treatment of refractory epilepsy in human patients. In his presentation Dr Schofield described the clinical, pre and intra-operative neurophysiological findings from a patient with severe temporal lobe epilepsy with mesial temporal sclerosis. Despite a relatively innocuous surface EEG, abnormal activity was recorded from an electrode in the left thalamus and was inhibited by stimulation of the right thalamus. Dr Mark Cunningham (co-organiser) presented data from surgical samples obtained from patients with tumour-associated epilepsy. Dr Cunningham's research team use the ability to maintain tissue slices prepared from this material in an in vitro environment. This approach permits access and manipulability to interrogate neuronal microcircuits for mechanistic insights. Dr Cunningham highlighted the large body of work concerning anatomical studies in peritumoural tissue but the lack of functional data, in the form of electrophysiology, from this work. In the context of partial seizure control following tumour resection Dr Cunningham suggested that greater attempts to understand neuronal dynamics in the peritumoural zone are required for better post-surgical outcomes. The final speaker of the day, Dr Andrew Jackson (Institute of Neuroscience, Newcastle University) outlined the work to be undertaken as part of a recently awarded grant to researchers at the Institute of Neuroscience. Termed CANDO (Controlling Abnormal Network Dynamics with Optogenetics) this project aims to develop a cortical implant that will function as a closed-loop feedback device, combining electrical recording from depth electrodes and local optogenetic stimulation. Combining unique access to human epileptic tissue, non-human primate and rodent models of epilepsy, the programme aims to achieve first-in-man trial of the device within seven years.

Following a long, but informative day, delegates retired to the bar and reflected on an enjoyable meeting. ◆

PREVIEW: 14th Annual Pain Therapeutics Conference

Conference details: 14th November, 2013; Stoke on Trent,UK. ***Report by:*** Dr George El-Nimr, Consultant Neuropsychiatrist, Clinical Tutor and Clinical Lead for Neuropsychiatry and Old Age Psychiatry Services, North Staffordshire Combined Healthcare NHS Trust.

SMi are proud to present their 14th Annual Pain Therapeutics Conference taking place in Central London on Monday 19th and Tuesday 20th May 2014.

Pain Therapeutics 2014 will evaluate the latest regulatory guidelines on pain indications and assess the pricing and reimbursement issues which are faced with generic incursion and patent expiration.

Hear an in-depth analysis of new pain therapeutic targets from bench to bedside and assess the pipeline of novel drugs for unique insights into developments that could restore positive growth in the market.

REASONS TO ATTEND:

- Discuss and evaluate the latest new therapeutic mechanisms from bench to bedside with key insight from Merck, Spinifiex, Eli Lilly, AbbVie and UCB
- Hear key presentations from Mundipharma, Nektar and on advances to opioids and strategies to reduce abuse potential
- Explore the latest in the area of Neuropathic pain for 2014 with the latest case studies from Neuroscience Technologies and GW Pharmaceuticals
- Evaluate the translation gap with case studies from a pre-clinical and clinical perspective from Karolinska Institutet and OGB Consulting.

KEY SPEAKERS:

- Jordi Serra, CSO, Neuroscience Technologies Ltd
- Samer Eid, Neuroscience Scientific Knowledge, Merck & Co.
- Tom McCarthy, Chief Executive Officer and Managing Director, Spinifex Pharmaceuticals
- Kathleen Kelly, Medical Leader, CNS/Pain, Johnson & Johnson
- Zara Sands, Computational Medicinal Chemist, UCB
- Birgit Priest, Senior Scientist, Eli Lilly
- Philip Kym, Associate Director II, Pain Discovery Research, Abbott Laboratories

SMi's Pain Therapeutics conference has been a premier conference in its field for more than a decade and the 14th instalment will bring together even more key industry experts and leading pioneers to discuss, debate and share ideas and challenges facing the pain management arena. ◆

For further details and to book your place, visit www.pain-therapeutics.co.uk

Alternatively contact Fateja Begum on +44 (0)20 7827 6184 or email fbegam@smi-online.co.uk

Report of the BioDynamics 2013 Workshop

Conference details: 11-13 September, 2013; Bristol, UK. ***Report by:*** John R Terry, Professor of Biomedical Modelling, College of Engineering, Mathematics and Physical Sciences, University of Exeter, Exeter, Devon.

BioDynamics 2013 was the first in a series of annual international workshops designed to bring together biologists, mathematicians, clinicians, physicists, and computer scientists who are interested in dynamical systems in the biological and medical sciences. The inaugural workshop took place from 11-13 September in Bristol at the Engineer's House and was attended by nearly 120 delegates from 11 countries – including New Zealand, the United States, and Brazil.

The theme of BioDynamics 2013 was "rhythms in biological systems" with each session focusing on a particular time frame – very slow rhythms, circadian rhythms, ultradian rhythms, and very fast rhythms. The major scientific fields included basic and clinical neuroscience (with a particular emphasis on epilepsy), endocrinology, and cardiovascular science.

There were seven keynote presentations delivered by world-leading scientists who talked about their cutting-edge current research and highlighted important future challenges within their respective fields.

There were two keynote talks on circadian rhythms. The first was given by Professor Russell Foster from the University of Oxford, who described the discovery, basic biology, and current clinical understanding of a new class of photoreceptor involved in light detection, which is crucial for maintaining circadian rhythmicity of a number of physiological functions, including sleep, metabolism and mood. A keynote presentation given by Professor Michael Hastings from the University of Cambridge was also focused on circadian biology. Professor Hastings discussed in detail the molecular genetic basis of circadian timekeeping in the SCN (suprachiasmatic nucleus) neuron, the role of neuropeptidergic and calcium signaling in synchronising the SCN clock circuitry, and the role of circadian clocks in disease.

Professor David Rand from the University of Warwick talked about how mathematical modeling and experimental work can help elucidate some aspects of systems biology, including the role of circadian clocks in the mammalian cell cycle, the role of Nrf2 in the response to cellular stress, and the mechanisms behind temperature compensation of circadian clocks.

There were three keynote talks on reproductive regulation. Professor Kevin O'Byrne from King's College London presented his current research on the neuronal mechanisms underlying the origin of GnRH pulsatility and he proposed a new concept of neuronal network of kisspeptin-releasing neurons in the arcuate nucleus, challenging the long-standing concept of a pacemaker within GnRH neurons. Professor Allan Herbison from the University of Otago talked about subcellular mechanisms underlying burst firing in GnRH neurons. His recent work, using transgenic mouse models and mathematical modeling, revealed new insights into the morphology and functioning of GnRH neurons and its implication in GnRH pulsatility. The third keynote talk on GnRH was given by Professor James Sneyd from the University of Auckland. Professor Sneyd described a novel mathematical model used to characterise the electrical property of GnRH neurons. He explained how the model predicts the existence of a new calcium-dependent potassium channel in GnRH neurons.

The final keynote of the conference was delivered by Professor David Hazlerigg from the University of Aberdeen, who discussed circannual timekeeping and the mechanisms of synchronisation underlying the regulation of synchrony between innate timers and the sidereal year.

In addition to the keynote presentations, there were two highlighted oral presentations. Professor Tallie Baram described how rhythms and patterns of maternal care affect brain development. His findings suggest that, compared to regular patterns of maternal care, fragmented maternal care leads to changes in hypothalamic neuronal activity in rat pups, and this is associated with increased vulnerability to stress. Dr Henryk Urbanski presented recent data showing age-related changes in circadian rhythms of a number of hormones and how these changes are linked to cognitive impairment and decreased immune function.

There were also a number of selected shorter talks, including a special session on "Rhythms in the Neuroendocrine System" organised by Professor Richard Bertram from Florida State University, and a special session on the "Dynamics of Epilepsy" organised by Professor Mark Richardson from the Institute of Psychiatry at King's College London. Both sessions featured talks from mathematicians and experimentalists. In addition, there was a poster session that provided an opportunity for students and early career scientists to present and discuss their work.

The inaugural BioDynamics workshop was an exciting event enabling scientists to present their data in a multidisciplinary forum and hear how collaborations between biological scientists, clinicians and mathematicians can provide major conceptual advances in our understanding of complex systems. Much of the work of the conference was of course outside the conference hall itself where there were always groups of experimentalists and theoreticians discussing potential new collaborations and investigating ways of furthering current and future research plans.

The success of this conference and feedback from the participants has certainly provided us with a lot of ideas for the follow-up meeting to be held in Edinburgh in 2014. ◆

Atlas of Nerve Conduction Studies and Electromyography

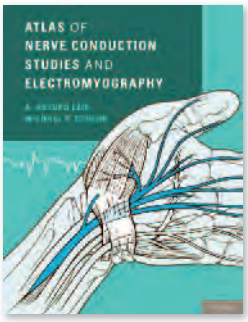
This is a book that aims to combine a bare bones 'how-to' guide for nerve conduction studies (NCS) and electromyography (EMG) with a few clinical pearls. It is presented as a companion to major books in Clinical Neurophysiology, such as Preston and Schapiro's bible 'Electromyography and Neuromuscular Disorders', now in its third edition. For Neurophysiology trainees, this atlas may offer a less bulky reference guide that can be more easily brought into the clinic. It provides greater at-a-glance clarity on anatomy and innervation at nerve, plexus and root level than larger books. It may thus prove valuable to neurologists, rehabilitationists or other interested clinicians who do not themselves practise in Neurophysiology but might want an attractive, easily accessible guide to functional neuroanatomy of the peripheral nervous system (PNS) and a guide to interpretation of an NCS/EMG report, nerve by nerve or muscle by muscle.

This book is an atlas and will be best used for reference, when neuroanatomical or neurophysiological details of particular nerves or muscles are sought. It is satisfyingly comprehensive, with virtually all the nerves and muscles of the limbs covered, along with the paraspinal muscles, the phrenic nerve/diaphragm and some muscles of the head and neck. After two clear and concise overviews, on NCS and EMG respectively, the chapters are based on the major peripheral nerves (or nerve groups). Each chapter begins with an illustration and detailed description of Anatomy, with clinical and neurophysiological details of syndromes specifically associated with the nerve(s) in question. There then follows a how-to of Neurophysiology for the nerve(s), including nerve conduction and EMG of relevant muscles. Each muscle has a page devoted to it, including a large pictorial representation, a schematic representation of its innervation, a photograph of the body part with EMG needle insertion point, and some text. The latter includes anatomical detail, and instructions on muscle activation, needle insertion, including pitfalls and 'pearls'.

The text becomes yawningly repetitive when read cover to cover, as I did for this review! This would be an unfair criticism, however, as the boringly consistent structure is a virtue in a reference text. Nonetheless, we might have been spared the news that the 'anode is 3 cm proximal to cathode', given with every nerve conduction study description, if this were stated at the beginning.

I was particularly pleased by the diagrams of each muscle and its innervation, hence the suggestion that the book might serve equally as an excellent guide to Functional Anatomy of the PNS and, as intended, as a guide to NCS/EMG practice and interpretation.

In summary, this is a useful book that offers something of value over other books. The 'atlas' concept works well in Neurophysiology, and seems to bring the subject to life. This book is painstakingly comprehensive yet wonderfully clear. It is both attractive and easy to use. I would recommend its acquisition both to Neurology and Neurophysiology departments for use by senior doctors and trainees. Though not cheap, neurophysiologists might value a personal copy as a handy alternative to reaching for one of the larger textbooks. It could also be a worthwhile acquisition for interested neurologists, probably as their sole Neurophysiology reference text.



Authors: A Arturo Leis, Michael P Schenk
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Published by: Oxford University Press, 2013
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Reviewed by: Dr James Holt, Consultant Neurologist, Walton Centre.

Harrison's Neurology in Clinical Medicine, 3rd Edition

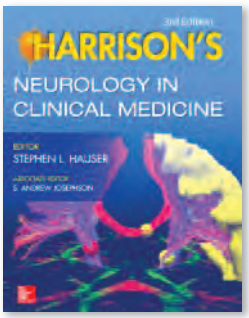
With hundreds of general neurology textbooks on the market, the decision to put in the hours required to read a certain book is an important one. One of the more popular medical tomes in America is *Harrison's Principles of Internal Medicine,* and its neurological chapters, published separately as *Harrison's Neurology in Clinical Medicine*, are in their third edition.

The book is laid out in a pleasing format, with three main sections: the first dealing with history, examination and principles of neurophysiology and imaging, then moving on to the main presenting complaints seen in practice, under headings such as headache, syncope, confusion etc. This allows the reader to be led through topics in a problem-based way, similar to seeing patients in the clinic. Finally, a lengthier section deals with each disease entity in a more systematic form. Three further sections are entitled Chronic Fatigue Syndrome (interestingly separate from the Diseases of the Nervous System chapter), Psychiatric Disorders and Alcoholism and Drug Dependency.

Improvements from previous editions include updates to sections on neuroimmunology and new chapters on disorders of smell and taste, hearing and the specialist area of Neuropsychiatric Illnesses in War Veterans, particularly relating to soldiers returning from Iraq and Afghanistan. There is also an expansion in the amount of online video material available. Rather than being an addendum to the text, this actually represents an important component of the volume (e.g. in areas such as neurological examination). Unfortunately, this material was quite difficult to access, and made the book seem less self-contained.

The text itself is delegated to over thirty contributors, exclusively American, with good use of illustration (although these are somewhat cartoon-like in places) and is supplemented by boxes and tables, which only occasionally become intrusive. An "Atlas of Neuroimaging" provides high quality MR and CT examples of common pathologies, which could have been more helpfully cross-referenced to other sections of the text. There is also a short multiple choice question paper at the end, with a good rationale for the answers. The text is not comprehensively referenced, which seems strange when dealing with topics such as cerebrovascular disease, but does make the narrative flow more easily.

Why should medical students or neurology trainees buy this textbook in preference to the numerous others available? It is certainly readable and well presented. At under fifty pounds it offers value for money compared to other books. It could usefully offer a middle ground between basic, introductory texts and weighty volumes such as *Brain's Diseases of the Nervous System*, being more thorough than the former and more portable than the latter. It is certainly a book to be bought by medical libraries and, if you liked the style, would be a useful read.



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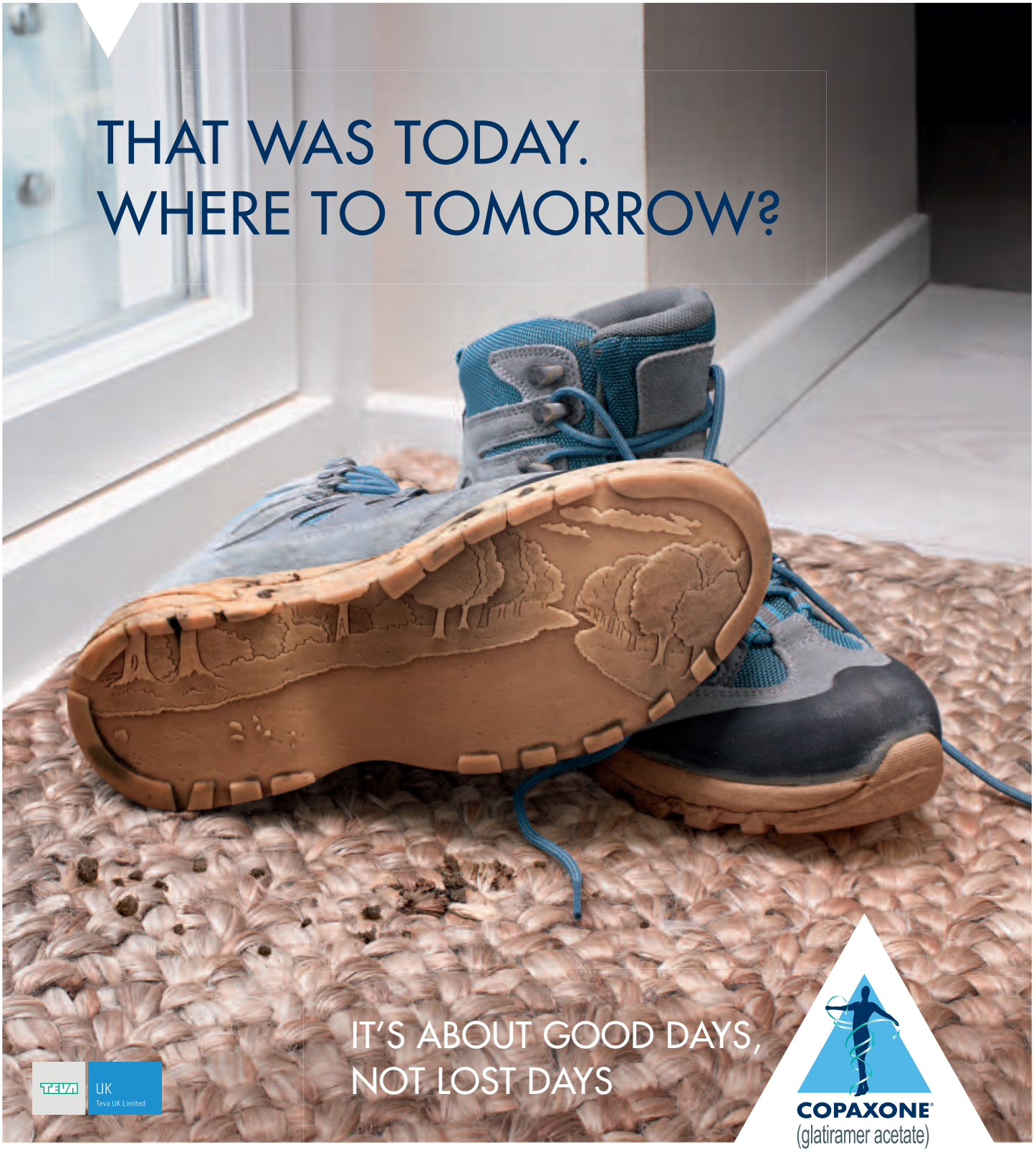

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