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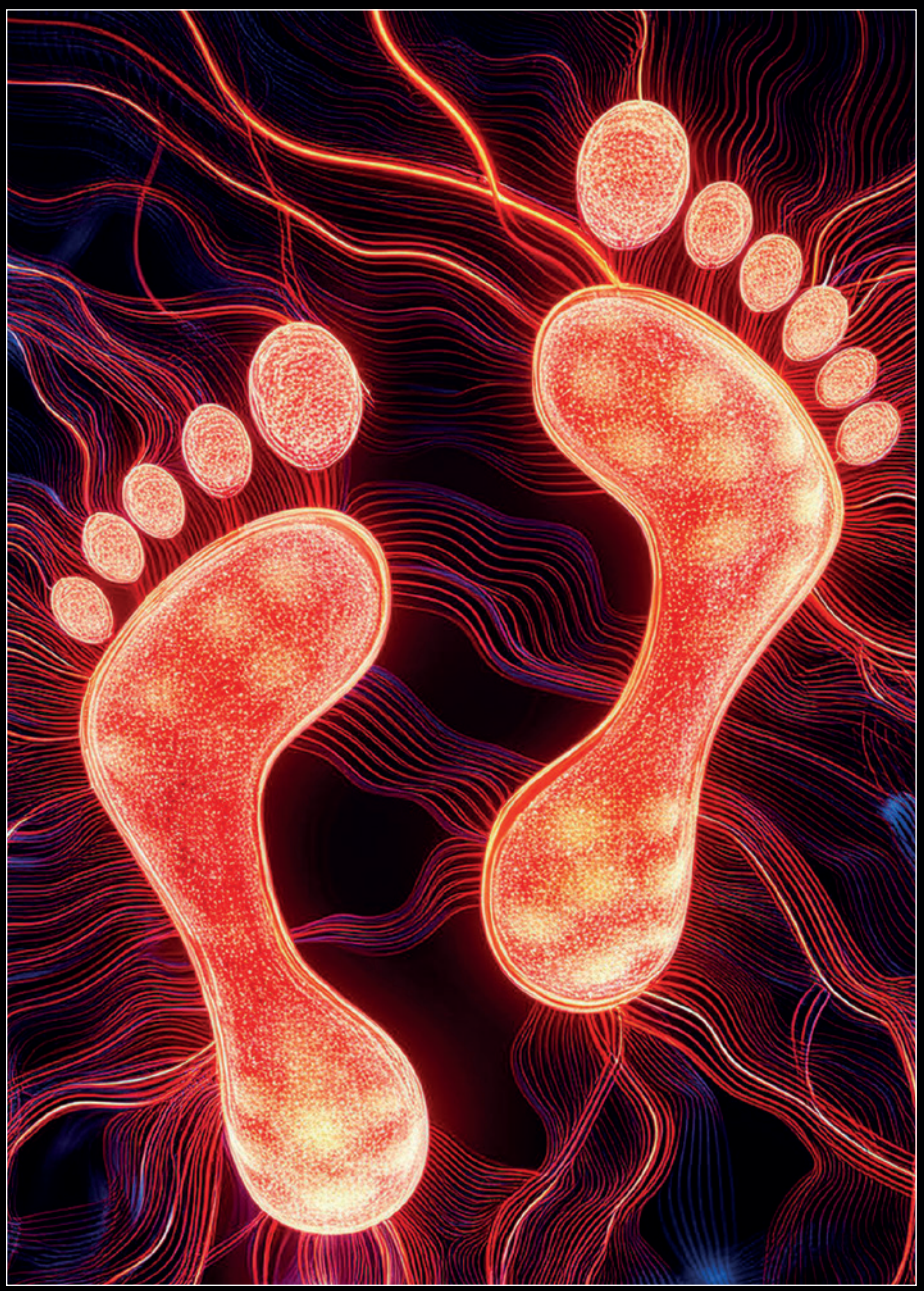

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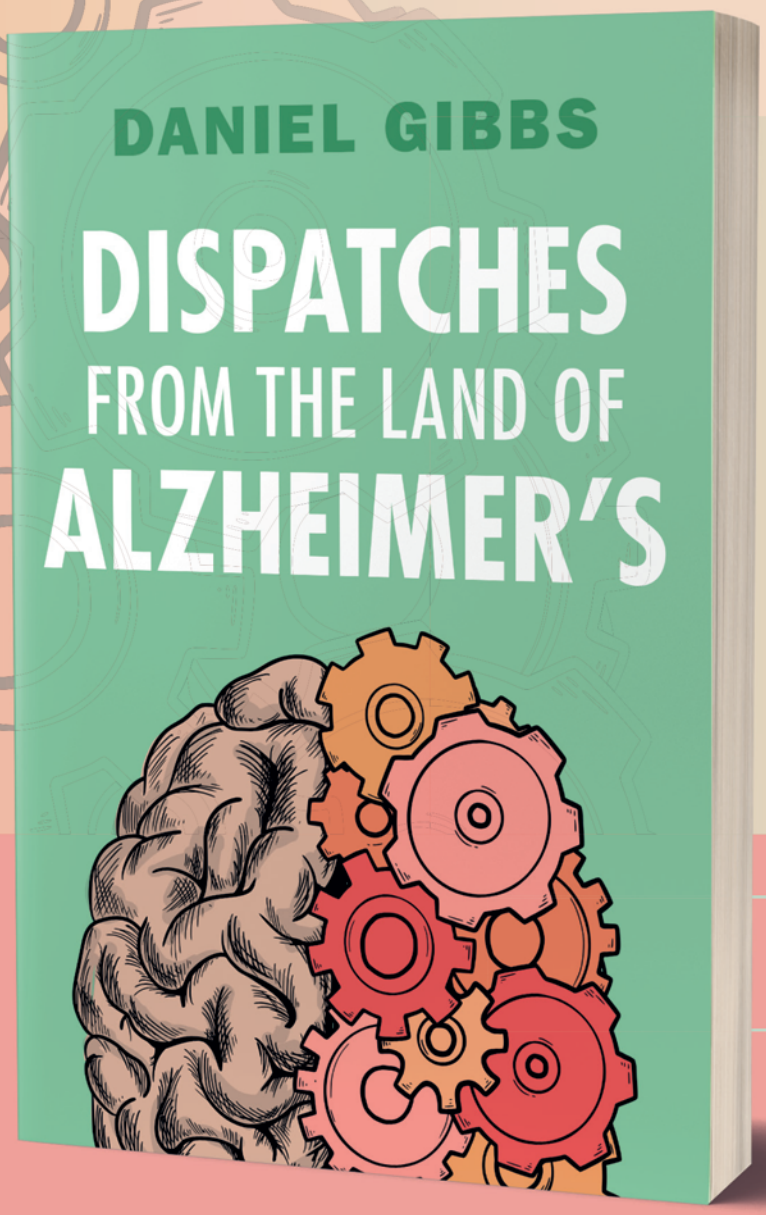


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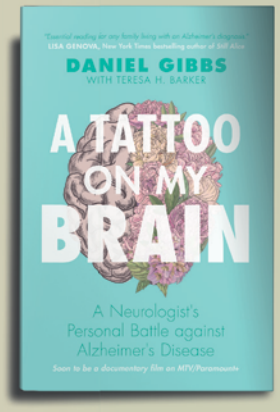


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It is July 2024, and again time to write another Editorial for ACNR. Sitting at the foot of the Mourne Mountains, near where I grew up, I am grateful to have the time and space to read through this issue of ACNR, and to contemplate the loss of some highly esteemed colleagues over the last few months.

There have been sad losses to the UK neurology community, and with permission from their families, we have provided obituaries for Dr Jenny Vaughan and Dr Richard Orrell, and there will be one more to follow.

The reason I chose neurology was in part, my admiration for my fellow neurologists, and reading about the work of neurologists past in the paper about Narcolepsy, and the John Hughlings Jackson description of 'treadlers cramp' reminds me of how relevant a rigorous clinical examination is, as well as our ability to accurately describe clinical patterns. This was particularly relevant to the Gait paper by Christopher Gilmartin, Sumranjit Sidhu and Nikos Evangelou which was a beautiful illustration of the pathophysiology of gait, with a comprehensive summary of most gait patterns we encounter in clinical practice.

ACNR is both a neurology and a rehabilitation journal, and the paper from Meenakshi Nayar et al at the Specialist Neurological Outreach Service from Charing Cross Regional Unit gives us a glimpse of where the future of specialist neurorehabilitation may lie - in the patient's home. This seven year project with 19 virtual beds, receiving rehabilitation with the same specialities and intensity as level two, has been demonstrably successful.

Looking into the future, the progressive MS series continues with Dr Sean Apap Mangion and Professor Jeremy Chataway looking at the UK experience with trials of treatment, and some specific details about how we may need to adapt our approach in the ageing population.

There are conference reports from SENA 2024 and TOXINS 2024 as well as an illuminating summary of The Brain: a national geographic special, by our book editor Dr Rhys Davies, from the Walton Centre, Liverpool.

I wish you all a lovely summer, and hope you enjoy this issue as much as I have.

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# How we walk: from underlying neurophysiology to gait disorders


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**Abstract**

Gait disorders are a frequent feature of neurology clinics, and are becoming more prominent within an ageing population. Gait is controlled by deep, evolutionarily ancient systems working in unison, predicting and enacting a walking model. Naturalistic gait involves multi-tasking and responding to environmental challenges, requiring higher cognitive processing. The control of gait is highly interconnected and so gait disorders may result from a wide array of neurological insults. This review provides a succinct summary of the underlying neurophysiology of gait for the busy clinician. We explore the neural networks controlling walking, from automated spinal cord networks through to cortical planning. Throughout, we highlight clinical phenotypes resulting from injury at each anatomical level and discuss future directions for the field.


## Introduction

Gait disorders carry significant functional ramifications and are very common, affecting ~35% of those aged 70 and older [1] and ~60% of neurology inpatients [2]. The examination of gait is a critical part of the neurological examination (Table 1)[3–6], informing diagnosis and rehabilitation. Gait characteristics may also have a role in prognostication, such as assessing dementia risk [7]. In this context, it is increasingly important for clinicians to understand the neural control for gait and how pathology may result. We will tackle the network anatomically, and start close to our effector muscles, deep within the spinal cord (Figure 1).

## Spinal central pattern generators activate muscles

Walking requires coordination of many muscle groups across multiple joints. This can be orchestrated by the spinal cord as was shown by the seminal work of Graham Brown in 1911, where decerebrated cat preparations had the same phases of movement with and without their dorsal roots severed [8]. This demonstrated that there are networks within the spinal cord capable of generating walking movements. These networks are central pattern generators (CPGs), and are composed of rhythmically firing interneurons. There are flexor-extensor CPGs for intralimb coordination, and left-right CPGs to coordinate the legs [9]. Initially CPGs were conceptualised as reciprocally inhibiting groupings (or "half-centres") of interneurons, but these concepts have evolved to consider separate rhythm- and pattern-generating circuitry [10,11]. A recent phase I/IIa clinical trial for patients with motor complete spinal cord injury used Spinalon™ (buspirone/levodopa/carbidopa) to target CPGs. Excitingly, some patients demonstrated rhythmic flexor-extensor activity, supporting a role for CPGs in humans [12]. Proprioceptive and cutaneous sensory afferents feed into spinal networks, including CPG interneurons [13]. They influence the timing and amplitude of locomotive activity, and are important for regulating the stance and swing phases [13]. Impairment of sensory pathways can lead to a sensory ataxic gait, as described in Table 1. Damage to the spinal cord itself may instead cause a spastic gait. Spasticity has multiple underlying mechanisms, but loss of reticulospinal inhibition to stretch reflex arcs is a significant factor [14]. In summary, CPGs are spinal interneuron networks that coordinate intralimb and interlimb movements and, in some mammals, stimulation can drive walking.

## The mesencephalic locomotor region - control of spinal central pattern generators

The automatic processes of CPGs require supraspinal modulation. An area within the midbrain and upper brainstem named the mesencephalic locomotor region (MLR) was proposed as a key initiator for gait, following electrical stimulation experiments eliciting controlled walking and running in a cat [15]. The MLR involves neurons within the pedunculopontine (PPN) and cuneiform nuclei (CnF), with input from the basal ganglia, amygdala, bed

nucleus of the stria terminalis and lateral hypothalamus [16]. The functions of the MLR range from postural tone to controlling the initiation, rhythm and speed of gait [17,18]. Overall, the CnF is associated with fast movements and the PPN with slower movements (Figure 2), though analysis of cellular subpopulations adds greater detail. Glutamatergic neurons in the CnF are associated with initiating gait and promoting faster walking while glutamatergic (and to some extent cholinergic) PPN neurons may promote slower walking [19,20] or support the stance phase [21,22]. An MLR GABAergic neuronal population inhibits locomotion [23]. The outputs from the PPN and CnF may also differ, with the CnF having a more localised output while the PPN may form more widespread networks, including with the basal ganglia and spinal networks via the reticulospinal tract [22]. Overall, the MLR and brainstem nuclei adjust CPG activity via the reticulospinal tract, vestibulospinal tract, tectospinal tract and monoaminergic pathways [16]. The PPN has become an experimental target for deep brain stimulation (DBS), with results highly variable between patients, although showing potential improvements for gait freezing and falls for some [24]. The MLR together has a role in initiating locomotion, with its constituent nuclei potentially favouring escape (CnF) and exploratory (PPN) behaviour [21].

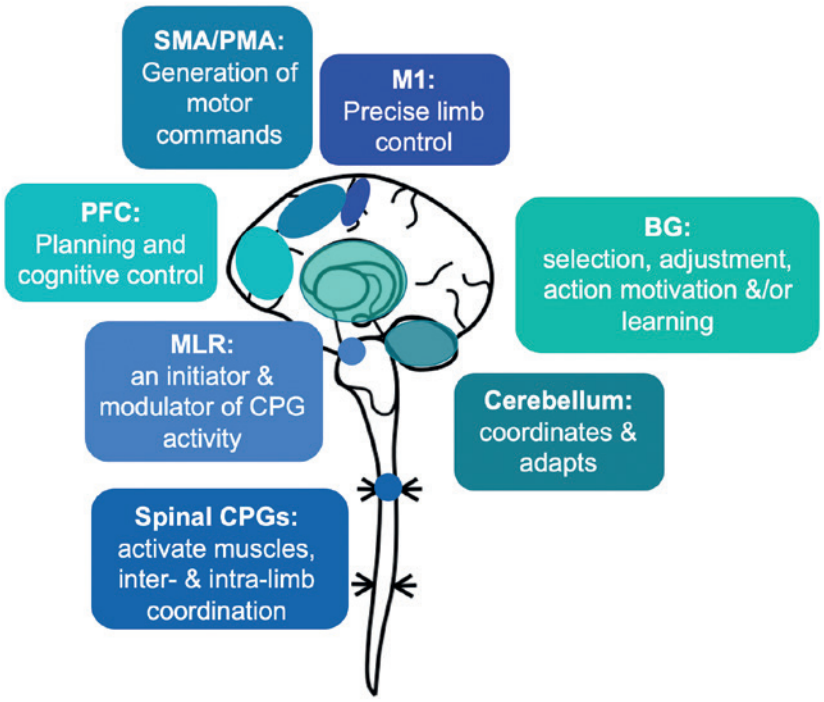


Figure 1: The roles of neural networks involved in gait - Spinal CPGs activate muscles via motor neurons, and coordinate multiple muscle groups to walk. The MLR is an initiator of gait and a controller in the process of walking. The cerebellum supports multi-joint functionality and can adapt and respond to external challenges to gait as they develop. he basal ganglia may regulate and adjust motor programmes, deliver the motivation or vigour for movement, and support procedural learning. The cortex integrates internal and external motivators to walk, with the premotor area generating motor commands and the prefrontal cortex involved in planning and cognitive control. The primary motor cortex delivers precise limb movements. CPG = central pattern generator; MLR = mesencephalic locomotor region, PFC = prefrontal cortex, SMA/PMA = premotor area including supplementary motor area, M1 = primary motor cortex, BG = basal ganglia; Figure incorporates 10.5281/zenodo.4724290 from Jon Perdomo on Scidraw.io.

**Cerebellum coordinates walking and responds to challenges**

Cerebellar lesions cause an ataxic gait, characterised by disordered multi-joint coordination. This highlights the role of the cerebellum in the control of limb movements and balance [25]. Lesions affect multi-joint functionality rather than specific muscles, or in other words cerebellar regions control actions rather than muscles in anatomical proximity [26,27]. The cerebellum projects largely to the brainstem, thalamus and spinal cord; direct projections which may be of importance for gait include from the fastigial nucleus to the vestibular nuclei and spinal cord, and from the dentate nucleus to the reticular nuclei [26].

The role of the cerebellum in coordination relies on its ability to learn motor sequences, preventing the need to consciously decompose every action. This learning occurs at Purkinje cells, which integrate information from two key cell types: climbing fibres (from the inferior olive) and granule cells with their parallel fibres (receiving input from mossy fibres) (Figure 3). Parallel fibres relay an efference copy of motor commands and provide sensory context. A single climbing fibre wraps itself like ivy around a Purkinje cell, provides error feedback (a teaching signal), and its firing triggers a Purkinje cell action potential [28,29]. Learning occurs through climbing fibre activation depressing simultaneous parallel fibre inputs, termed long-term depression (LTD) [30,31]. Disruption of LTD has been shown to specifically impact the adaptability of gait [32]. The cerebellum is important for responding to unexpected challenges to gait in humans: cerebellar patients respond irregularly to alterations in treadmill speed, while controls respond in rhythm with the normal locomotor cycle [33].

The cerebellum may also influence the initiation of gait. Stimulation of a restricted region of midline cerebellar white matter (the hook bundle of Russell) produced well-coordinated, bilaterally symmetrical, fore- and hind-limb movements in a supported decerebrated cat. This was evident even with MLR ablation [34], indicating that this 'cerebellar locomotor region (CLR)' may act through an independent pathway to the MLR. Overall, the cerebellum acts to coordinate multi-joint movements and respond to postural challenges.

**Basal ganglia may select motor commands, adjust movements, deliver action motivation, and/or contribute to motor learning**

The basal ganglia (BG) are central to the understanding of movement disorders: substantia nigra atrophy and dopamine loss in Parkinson's disease is associated with a paucity of movement (including shuffling gait), while striatal degeneration is associated with hyperkinesis in Huntington's disease [35]. The BG do not initiate movement, as the output region of the BG, the internal globus pallidus, is active after the onset of muscle contraction. The anatomical circuitry of the BG has favoured a 'brake-accelerator model': an indirect pathway (striatum D2 to external pallidum to subthalamic nucleus to internal pallidum) inhibits the thalamus, while a direct pathway (striatum D1 to internal pallidum) releases this inhibition (Figure 4). Running with this model, the BG may disinhibit the desired movement while inhibiting undesired movements [36]. One supportive example is how GABAergic fast-spiking interneurons (FSIs) in the striatum fire when a chosen action is initiated and a highly trained alternative is suppressed [37]. The BG project to the MLR and can activate or suppress MLR glutamatergic neurons, as would be required for such a model [23]. However, some have argued that the BG may not be active early enough in movement planning for this role [38]. The BG have also been proposed to adjust the speed and size of movement, which may account for the signs of bradykinesia, micrographia and hypophonia in Parkinson's disease [39]. Alternatively, the BG may be involved in movement cost-reward calculations, and so influence motivation or vigour [38]. This may explain how people with Parkinson's disease may be capable of moving as quickly as healthy individuals, but are naturally bradykinetic [38,40]. The BG further act in procedural learning (rather than retention or recall) [38], with long term potentiation and depression occurring in the striatum [41].

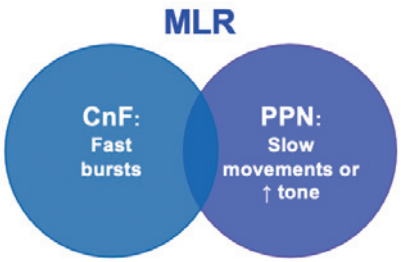


Figure 2: Diagram illustrating how MLR consists of CN and PPN with closely intertwined functionality. MLR = mesencephalic locomotor region, CN = cuneiform nucleus, PPN = pedunculopontine nucleus

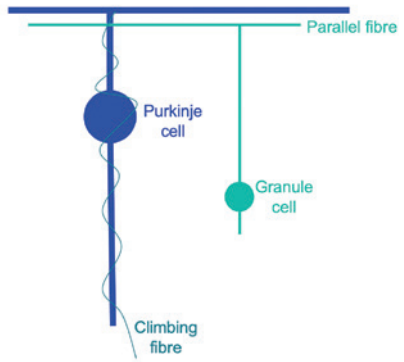


Figure 3: Diagrammatic illustration of cerebellar cortex cells

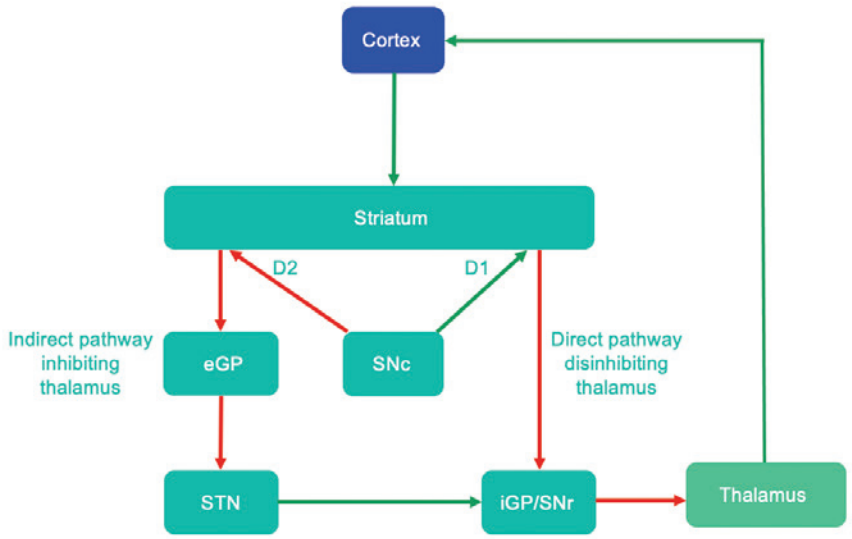


Figure 4: Traditional concept of basal ganglia circuitry - direct and indirect pathways. Green arrows indicate excitatory glutamatergic pathways, while red arrows indicate GABAergic inhibitory pathways. D1 and D2 indicate dopamine receptor subtypes. This is known to be a simplification, with further modulatory transverse pathways present, e.g. see Lanciego et al., 2012 [75]. Abbreviations: eGP = external globus pallidus, iGP = internal globus pallidus, SNc = substantia nigra pars compacta, SNr = substantia nigra pars reticulata, STN = subthalamic nucleus

Altogether, the roles of the BG may include selecting desired motor commands, adjusting the speed and size of movements, delivering the motivation or vigour for movement, and/or motor learning.

**Cortex - deciding to walk**

The cortex acts in the preparation, decision and initiation phases of gait. It weighs up the motivational drive to walk with the social and environmental context. The prefrontal cortex (PFC) is a key region for this goal-directed executive decision making [16,42]. The supplementary motor areas (SMA) and other premotor area (PMA) regions generate the motor commands following communication from the PFC. This is conveyed by corticoreticular fibres to the MLR and brainstem reticular formation, and in turn to CPGs. In parallel, the SMA/PMA communicates with M1, which controls foot and precise limb movements via the corticospinal tract [16,17] (Figure 1). This spreading recruitment of cortical regions can be seen on electroencephalography (EEG) and is termed the Bereitschaftspotential or readiness potential (RP), and is seen approximately two seconds prior to movement [43,44]. Of note, sensory information about the external environment, and the location of the body within it, requires input from all sensory modalities. Significant sensory processing occurs in the parietal cortex [16,45]. In keeping with the role of the cortex in the initiation of gait, higher level gait disorders (HLGD) have a phenotype including hesitant starts and turns [6,46].

M1 is active during the conscious drive to move, particularly for fine motor tasks. It has a somatotopic architecture (homunculus), with specific M1 regions linked with movements of distinct regions of the body [47]. Giant pyramidal neurons characterise M1, and these fast acting neurons synapse directly on anterior horn motor neurons or on associated spinal interneurons, enabling rapid and specific movements [48].The corticospinal tract is not however composed solely of M1 axons, but includes axons from the SMA, superior parietal lobule and primary somatosensory cortex [4]. Similarly not all M1 pyramidal neurons project to the corticospinal tract: some have projections across the cortex, basal ganglia, cerebellum and brainstem [49], some projecting to multiple distant sites [50]. Additionally, there may be highly connected control areas interspersed between motor control regions in M1. This new model (proposed by Gordon et al., Nature 2023) offers a tantalising means by which motor commands may be integrated with whole-body, metabolic and physiological control [51].

The SMA/PMA are important for motor programming and generating motor commands. The premotor area has been associated with sequencing tasks and reward-directed movements (specifically pre-SMA and dorsal premotor areas) [52]. These regions are important for switching away from routine movements when the environment changes and that routine is no longer appropriate [53]. The SMA helps prepare for the centre of gravity moving during walking (anticipatory postural adjustment)[16]. The caudal premotor area including the SMA maintains a somatotopic representation, although not as clear as that of M1.

The PFC has widespread functions in gait as an executive region, with roles in decision making, attention, working memory, planning task sequencing and personality [16,42]. Increased PFC activation has been consistently noted in dual task walking, reflecting its role in attention. Unlike walking on a treadmill in a controlled setting, navigating the real world requires a constant interplay between planning and execution: we avoid static and moving obstacles, often while talking. The gait pattern of healthy young adults changes when dual tasking; this would only be expected if higher cognitive attention is required for walking [54]. For those with stroke, multiple sclerosis, or in healthy older adults, even normal walking has been associated with increased PFC activation, which may represent a compensatory mechanism [49,50]. The PFC is integrated into the limbic or emotional network through connections with the hypothalamus and periaqueductal grey, critical for goal-directed naturalistic walking [16]. Further centres included in this network are the amygdala, hippocampus and nucleus accumbens, incorporating emotional drivers for gait.

An exceptional recent review (Gait control by the frontal lobe, Handbook of Clinical Neurology, Takakusaki) highlighted how the prefrontal and premotor areas have extensive connectivity across the central nervous system. Key pathways include a parieto-prefrontal ('where') pathway transferring spatial information to the PFC and a parieto-premotor

**Table 1: Characteristics of classical gait disorders and their causes**

| Gait | Characteristics | Causes include |
|---|---|---|
| Broad-based ataxic gaits | | |
| Sensory ataxic gait (including a stomping gait) | Broad-based. Impaired tandem gait. May watch feet when walking. Gait and stability worsens when eyes are closed. Romberg's test positive: will be able to stand with feet together and eyes open, but on closing eyes will sway significantly. May stamp feet against ground with increased force to compensate for a proprioception deficit. Abnormal head impulse test in vestibulopathy. | Sensory peripheral neuropathy or dorsal column disease: endocrine and metabolic (diabetes mellitus, hypothyroidism, renal failure, liver failure), nutritional (vitamin B12, B1, B6, E deficiency), toxic (alcohol, medications incl. isoniazid, amiodarone, chemotherapies), inflammatory (paraneoplastic, Sjögren's, vasculitis), genetic (CMT, Friedreich's ataxia), infections (HIV, leprosy, syphilis).<br>Bilateral vestibulopathy. |
| Cerebellar ataxic gait | Broad-based. Irregular step-length and rhythm. May sway. Inability to adapt to factors threatening stability, with instability worsening with abrupt changes such as standing from sitting or when quickly turning. Impaired tandem gait. Romberg negative (in contrast to sensory ataxic gait) – may be unable to stand with feet together with eyes open. If one cerebellar hemisphere is involved, there is deviation towards the affected side. | Cerebellar pathology: SOL and structural disease (neoplasm, Arnold-Chiari, AVM), toxic (alcohol, phenytoin, carbamazepine, lithium), inflammatory (MS, ADEM, paraneoplastic, Miller Fisher syndrome), vascular (infarction or haemorrhage), metabolic (hypothyroidism), nutritional (vitamin B12, E or copper deficiency, coeliac disease), genetic (SCA, Friedreich's ataxia, ataxia telangiectasia, VHL), degenerative (MSA-C, prion). |
| Stiff (spastic) gaits | | |
| Scissor gait | Spastic paraparesis results in a bilateral version of hemiplegic gait, with circumduction of both lower limbs. Thighs may be adducted together. Gait is effortful and may be described as 'walking through mud'. | Spastic paraparesis from cord or parasagittal lesion: SOL and structural disease (neoplastic, syringomyelia, spinal degenerative disease, parasagittal meningioma), inflammatory (TM, MS, NMO, MOGAD, sarcoidosis), vascular (anterior spinal artery syndrome, AVM), genetic (HSP, adrenoleukodystrophy), infections (HIV, HTLV-1, syphilis), nutritional (vitamin B12 or copper deficiency), cerebral palsy, degenerative (MND). |
| Hemiplegic spastic gait | Affected leg is stiff, with little flexion at hip, knee or ankle (power of extensor muscles great than flexors). To compensate, the leg is swung outward in a semicircle (circumduction). Foot may scuff the floor – shoes may have excessive wear around outer border and toes. Arm on affected side may also be stiff and weak, and may be flexed with altered swing (localising lesion to cervical cord or above). | Unilateral hemisphere, brainstem or cord lesion: SOL and structural disease (neoplastic, spinal degenerative disease), vascular (ischaemia or haemorrhage), inflammatory (TM, MS, NMO, MOGAD, sarcoidosis), degenerative (MND), hemiplegic cerebral palsy. |
| Shuffling gaits | | |
| Parkinsonian gait | Small stepping, shuffling gait. Diminished arm swing. Turning en bloc. Base narrow or normal. Hesitation when starting to walk. Freezing may occur when approaching obstacles or during turns. Parkinson's disease is typically asymmetric on onset and improves with visual or auditory cues. In more severe disease, festination (involuntary hastening of gait) may occur– as walking commences, the torso advances ahead of the lower limbs, leading to increasingly fast and short steps.* | Differentials for parkinsonism: idiopathic PD (asymmetric), Parkinson's plus syndromes (MSA, PSP, CBD, DLB), medication (dopamine antagonists), genetic (familial PD), Wilson's, Huntington's disease (akinetic-rigid variant), dopa-responsive dystonia |
| Higher level gait disorder (or gait apraxia or frontal gait) | Small shuffling steps ('marche à petits pas'). Difficulty initiating walking. Unstable and may have widened base (particularly in NPH). Typically preserved arm swing. Patients with frontal lobe disorders (including NPH) are able to perform the motions of walking when sitting or lying, but have difficulty when upright and attempting to walk. | NPH, cerebral small vessel disease and other cortical, subcortical or network pathology including vascular causes, space occupying lesions or degenerative disease. |
| Twisting movements | | |
| Choreoathetotic and dystonic gaits | Choreoathetosis is continuous irregular, jerking or twisting movements of face, neck, trunk and limbs. Dystonia results from co-contraction of antagonistic muscles and leads to twisting and repetitive movements and postures. Dystonic gait may have an abnormal foot posture, e.g. with plantar flexion, inversion and extension of the big toe. Dystonic postures may be triggered by exercise. Worsened by walking on sides of feet. Geste antagoniste (sensory stimulation e.g. touching hair) may improve dystonic gait for some. | Basal ganglia disorders including genetic conditions such as Huntington's disease, vascular damage, immunological disease (e.g. Syndenham's chorea, SLE, APLS, chorea gravidarum) and drug-related (including dopamine). |
| Characteristic gaits linked to muscle weakness or paralysis | | |
| Steppage gait (or foot drop gait) | Foot drop is failure to dorsiflex the foot. Excessive flexion of the hip is required to compensate for foot drop to enable the foot to clear the ground during the swing phase. There may be foot slapping. | Peroneal or L5 root damage classically - foot inversion is preserved in common peroneal palsy while weak in L5 radiculopathy (eversion weak in both). Foot drop may result from systemic neuropathies (e.g. diabetic, toxic, nutritional, inflammatory), radiculopathies, degenerative neuromuscular pathology (e.g. MND), genetic causes (such as CMT, spinal muscular atrophy or muscular dystrophies) or poliomyelitis. |
| Waddling gait | Hips drop on the contralateral side to the weightbearing limb during walking (Trendelenburg sign). This results from proximal muscle weakness of the weightbearing limb, particularly the gluteal muscles. May have difficulty standing-up with arms folded. | Myopathies (incl. muscular dystrophies, inflammatory myopathies, drug-induced myopathies), spinal muscular atrophy, lumbosacral nerve root damage, congenital dislocation of hips. |
| Unilateral falls | | |
| Unilateral falls | Falls to one side.<br>Vestibular disease: gait deteriorates with eye closure and Unterberger positive (when walking on spot with eyes closed, rotation to side of labyrinth dysfunction). Abnormal head impulse test. | Ipsilateral falls are associated with unilateral vestibular disease, cerebellar and medullary lesions.<br>Thalamic damage is associated with contraversive falls (pusher syndrome).<br>Tendency to fall backwards with midbrain lesions. |
| Other characteristic gaits | | |
| Cautious gait | Slow gait with shorter steps and broader base. Improvement with mobility aids. | Nonspecific response to perceived disequilibrium or fear of falling. |
| Antalgic gait | Reduced stance phase on affected limb, leading to a limp. | Pain of affected limb. |
| Functional gait disorder | Variability. Improvement in gait when distracted. Internal inconsistency. May show instability, yet usually able to regain balance prior to falling. | Functional neurological disorder. |

*See Mermelstein et al., Pract Neurol 2024 [74] for discriminating atypical parkinsonian syndromes.

Abbreviations: ADEM = acute disseminated encephalomyelitis, APLS = antiphospholipid syndrome, AVM = arteriovenous malformation, CBD = corticobasal degeneration, CMT = Charcot-Marie-Tooth disease, DLB = dementia with Lewy bodies, MS = multiple sclerosis, MSA = multiple system atrophy, MSA-C = MSA with predominant cerebellar features, MND = motor neuron disease, MOGAD = myelin oligodendrocyte glycoprotein antibody disease, NMO = neuromyelitis optica, NPH = normal pressure hydrocephalus, PD = Parkinson's disease, SCA = spinocerebellar ataxias, SLE = systemic lupus erythematosus, SOL = space-occupying lesion, TM = transverse myelitis

Figure 5: an example of a wearable OPM-MEG being used to investigate cortical activity at the Sir Peter Mansfield Imaging Centre, University of Nottingham

('how') pathway for visually guided movements. Further cortical networks important for gait include an occipito-temporal ('what') pathway for visual processing and a parieto-medial temporal pathway for route navigation and long-term spatial memory [16].

In summary, as walking is a purposeful action within the environment, it involves not only motor cortex activity, but also sensory systems and higher cognitive processing. It is therefore unsurprising that neurological disorders so commonly cause gait disturbance.

**Neuroimaging approaches are furthering our understanding of gait disorders**

Our understanding of gait disorders is still limited by our inability to image individuals while moving with high temporal resolution. This is especially evident for HLGD, where our knowledge is particularly limited [55].

One approach has been to utilise EEG to investigate cortical activity in gait. Through this, researchers have characterised the electrical activity when standing [56], during the gait cycle [57] and even with distractions when walking across a university campus [58]. EEG has further been thoroughly utilised to investigate disease states, such as freezing of gait in Parkinson's disease [59]. The utility of EEG however is limited by noise and its poorer spatial resolution when compared with other modalities.

Functional near-infrared spectroscopy (fNIRS) has been extensively used for investigating the neuroscience of movement [60]. Near-infrared light determines haemoglobin concentrations in tissues, and so their aerobic metabolic demand. There may be a time-lag of 4-7 seconds between cortical activity and haemodynamic response however [61–63]. fNIRS can offer improved spatial resolution compared to EEG (previously estimated as 5mm vs 10mm) [64]. Similar to EEG, fNIRS is appropriate for studies of the cortex rather than deeper structures, as it relies on the penetration of infrared light to those tissues [64]. fNIRS has been applied for researching gait [65], preparation for walking [66], gait in disease states [67] and dual task walking [68].

Another approach taken has been to utilise [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET), whereby subjects walk, are injected with tracer, then continue walking, following which imaging is performed. This relies on cerebral glucose utilisation being weighted to the first 10-15 minutes after [18F]-FDG injection [69]. The Newcastle group using PET [70] have reported two resting covariance networks associated with gait characteristics in Parkinson's disease [71].

Magnetoencephalography with optically pumped magnetometers (OPM-MEG)s offers a novel approach to investigate movement and could prove a real game-changer in the study of gait. It offers a finer spatial resolution than EEG and greater temporal resolution than fNIRS: MEG has quoted temporal resolution in the millisecond range and spatial resolution of c.2–5 mm [72]. The spatial resolution is not as detailed as fMRI for deep structures, although new approaches are ongoing for enhancing this, with a recent study adapting OPM-MEG to analyse the hippocampus [73]. OPM-MEG is integrated into a wearable helmet, offering an exciting opportunity to investigate gait disorders directly (as shown in Figure 4) – only time will tell if it will realise a role as a functional neuroimaging tool for gait.

**Conclusions**

Locomotion relies on deep and interconnected neural networks. The MLR initiates gait through spinal CPGs. This is informed by cortical regions, particularly prefrontal and premotor areas, integrating sensory information with the desire and motivation to walk. The cerebellum coordinates walking and adapts to challenges. The basal ganglia may have roles in selecting motor commands, adjusting movements, delivering action motivation, and/or contributing to motor learning, Together, these different regions work in unison, predicting and enacting a walking model. Naturalistic gait is goal-directed and responsive to a changing environment, requiring higher cognitive processing. Given how interdependent all these regions are for walking, gait disorders result from disruption of any part of this pathway from cortex to muscle. OPM-MEG offers the potential opportunity to measure gait disorders with greater spatial resolution than EEG and finer temporal resolution than fNIRS.

References


1. Verghese J, LeValley A, Hall CB, Katz MJ, Ambrose AF, Lipton RB. Epidemiology of Gait Disorders in Community-Residing Older Adults. J Am Geriatr Soc. 2006;54(2):255-261. https://doi.org/10.1111/j.1532-5415.2005.00580.x
2. Stolze H, Klebe S, Baecker C, et al. Prevalence of gait disorders in hospitalized neurological patients. Mov Disord. 2005;20(1):89-94. https://doi.org/10.1002/mds.20266
3. Pirker W, Katzenschlager R. Gait disorders in adults and the elderly. Wien Klin Wochenschr. 2017;129(3):81-95. https://doi.org/10.1007/s00508-016-1096-4
4. Allan H. Ropper, Martin A. Samuels. Adams and Victor's Principles of Neurology. 9th ed. McGraw-Hill Education; 2009.
5. Neurological gait disorders in elderly people: clinical approach and classification. Lancet Neurol. 2007;6(1):63-74. https://doi.org/10.1016/S1474-4422(06)70678-0
6. Baker JM. Gait Disorders. Am J Med. 2018;131(6):602-607. https://doi.org/10.1016/j.amjmed.2017.11.051
7. Gait analysis as a clinical tool for dementia: current perspectives and future challenges. ACNR Adv Clin Neurosci Rehabil. Published online May 21, 2021. Accessed July 20, 2023. https://acnr.co.uk/articles/gait-analysis/ https://doi.org/10.47795/OBXA9271
8. Brown TG. The intrinsic factors in the act of progression in the mammal. Proc R Soc Lond Ser B Contain Pap Biol Character. 1911;84(572):308-319. https://doi.org/10.1098/rspb.1911.0077
9. Minassian K, Hofstoetter US, Dzeladini F, Guertin PA, Ijspeert A. The Human Central Pattern Generator for Locomotion: Does It Exist and Contribute to Walking? The Neuroscientist. 2017;23(6):649-663. https://doi.org/10.1177/1073858417699790
10. Grillner S, Wallén P. Central pattern generators for locomotion, with special reference to vertebrates. Annu Rev Neurosci. 1985;8. https://doi.org/10.1146/annurev.ne.08.030185.001313
11. McCrea DA, Rybak IA. Organization of mammalian locomotor rhythm and pattern generation. Brain Res Rev. 2008;57(1):134-146. https://doi.org/10.1016/j.brainresrev.2007.08.006
12. Radhakrishna M, Steuer I, Prince F, et al. Double-Blind, Placebo-Controlled, Randomized Phase I/IIa Study (Safety and Efficacy) with Buspirone/Levodopa/Carbidopa (SpinalonTM) in Subjects with Complete AIS A or Motor-Complete AIS B Spinal Cord Injury. Curr Pharm Des. 2017;23(12):1789-1804. https://doi.org/10.2174/1381612822666161227152200
13. Frigon A, Rossignol S. Experiments and models of sensorimotor interactions during locomotion. Biol Cybern. 2006;95(6):607-627. https://doi.org/10.1007/s00422-006-0129-x
14. Chakravarty A, Mukherjee A. Spasticity Mechanisms - for the Clinician. Front Neurol. 2010;1. Accessed July 17, 2023. https://www.frontiersin.org/articles/10.3389/fneur.2010.00149 https://doi.org/10.3389/fneur.2010.00149
15. Shik ML, Severin FV, Orlovskiĭ GN. [Control of walking and running by means of electric stimulation of the midbrain]. Biofizika. 1966;11(4):659-666.
16. Takakusaki K. Gait control by the frontal lobe. Handb Clin Neurol. 2023;195:103-126. https://doi.org/10.1016/B978-0-323-98818-6.00021-2
17. Takakusaki K. Neurophysiology of gait: from the spinal cord to the frontal lobe. Mov Disord Off J Mov Disord Soc. 2013;28(11):1483-1491. https://doi.org/10.1002/mds.25669

18. Lau B, François C, Karachi C. Structure and function of the mesencephalic locomotor region in normal and parkinsonian primates. Curr Opin Physiol. 2019;8:121-128. https://doi.org/10.1016/j.cophys.2019.01.010
19. Caggiano V, Leiras R, Goñi-Erro H, et al. Midbrain circuits that set locomotor speed and gait selection. Nature. 2018;553(7689):455-460. https://doi.org/10.1038/nature25448
20. Josset N, Roussel M, Lemieux M, Lafrance-Zoubga D, Rastqar A, Bretzner F. Distinct Contributions of Mesencephalic Locomotor Region Nuclei to Locomotor Control in the Freely Behaving Mouse. Curr Biol. 2018;28(6):884-901.e3. https://doi.org/10.1016/j.cub.2018.02.007
21. Ali F, Benarroch E. What Is the Brainstem Control of Locomotion? Neurology. 2022;98(11):446-451. https://doi.org/10.1212/WNL.0000000000200108
22. Dautan D, Kovács A, Bayasgalan T, Diaz-Acevedo MA, Pal B, Mena-Segovia J. Modulation of motor behavior by the mesencephalic locomotor region. Cell Rep. 2021;36(8):109594. https://doi.org/10.1016/j.celrep.2021.109594
23. Roseberry TK, Lee AM, Lalive AL, Wilbrecht L, Bonci A, Kreitzer AC. Cell-Type-Specific Control of Brainstem Locomotor Circuits by Basal Ganglia. Cell. 2016;164(3):526-537. https://doi.org/10.1016/j.cell.2015.12.037
24. Thevathasan W, Debu B, Aziz T, et al. Pedunculopontine nucleus deep brain stimulation in Parkinson's disease: A clinical review. Mov Disord. 2018;33(1):10-20. https://doi.org/10.1002/mds.27098
25. Ilg W, Giese MA, Gizewski ER, Schoch B, Timmann D. The influence of focal cerebellar lesions on the control and adaptation of gait. Brain J Neurol. 2008;131(Pt 11):2913-2927. https://doi.org/10.1093/brain/awn246
26. Thomas Thach W, Bastian AJ. Role of the cerebellum in the control and adaptation of gait in health and disease. In: Progress in Brain Research. Vol 143. Brain Mechanisms for the Integration of Posture and Movement. Elsevier; 2004:353-366. https://doi.org/10.1016/S0079-6123(03)43034-3
27. Botterell EH, Fulton JF. Functional localization in the cerebellum of primates III. Lesions of hemispheres (neocerebellum). J Comp Neurol. 1938;69(1):63-87. https://doi.org/10.1002/cne.900690106
28. Dean P, Porrill J. Adaptive-filter Models of the Cerebellum: Computational Analysis. The Cerebellum. 2008;7(4):567-571. https://doi.org/10.1007/s12311-008-0067-3
29. Surdin T, Preissing B, Rohr L, et al. Optogenetic activation of mGluR1 signaling in the cerebellum induces synaptic plasticity. iScience. 2023;26(1):105828. https://doi.org/10.1016/j.isci.2022.105828
30. Ito M. Long-term depression. Annu Rev Neurosci. 1989;12:85-102. https://doi.org/10.1146/annurev.ne.12.030189.000505
31. Yanagihara D, Kondo I. Nitric oxide plays a key role in adaptive control of locomotion in cat. Proc Natl Acad Sci U S A. 1996;93(23):13292-13297. https://doi.org/10.1073/pnas.93.23.13292
32. Rand MK, Wunderlich DA, Martin PE, Stelmach GE, Bloedel JR. Adaptive changes in responses to repeated locomotor perturbations in cerebellar patients. Exp Brain Res. 1998;122(1):31-43. https://doi.org/10.1007/s002210050488
33. Mori S, Matsui T, Kuze B, Asanome M, Nakajima K, Matsuyama K. Stimulation of a restricted region in the midline cerebellar white matter evokes coordinated quadrupedal locomotion in the decerebrate cat. J Neurophysiol. 1999;82(1):290-300. https://doi.org/10.1152/jn.1999.82.1.290
34. Papoutsi M, Labuschagne I, Tabrizi SJ, Stout JC. The cognitive burden in Huntington's disease: Pathology, phenotype, and mechanisms of compensation. Mov Disord. 2014;29(5):673-683. https://doi.org/10.1002/mds.25864
35. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol. 1996;50(4):381-425. https://doi.org/10.1016/S0301-0082(96)00042-1
36. Gage GJ, Stoetzner CR, Wiltschko AB, Berke JD. Selective activation of striatal fast-spiking interneurons during choice execution. Neuron. 2010;67(3):466-479. https://doi.org/10.1016/j.neuron.2010.06.034
37. Turner RS, Desmurget M. Basal Ganglia Contributions to Motor Control: A Vigorous Tutor. Curr Opin Neurobiol. 2010;20(6):704-716. https://doi.org/10.1016/j.conb.2010.08.022
38. Spraker MB, Yu H, Corcos DM, Vaillancourt DE. Role of individual basal ganglia nuclei in force amplitude generation. J Neurophysiol. 2007;98(2):821-834. https://doi.org/10.1152/jn.00239.2007
39. Mazzoni P, Hristova A, Krakauer JW. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. J Neurosci Off J Soc Neurosci. 2007;27(27):7105-7116. https://doi.org/10.1523/JNEUROSCI.0264-07.2007
40. Lerner TN, Kreitzer AC. Neuromodulatory control of striatal plasticity and behavior. Curr Opin Neurobiol. 2011;21(2):322-327. https://doi.org/10.1016/j.conb.2011.01.005
41. Carlén M. What constitutes the prefrontal cortex? Science. 2017;358(6362):478-482. https://doi.org/10.1126/science.aan8868
42. Shibasaki H, Hallett M. What is the Bereitschaftspotential? Clin Neurophysiol. 2006;117(11):2341-2356. https://doi.org/10.1016/j.clinph.2006.04.025
43. Armstrong S, Sale MV, Cunnington R. Neural Oscillations and the Initiation of Voluntary Movement. Front Psychol. 2018;9. Accessed April 14, 2023. https://www.frontiersin.org/articles/10.3389/fpsyg.2018.02509 https://doi.org/10.3389/fpsyg.2018.02509
44. Drew T, Marigold DS. Taking the next step: cortical contributions to the control of locomotion. Curr Opin Neurobiol. 2015;33:25-33. https://doi.org/10.1016/j.conb.2015.01.011
45. Nutt JG. Higher-level gait disorders: An open frontier. Mov Disord. 2013;28(11):1560-1565. https://doi.org/10.1002/mds.25673
46. Penfield W, Boldrey E. Somatic Motor and Sensory Representation in the in the Cerebral Cortex of Man as studied by Electrical Stimulation. Brain. 1937;60(4):389-443. https://doi.org/10.1093/brain/60.4.389
47. Squire L, Berg D, Bloom FE, et al. Fundamental Neuroscience. Academic Press; 2008.
48. Park J, Phillips JW, Guo JZ, Martin KA, Hantman AW, Dudman JT. Motor cortical output for skilled forelimb movement is selectively distributed across projection neuron classes. Sci Adv. 2022;8(10):eabj5167. https://doi.org/10.1126/sciadv.abj5167
49. Winnubst J, Bas E, Ferreira TA, et al. Reconstruction of 1,000 projection neurons reveals new cell types and organization of long-range connectivity in the mouse brain. Cell. 2019;179(1):268-281.e13. https://doi.org/10.1016/j.cell.2019.07.042
50. Gordon EM, Chauvin RJ, Van AN, et al. A somato-cognitive action network alternates with effector regions in motor cortex. Nature. 2023;617(7960):351-359. https://doi.org/10.1038/s41586-023-05964-2
51. Hikosaka O, Isoda M. Switching from automatic to controlled behavior: cortico-basal ganglia mechanisms. Trends Cogn Sci. 2010;14(4):154-161. https://doi.org/10.1016/j.tics.2010.01.006
52. Nakajima T, Hosaka R, Mushiake H. Complementary Roles of Primate Dorsal Premotor and Pre-Supplementary Motor Areas to the Control of Motor Sequences. J Neurosci. 2022;42(36):6946-6965. https://doi.org/10.1523/JNEUROSCI.2356-21.2022
53. Srygley JM, Mirelman A, Herman T, Giladi N, Hausdorff JM. When does walking alter thinking? Age and task associated findings. Brain Res. 2009;1253:92-99. https://doi.org/10.1016/j.brainres.2008.11.067
54. Walusinski O. From hysteria to gait dementia: History of the concept of astasia-abasia. Rev Neurol (Paris). 2023;179(6):523-532. https://doi.org/10.1016/j.neurol.2022.12.012
55. Zhavoronkova LA, Zharikova AV, Kushnir EM, Mikhalkova AA. EEG markers of upright posture in healthy individuals. Hum Physiol. 2012;38(6):604-612. https://doi.org/10.1134/S0362119712050131
56. Gwin JT, Gramann K, Makeig S, Ferris DP. Electrocortical activity is coupled to gait cycle phase during treadmill walking. NeuroImage. 2011;54(2):1289-1296. https://doi.org/10.1016/j.neuroimage.2010.08.066
57. Liebherr M, Corcoran AW, Alday PM, et a l. EEG and behavioral correlates of attentional processing while walking and navigating naturalistic environments. Sci Rep. 2021;11(1):22325. https://doi.org/10.1038/s41598-021-01772-8
58. Stuart S, Wagner J, Makeig S, Mancini M. Brain Activity Response to Visual Cues for Gait Impairment in Parkinson's Disease: An EEG Study. Neurorehabil Neural Repair. 2021;35(11):996-1009. https://doi.org/10.1177/15459683211041317
59. Hamacher D, Herold F, Wiegel P, Hamacher D, Schega L. Brain activity during walking: A systematic review. Neurosci Biobehav Rev. 2015;57:310-327. https://doi.org/10.1016/j.neubiorev.2015.08.002
60. Cui X, Bray S, Reiss AL. Speeded Near Infrared Spectroscopy (NIRS) Response Detection. PLOS ONE. 2010;5(11):e15474. https://doi.org/10.1371/journal.pone.0015474
61. Tong Y, Frederick B deB. Time lag dependent multimodal processing of concurrent fMRI and near-infrared spectroscopy (NIRS) data suggests a global circulatory origin for low-frequency oscillation signals in human brain. NeuroImage. 2010;53(2):553-564. https://doi.org/10.1016/j.neuroimage.2010.06.049
62. Vitorio R, Stuart S, Rochester L, Alcock L, Pantall A. fNIRS response during walking - Artefact or cortical activity? A systematic review. Neurosci Biobehav Rev. 2017;83:160-172. https://doi.org/10.1016/j.neubiorev.2017.10.002
63. Nicolas-Alonso LF, Gomez-Gil J. Brain Computer Interfaces, a Review. Sensors. 2012;12(2):1211-1279. https://doi.org/10.3390/s120201211
64. Herold F, Wiegel P, Scholkmann F, Thiers A, Hamacher D, Schega L. Functional near-infrared spectroscopy in movement science: a systematic review on cortical activity in postural and walking tasks. Neurophotonics. 2017;4(4):041403. https://doi.org/10.1117/1.NPh.4.4.041403
65. Suzuki M, Miyai I, Ono T, Kubota K. Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. NeuroImage. 2008;39(2):600-607. https://doi.org/10.1016/j.neuroimage.2007.08.044
66. Bishnoi A, Holtzer R, Hernandez ME. Brain Activation Changes While Walking in Adults with and without Neurological Disease: Systematic Review and Meta-Analysis of Functional Near-Infrared Spectroscopy Studies. Brain Sci. 2021;11(3):291. https://doi.org/10.3390/brainsci11030291
67. Sui SX, Hendy AM, Teo WP, Moran JT, Nuzum ND, Pasco JA. A Review of the Measurement of the Neurology of Gait in Cognitive Dysfunction or Dementia, Focusing on the Application of fNIRS during Dual-Task Gait Assessment. Brain Sci. 2022;12(8):968. https://doi.org/10.3390/brainsci12080968
68. la Fougère C, Zwergal A, Rominger A, et al. Real versus imagined locomotion: A [18F]-FDG PET-fMRI comparison. NeuroImage. 2010;50(4):1589-1598. https://doi.org/10.1016/j.neuroimage.2009.12.060
69. FDG PET & Gait. Brain and Movement Newcastle University. Accessed July 12, 2023. https://www.bam-ncl.co.uk/fdg-pet-gait
70. Sigurdsson HP, Yarnall AJ, Galna B, et al. Gait-Related Metabolic Covariance Networks at Rest in Parkinson's Disease. Mov Disord. 2022;37(6):1222-1234. https://doi.org/10.1002/mds.28977
71. Brookes MJ, Leggett J, Rea M, et al. Magnetoencephalography with optically pumped magnetometers (OPM-MEG): the next generation of functional neuroimaging. Trends Neurosci. 2022;45(8):621-634. https://doi.org/10.1016/j.tins.2022.05.008
72. Tierney TM, Levy A, Barry DN, et al. Mouth magnetoencephalography: A unique perspective on the human hippocampus. Neuroimage. 2021;225:117443. https://doi.org/10.1016/j.neuroimage.2020.117443
73. Lanciego JL, Luquin N, Obeso JA. Functional Neuroanatomy of the Basal Ganglia. Cold Spring Harb Perspect Med. 2012;2(12):a009621. https://doi.org/10.1101/cshperspect.a009621Reference list [choose style List Paragraph] no hard returns between each reference and DOI number in same para as reference it belongs to.

# Accidental pneumothorax secondary to a malpositioned nasogastric tube in a patient presenting with acute ischaemic stroke

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***Key words:*** Feeding tube; Nasogastric tube; Pneumothorax; Stroke

***Consent:*** Informed patient consent was obtained prior to publication of this case report.

**Abstract**

A 77-year-old woman presenting with severe acute ischaemic stroke failed a swallow screening test on admission. A nasogastric (NG) tube was inserted to initiate enteral feeding. She required multiple NG tube placements due to agitation with repeat malposition into the right bronchus demonstrated on chest radiographs. Further radiographs to confirm NG tube position showed a right apical pneumothorax that was missed on initial imaging reviews. The patient remained clinically stable with no respiratory compromise and the pneumothorax resolved spontaneously without directed treatment.

**Key points**

1. Thoracic complications, of which pneumothorax is the most common, can occur after inadvertent malposition of nasogastric tubes into the tracheobronchial tree

2. Chest x-rays to confirm for nasogastric tube position should always be evaluated for pulmonary complications, especially in the context of recent malposition

3. Challenging or multiple nasogastric tube placements confer an increased risk of tracheobronchial complications

## Background

Nasogastric tubes play a vital role in the nutritional support of patients with acute dysphagia or decreased level of consciousness following acute stroke. Though generally seen as safe, the procedure of nasogastric tube insertion is not without risks. We present the case of a pneumothorax following repeated nasogastric tube insertion into the right tracheobronchial tree.

## Case Presentation

A 77-year old woman with a history of hypertension was admitted to hospital after presenting with vomiting, aphasia and right-sided weakness. A CT head scan showed an acute left middle cerebral artery (MCA) territory infarction, with suspicion of a thrombus within the M2 branches of the left MCA. National Institutes of Health Stroke Scale score on presentation to the Emergency Department was 28, but the patient was not eligible for acute reperfusion therapy due to wake-up stroke. She failed a swallow screening test on admission and a nasogastric (NG) tube was inserted to initiate emergency enteral feeding.

Her early nutritional management was complicated by repeated NG tube displacement or removal due to agitation, despite the use of safety mittens and a nasal bridle to mitigate this risk. Seven NG tube reinsertions were required within the first eight days of her admission. On days six and eight of the admission, two separate chest radiographs to check NG tube placement were performed; these demonstrated malposition into the right main bronchus and over the right lung field (Figures 1 and 2). On both radiographs, there was no obvious pneumothorax present.

A subsequent chest radiograph to check NG tube placement on day nine showed a new right apical pneumothorax (Figure 3). The NG tube was deemed safe to use but no acknowledgement of the pneumothorax was made in the radiograph report or the patient's clinical notes.

Two days later, after a further chest radiograph was performed to confirm NG tube placement, the on-call radiologist contacted the treating medical team to inform them of the right apical pneumothorax, which had persisted on sequential radiographs. The patient was re-reviewed clinically and found to have reduced air entry on chest auscultation of the right upper zone. She remained stable with no respiratory symptoms and maintained target oxygen saturations (94-98%) on room air. The patient was observed, and subsequent chest radiograph two days after the initial radiological finding showed spontaneous resolution of the pneumothorax (Figure 4).

The patient was 146cm tall, weighing 71.6kg, with a body mass index of 33.5kg/m2. She did not fit the archetypal patient (namely "tall, thin, young and male") that might present with

primary spontaneous pneumothorax (PSP), nor was there a positive family history of PSP. She was a never-smoker with no known underlying lung conditions. The treating team considered performing a CT thorax to screen for secondary causes of spontaneous pneumothorax - but after discussion with the radiology team this was deemed not necessary, with the probable aetiology being iatrogenic following NG tube misplacement.

The patient suffered no complications from the event and made a full recovery. She was successfully switched to oral feeding after a videofluoroscopy swallow study (VFSS).

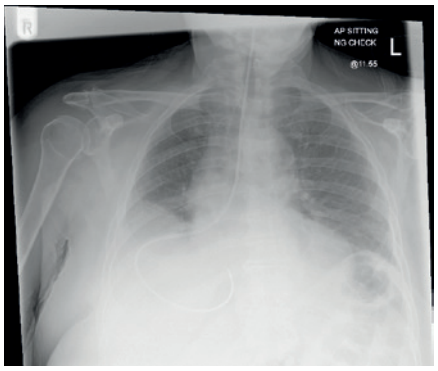

Figure 1: Chest radiograph showing passage of NG tube into the right main bronchus

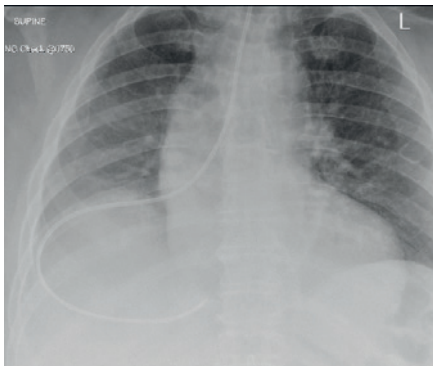

Figure 2: Second malpositioned NG tube insertion into the right lung

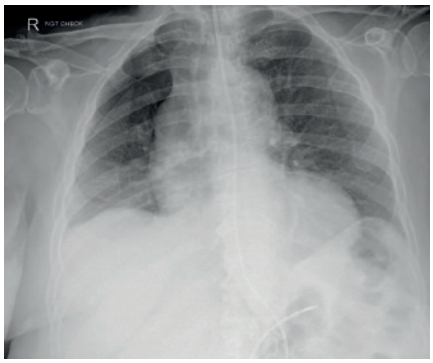

Figure 3: Right pneumothorax

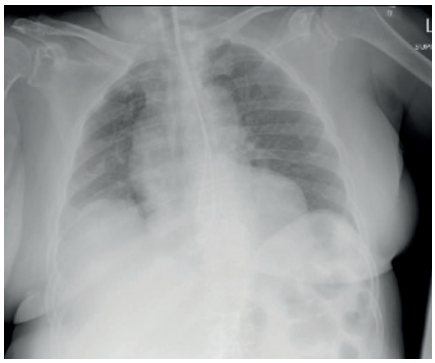
Figure 4: Spontaneous resolution of pneumothorax

**Discussion**

Nasogastric tube insertion is a common but invasive bedside procedure for hospitalised patients, and insertion is usually performed blindly without endoscopic or radiographic guidance. The first-line method for NG tube placement confirmation, recommended by the National Institute for Health and Care Excellence, is pH testing of NG tube aspirates [1]. However, chest radiographs, which are considered the gold-standard for confirming proper position, are often obtained if this is unsuccessful. Chest radiographs must be interpreted carefully in this context and a four-point algorithm is often used to confirm correct NG tube position [1].

In the case we have presented, the right apical pneumothorax was missed on initial reviews on two separate radiographs by both the treating team and reporting clinicians. The underlying causes of such 'perceptual' errors, which occur during the initial phase of image interpretation, have been explored by Bruno et al. and include poor conspicuousness of the abnormality, environmental distractions and reader fatigue [2]. The 'satisfaction of search' error, where the interpreter fails to continue to search for additional findings after identifying an initial one, may have also played a role here; with an attentional bias towards checking for NG tube position, once this was confirmed the interpreting clinicians may have been less conscientious of other radiographical abnormalities.

Studies have reported the incidence of inadvertent malposition of NG tubes into the tracheobronchial tree to be 0.3-15% [3,4]. Thoracic complications include pneumonia, lung abscess, pneumothorax, empyema and pulmonary haemorrhage – of these, pneumothorax is the most common [4]. Patients may not present with symptoms indicative of malposition, but it is important to be mindful of potential pulmonary sequelae, especially in the context of repeated insertion after previous pulmonary misadventure.

The risk of challenging or multiple NG tube placements is increased by patient factors including critical illness, altered mental status, non-cooperativeness and an impaired cough reflex [5] – factors which are not uncommon in the acute stroke patient cohort. Over the first eleven days of the patient's admission, NG tube malposition was confirmed by chest radiograph on eight occasions. Given the increased risk, we suggest that any future NG tube insertion attempts for this patient should be performed under fluoroscopic guidance, which can provide real-time continuous visualisation of the tube as it passes through the pharynx and oesophagus into the stomach, reducing the risk of placement into the respiratory tree [5]. Another technique to prevent tracheobronchial NG tube insertion is Roubenoff and Ravich's two-step method [6]. However, it is time-intensive and its need for two radiographs limits its practicality and cost-effectiveness in acute care settings.

Acute stroke patients whose nutrition and medication administration are adversely affected by NG tube problems may also benefit from early VFSS, with the aim of facilitating safe but earlier oral intake and NG tube removal. One study showed VFSS performed within 7 days of stroke onset led to relaxation in feeding restrictions for over a quarter of the patient cohort [7]. Swallow function in the acute stroke phase is dynamic, with the potential for rapid spontaneous recovery.

It is imperative for clinicians to be vigilant of the pulmonary complications of NG tube insertion and scrutinise fully radiographs which may have only been requested to confirm NG tube position.

References

1. National Patient Safety Agency guidance (https://www.england.nhs.uk/wp-content/uploads/2016/07/Resource_set_-_Initial_placement_checks_for_NG_tubes_1.pdf)
2. Bruno MA, Walker EA, Abujudeh HH. Understanding and confronting our mistakes: the epidemiology of error in radiology and strategies for error reduction. Radiographics. 2015 Oct;35(6):1668-76. https://doi.org/10.1148/rg.2015150023
3. Rassias AJ, Ball PA, Corwin HL. A prospective study of tracheopulmonary complications associated with the placement of narrow-bore enteral feeding tubes. Critical Care. 1998 Jun;2(1):1-4. https://doi.org/10.1186/cc120
4. Pillai JB, Vegas A, Brister S. Thoracic complications of nasogastric tube: review of safe practice. Interactive cardiovascular and thoracic surgery. 2005 Oct 1;4(5):429-33. https://doi.org/10.1510/icvts.2005.109488
5. Kim J, Shin JH. Placement of feeding tubes using fluoroscopy guidance and over-the-wire technique: A technical review. Gastrointestinal Intervention 2017; 6(2): 135-1395. https://doi.org/10.18528/gii160022
6. Roubenoff R, Ravich WJ. Pneumothorax due to nasogastric feeding tubes: report of four cases, review of the literature, and recommendations for prevention. Archives of Internal Medicine. 1989 Jan 1;149(1):184-8. https://doi.org/10.1001/archinte.149.1.184
7. Kim et al. Usefulness of early videofluoroscopic swallowing study in acute stroke patients with dysphagia. Annals of Rehabilitation Medicine. 2018 Feb 42(1): 42-51. https://doi.org/10.5535/arm.2018.42.1.42

# Progressive multiple sclerosis treatment considerations in the UK: experience from trials and real-world population


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**Abstract**

The recent availability of disease modifying treatments (DMTs) for progressive multiple sclerosis (PMS) is a welcome change, yet the limitations of clinical trial design and the real-world makeup of the PMS population necessitate a balanced view of their potential benefits and risks in a population that is on average older than the relapsing-remitting MS (RRMS) population, and more likely to have or develop comorbidities over time. Here we will review the available data for DMT efficacy and risks in PMS with a view to guiding clinician and patient in joint care decision making.


## Introduction

People with RRMS (pwRRMS) comprise the majority of new MS diagnoses, however a significant proportion of pwRRMS go on to develop secondary progressive (SPMS). Early natural history studies suggested this to be as high as 90% of pwRRMS by 25 years, at a conversion rate of approximately 2-3% per year [1,2], though recent studies suggest this might be lower (35-62% by 20 years, up to 75% by 30 years) due to DMT use [3-7] and predicated on other risk factors [8-10]. In addition, 10-15% of new diagnoses consist of primary progressive MS (PPMS) [11]. Considering that the total number of people with MS (pwMS) in the United Kingdom (UK) is approximately 130,000 [12], this means that there are at least 50,000 people with PMS at any one time point [13]. Lastly, with the advent of multiple high efficacy therapies, it's appreciated that MS exists on a spectrum, with progression occurring independently of relapses, and during the RRMS phase [14-16].

The licensed treatment option in the UK for active PPMS is ocrelizumab [17], and for active SPMS include either siponimod [18] or rarely, Interferon beta-1b (brand name Extavia) [18]. Their initiation requires evidence of MRI or clinical relapse to be eligible. Trial design, however, targets statistical significance for the primary efficacy outcome measure rather than secondary safety analyses, and there is no agreed gold standard definition of a true risk signal from safety monitoring. These issues are compounded by the recruitment of a lower-risk population, inconsistencies in adverse event reporting and misclassification, and lack of generalisability from either the trial population or a restricted dosage regime [19].

This is of salience in PMS which occurs more frequently in an older and more vulnerable population group (mean age of onset is 45 years in SPMS [20], and 40 years in PPMS [21]), as well as the increasing mean life expectancy in MS, from a historic expectancy of 66 years to more recent studies suggesting around 75 years [22-26].

## The Importance of Age

Age appears to be a major determinant of DMT effect, a meta-analysis of clinical trial data identified reduced likelihood of efficacy after age 53 in the average pwMS [20]. Compounding this is the potential risk of side effects such as opportunistic infection, malignancy, and autoimmune events, which are more likely with advancing age or greater duration of treatment [27-30].

Immunosenescence is more likely with advancing age, with age-related changes in both adaptive and innate immune cells [31] being seen. This can contribute to the risk of cancer [32], opportunistic infections (including rare cases of progressive multifocal leukoencephalopathy ((PML)), or worse outcomes following infection [22,33-34].

Additional risk arises from other conditions that more commonly develop with age, such as hypertension, diabetes, ocular pathology, and cardiovascular disease. A recent UK-based study simulated evidence that 2/3 of the adult population older than 65 years will be living with multiple comorbidities by 2035 [35].

## Beta Interferons (INF-β)

Extavia (interferon β-1b, INF- β-1b) is

**Table 1. Impact of interferons on infection risk - from [42]**

| | Bacterial Infection | Viral Infections | Fungal Infections | Protozoa and parasites |
|---|---|---|---|---|
| INF- β-1b | ● No increased risk of infections<br>● Local infections at injection site possible | Possible antiviral effect on HBV/ HCV, no risk of reactivation in chronic viral hepatitis | No increased risk of infections | Possible protective effect against Leishmania |

licensed for SPMS with relapses by NICE [36], however from internal calculations the overall number of pwSPMS on Extavia is likely to be ≤1%. INF- β-1b has been the subject of extensive experience and longitudinal study and has consistently been found to be a safe medication [37-40].

The infection risk is limited, with a minimal demonstrable increased rate of crude infections compared to the general population (incidence rate, 8.9% vs 5.2% per 1000 person years) [41]. It is not associated with opportunistic infections [42], and the only reported case of PML with interferon monotherapy occurred in an individual with common variable immunodeficiency syndrome [43].

Within one observational study over 12 years [40], a non-significant trend towards risk of breast cancer cases in those treated with INF-β (OR 1.77) was seen – however without a dose-response effect or discrepancies in tumour size. Another, smaller study from Israel of 1,338 pwMS demonstrated a borderline association with non-breast cancer risk that did not reach statistical significance [40].

Larger studies, including a French study involving 12 MS centres, revealed no increased risk of cancer with any IFN-β exposure [44], supported by post-marketing industry-sponsored studies of insurance claims showing no increase in cancer rates – however both were over a brief 2–3-year period only [45-46].

The efficacy of continued interferon use is debatable; an Italian study [47] demonstrated that of an SPMS cohort, divided into two groups, one continuing treatment for a minimum of 36 months, and the other stopping, there was no difference in accrual of an extended disability score (EDSS) of 7.0 over a 10-year period.

**Siponimod for SPMS**

Siponimod rapidly depletes T lymphocytes from the peripheral circulation by sequestering them within lymphoid tissue, thereby preventing them from migrating to the central nervous system (CNS), and potential further impact on CNS cells [48]. Siponimod acts only on sphingosine-1-phosphate-receptors 1 and 5, reducing the risk of adverse effects [49-50].

The EXPAND trial demonstrated siponimod's efficacy in cases of active SPMS in 2018, with a significant reduction in 3-month confirmed disability progression (CDP) (21% reduced HR), and subgroup analysis demonstrating a marked reduction in both 3-month CDP (36% reduced HR) and 6-month CDP (41% reduced HR) versus placebo [51]. Its side effect profile is well documented and summarised in Table 2.

A German retrospective multi-site observational study [50] of 227 pwSPMS over an 18-month period, supported the benefits of siponimod. At 12 months, almost 65% had experienced disease stability (and improvement in 21.4%).

EXPAND highlighted infection as a significant complication of siponimod vs placebo, specifically for varicella zoster virus (VZV) reactivation (2% vs 1%) and herpes infection (5% vs 3%), including one case of herpes zoster (HZ) meningitis. In the context of age and age-related co-morbidities, 68% of VZV infections in the general population occur after the age of 50 [49,50], with relative risk of infection increasing by 1.65 times after the age of 60. A variety of comorbidities (including diabetes, cardiovascular and renal disease, and rheumatoid arthritis) contribute to this risk further (RR range, 2.08-1.23) [53].

COVID-19 related data has been encouraging, with evidence that siponimod use doesn't predispose to higher risk of severe outcomes [54], however it does impair the humoral vaccine response [55,56].

PML has been reported in 3 cases, one in the EXPAND trial extension, and two in post-marketing. Two have been attributed to siponimod directly, in a 63-year-old male and 62-year-old female, with the duration of use being 6.5 years and 8 years respectively [57].

Though skin cancer rates in the EXPAND study were similar between cases and controls (all skin neoplasms n=14/1099 vs n=8/546, and BCC n=11/1099 vs n=6/546, respectively), it raised concern of potentially increased skin cancer risk [51]. A recent real-world study utilising the FDA adverse event reporting system, showed patients on siponimod were 11.32 times more likely to develop skin cancer (crude reported odds ratio). On further sensitivity analysis, basal cell carcinoma (BCC) was 22.83 times more likely to occur in the treatment group vs placebo [58].

Significant lymphopaenia did not appear to be a major adverse event in the original study [51], with only 1% of participants experiencing a grade IV lymphopaenia (absolute lymphocyte count <200cells/mm¬¬3), and normalisation occurring within 2 months of discontinuation [48]. The German group's findings support this, with lymphopaenia affecting 38.1% of their enrolled participants, however only resulting in treatment discontinuation in a minority [50].

The long-term development of hypertension in an older population with siponimod use, occurred in 16.2% of the 227 pwSPMS in the German study [50], and potentially greater risk of macular oedema in the context of diabetes, uveitis, or other underlying retinal disease [52].

The cardiac safety profile of siponimod from EXPAND was favourable compared to fingolimod [51], with only a small mean decrease in heart rate (by 3.1 beats/minute) by 7 days being seen, and no second- or third-degree heart block on telemetry lasting up to 6 days.

The AMASIA study is a German prospective non-interventional observational study, assessing the long-term effectiveness and safety of siponimod in routine clinical use for SPMS. It is running across 250 sites, was initiated in 2020, and is due to conclude in 2025 [59]. Ultimately, though it is unclear when siponimod should be discontinued, the Canadian agency for drugs and technologies in health recommends discontinuation if the EDSS reaches 7 (i.e., being wheelchair bound), or if there is a worsening of timed-25-foot walk of ≥20% while on siponimod [60].

As lymphopaenia was the most common side effect [50], it's important to be aware of the recommended management steps; should an absolute lymphocyte count drop below 0.2 x 109/l, the dose should be reduced from 2mg to 1mg, and if persistent, treatment should be interrupted until counts recover to 0.6 x 109/l before considering re-initiation [52]. The management of hypertension should also be considered, but broadly speaking this would involve weighing a risk/benefit decision regarding continuing siponimod, and then (via GP) typically initiating either an angioten-

**Table 2. Siponimod side effects of note (from Electronic Medicines Compendium, 2023a)**

| | |
|---|---|
| Very Common (≥1/10) | Hypertension |
| Common (≥1/100 to <1/10) | Herpes zoster<br>Basal cell carcinoma<br>Lymphopaenia<br>Macular oedema<br>Convulsions<br>Tremor<br>Bradycardia<br>Atrioventricular (1st and 2nd degree) block<br>Pulmonary function test dysfunction<br>Liver function test derangement |

**Table 3. Ocrelizumab adverse events from Schweitzer et al., 2019**

| Most important events | Risk with age |
|---|---|
| HSV1/VZV reactivation | Increased |
| HBV | Increased |
| Breast cancer | Increased |
| Hypogammaglobulinaemia | Potentially increased |
| PML (carry over) | Potentially increased |

sin-converting enzyme inhibitor or angiotensin II receptor blocker in those under the age of 55 years, or a calcium channel blocker in those aged 55 or over or of African/Caribbean descent [61].

### Ocrelizumab for PPMS

Ocrelizumab is a humanised anti-CD20 antibody that depletes mature and immature B cells, while sparing long-lived CD20-negative plasma cells [62].

The ORATORIO trial demonstrated efficacy in active primary progressive MS in 2017 [63], reducing rates of 12-week CDP over a 120-week period against placebo (24% reduced HR), with subgroup analyses supporting its benefit on 12-week CDP in patients with gadolinium-positive scans at baseline (35% reduced HR), resulting in approval for its use in the UK in 2019 [64]. The risk profile is clearly described (highlighted in Table 3) and is shared with B-cell depleting therapies (BCDTs) [65].

Studies have suggested that being ≥60 years old confers greater risk of hypogammaglobulinaemia, neutropaenia, and infections generally [66,67]. Concerns of immunosuppression have been highlighted by case reports of severe infections in patients over the age of 70 with rituximab related hypogammaglobulinaemia that could not be controlled with antimicrobial therapy [68], increased rates of herpetic reactivation [69], and loss of historic immunity to VZV [70]. This is supported by data demonstrating a greater risk of severe COVID19 outcomes in pwMS on ocrelizumab, as well as older ages, males with comorbidities, greater disability, and a longer duration of MS diagnosis [71,72]. Similarly, the use of ocrelizumab has been found to result in lower seroconversion and humoral immunity response rates following COVID19 vaccination [55,73].

There have been 12 reported cases of PML in pwMS while on ocrelizumab (reflecting 0.00005% of the worldwide population on ocrelizumab, or 1/20, 833 cases) [74,75], 10 of which were attributed to a cross-over effect, having occurred up to several months following conversion from a previous drug that was known to increase the risk of PML, with similar findings in rituximab [30]. The remaining two cases had no history of immunosuppression or use of immunosuppressants; one patient was in their fifties, and the other in their seventies with an underlying immunosenescence and low pre-ocrelizumab lymphocytes count. Ultimately both individuals died from PML-related complications [74].

The ORATORIO trial demonstrated a non-significant increase in the number of malignancies in patients treated with ocrelizumab (11/486 cases, 2.3%, versus placebo 2/239 cases, 0.84%) [63]. Assessment of all trial data by Genetech of the breast cancer risk also shows a non-significant increase in rates of females treated with ocrelizumab (6/781, 0.77%, versus 0/668 controls treated with Rebif or placebo [74]. However, the rate was within the background rate expected for an MS population, which is important to consider in the context of individual cancer risks. Similarly, BCC incidence appeared to be greater between years 3-4 of treatment, but this was not sustained in subsequent years and again was in keeping with background MS rates (Schweitzer et al., 2019; Electronic Medicines Compendium, 2023).

A large German prospective non-interventional observational study, CONFIDENCE, for 3,000 RRMS and PPMS treated with ocrelizumab launched in 2020 and will provide significant long-term real world safety data [77].

### Alternative and Emerging Potential Treatments

Treatment regulation varies between countries; it is helpful to be aware that most treatments available for RRMS are also options in active PMS in other countries, such as the United States of America (USA) [78]. Among those is the Federal Drug Association (FDA) licensed Ofatumamab, a fully human anti-CD20 monoclonal antibody and BCDT [79]. The phase 3 ASCLEPIOS I and II trials involved both pwRRMS and active SPMS, and showed, compared to Teriflunomide, a reduction in annualised relapse rates (0.11 versus 0.22) and lower 3-month CDP (HR 0.68) [80], with only a limited increase in serious infections (2.5% versus 1.8%) [80], and sustained safety evidence in the 4-year ALITHIOS study and phase 2 MIRROR study in pwRRMS [81]. Specifically, the ALITHIOS study showed no increase in infection rates by exposure duration, episodes of opportunistic infection, hepatitis B reactivation, or PML [82,83]. Similarly, there was no evidence of increased neoplasm rates, or clustering of malignancies in the original study, and the follow up 4-year safety data identified malignancies in 11 patients (0.6%), with no increase

**Table 4. Investigation and management of select condition**

| Condition | Manifestations | Pre-treatment screening/management | Work-up | Management |
|---|---|---|---|---|
| Secondary Hypogammaglobulinaemia [83 – 88] | ● Recurrent infections<br>● Recurrent *Streptococcus pneumoniae*, or *Haemophilus influenzae* infection<br>● Opportunistic infections | Can consider FBC, IgG, IgA, and IgM levels where relevant | ● FBC<br>● IgG, IgM, IgA levels<br>● Consider IgG subclasses | Cessation of treatment should be considered, alongside active treatment of concurrent infection with a bacterial agent.<br>Can consider:<br>● IVIg 400-600mg/kg depending on IgG level.<br>● Long-term antimicrobials<br>● CT-chest |
| HSV [89 – 90] | Oral or genital herpes | N/A | Not typically required but in the event of diagnostic uncertainty or initial treatment failure can consider:<br>● Viral swab PCR<br>● Viral culture,<br>● Serological testing gG1 / gG2 | Treatment within 48 – 72 hours of onset with a 5 – 10-day course of either oral:<br>● Acyclovir 400mg x5d<br>● Valacyclovir 1g BD<br>● Famciclovir 500mg BD<br>Plus, oral analgesia<br>Can consider: IV foscarnet. |
| VZV [91 - 93] | Shingles; dermatomal pain and typical papular rash | VZV IgG status<br>Management:<br>● Vaccination should be performed in cases with either weakly positive or negative titres, prior to treatment initiation.<br>● In the immunocompromised the recombinant Shivrix vaccine is preferrable | N/A | Treatment within 1w of onset (and up to rash crusting) 7d course of either oral:<br>● Acyclovir 800mg x5/d<br>● Famciclovir 500mg TDS<br>● Valaciclovir 1g TDS<br>Plus, oral analgesia and chamomile lotion<br>N.B: If severe or risk of ocular involvement would require IV treatment at 10mg/kg TDS |

in incidence rates over time of exposure, with the only clustering being of BCC (n=4) and invasive breast carcinoma (n=2) [82,83].

Bruton Tyrosine Kinase Inhibitors (BTKi) are a novel drug class of small molecules capable of crossing the blood brain barrier, that have the potential to target both the adaptive and innate immune mechanisms of both the peripheral and central nervous system [84]. Multiple agents are undergoing phase 3 trials currently, however phase II and extension safety data has been largely reassuring with the most common reported events being upper respiratory tract infections, headache, and raised liver enzymes [84].

The MS-STAT2 trial, investigating the effect of high-dose (80mg) simvastatin in pwSPMS is due to conclude in late-2024 [85]. Simvastatin is a 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor, with PMS-relevant properties [86], and directly effects vascular co-morbidity, which has been shown to influence PMS outcomes [87]. Its benefit and safety profiles are well recognised from its common use in vascular diseases [88], which has been mirrored in safety data from the MS-STAT1 trial [89].

Lastly, an in depth summary of the trials landscape in progressive MS has recently been published, which further details the above alongside other completed and ongoing PMS trials [90].

**Select Treatment Considerations**

Among the described treatment options certain complications arise with greater frequency and therefore prophylactic considerations or management is worth elaborating on; this is summarised in Table 4 below.

There has been an intense development in our understanding of vaccination success in patients with MS on DMTs since the COVID19 pandemic, it is worth noting the importance of seasonal influenza vaccination generally, and the administration of the 23-valent pneumococcal polysaccharide vaccine (PPV23), in those on long-term immunosuppressive therapy. PPV23 should ideally be administered at least 2 weeks before initiation of maintenance immunosuppressives, and is also recommended for those established on treatment [91,92]. In those already established on ocrelizumab, which can particularly impair the humoral response, antibody titers can be considered to assess whether repeat vaccination is required [93].

**Conclusion**

In summary, the use of INF- β-1b in relapsing PMS has the most limited risk profile, without convincing evidence of significant adverse effects generally, or infections/cancer specifically – however the evidence of gain from a clinical progression viewpoint is limited, and in the UK is rarely used.

When prescribing siponimod it is important to primarily weigh up the potentially increased risks of herpetic reactions, reduced vaccination efficacy, BCC, hypertension, and macular oedema, in the context of age-related risks. The risk profile for ocrelizumab is greater, with more risk of immunocompromise, severe infection outcomes, impaired vaccine responses and the potential to lose historic immunity, however the cancer risk is less convincing at present and requires a more nuanced approach to an individual's history.

Ultimately, larger prospective observational data, such as from AMASIA for siponimod and CONFIDENCE for ocrelizumab, are needed to better guide decision making, with planned completion in 2025 and 2028 respectively. In the interim, an open discussion about the above potential benefits, reduced likelihood of DMT impact, and shift in risk profiles with advancing age, needs to be had in order to reach a care decision that takes into consideration an individual's views and opinions on the potential risks and benefits of continued treatment.

References


1. Weinshenker BG et al. The Natural History of Multiple Sclerosis: A Geographically Based Study I. Clinical Course and Disability. 1989. https://doi.org/10.1093/brain/112.1.133
2. Barzegar M, Najdaghi S, Afshari-Safavi A, Nehzat N, Mirmosayyeb O, Shaygannejad V. Early predictors of conversion to secondary progressive multiple sclerosis. Mult Scler Relat Disord. 2021;54. https://doi.org/10.1016/j.msard.2021.103115
3. Tedeholm H et al. Effectiveness of first generation disease-modifying therapy to prevent conversion to secondary progressive multiple sclerosis. Mult Scler Relat Disord. 2022;68:104220 https://doi.org/10.1016/j.msard.2022.104220
4. Scalfari A, Neuhaus A, Daumer M, Ebers GC, Muraro PA. Age and disability accumulation in multiple sclerosis. Neurology. 2011;77(13):1246-1252. https://doi.org/10.1212/WNL.0b013e318230a17d
5. Fambiatos A et al. Risk of secondary progressive multiple sclerosis: A longitudinal study. Multiple Sclerosis Journal. 2020;26(1):79-90. https://doi.org/10.1177/1352458519868990
6. Coret F et al. Onset of secondary progressive multiple sclerosis is not influenced by current relapsing multiple sclerosis therapies. Mult Scler J Exp Transl Clin. 2018;4(2)205521731878334. https://doi.org/10.1177/2055217318783347
7. Cree BAC et al. Long-term evolution of multiple sclerosis disability in the treatment era. Ann Neurol. 2016;80(4):499-510. https://doi.org/10.1002/ana.24747
8. Barzegar M, Shaygannejad V, Mirmosayyeb O, Afshari A. Progression to Secondary Progressive Multiple Sclerosis and its Early Risk Factors: A Population-based Study (2171) Neurology. 2020;94(15) Supplement(2171). https://doi.org/10.1212/WNL.94.15_supplement.2171
9. Taylor BV. Time to onset of secondary progression as an outcome in MS trials: a new paradigm? J Neurol Neurosurg Psychiatry.2014;85(1)3. https://doi.org/10.1136/jnnp-2012-304611
10. Cree BAC et al. Secondary Progressive Multiple Sclerosis. Neurology. 2021;97(8):378-388. https://doi.org/10.1212/WNL.0000000000012323
11. Weinshenker BG. Natural History of Multiple Sclerosis. 1994. https://doi.org/10.1002/ana.410360704
12. MS Society. MS in the UK Estimates of incidence and prevalence of MS in the UK. 2022.
13. Vasanthaprasad V, Khurana V, Vadapalle S, Palace J, Adlard N. Systematic literature review and meta-analysis of the prevalence of secondary progressive multiple sclerosis in the USA, Europe, Canada, Australia, and Brazil. BMC Neurol 2022;22(1) https://doi.org/10.1186/s12883-022-02820-0
14. Scalfari A, Neuhaus A, Daumer M, DeLuca GC, Muraro PA, Ebers GC. Early Relapses, Onset of Progression, and Late Outcome in Multiple Sclerosis. JAMA Neurol, 2013;70(2):214 https://doi.org/10.1001/jamaneurol.2013.599
15. Portaccio E et al. Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study. Brain. 2022;145(8):2796-2805. https://doi.org/10.1093/brain/awac111
16. Kaufmann M et al. Identification of early neurodegenerative pathways in progressive multiple sclerosis. Nat Neurosci. 2022;25(7):944-955. https://doi.org/10.1038/s41593-022-01097-3
17. National Institute for Clinical Excellence (NICE). Ocrelizumab for treating primary progressive multiple sclerosis. 2019. [Online]. Available: www.nice.org.uk/guidance/ta585
18. National Institute for Clinical Excellence (NICE), Siponimod for treating secondary progressive multiple sclerosis. 2020. [Online]. Available: www.nice.org.uk/guidance/ta656
19. Singh S, Loke YK. Drug safety assessment in clinical trials: methodological challenges and opportunities. Trials. 2012;13(20).https://doi.org/10.1186/1745-6215-13-138
20. Kes VB, Grbić N, Jurašić MJ, Zavoreo I, Matovina LZ. Secondary progressive multiple Sclerosis. Acta Medica Croatica. 2018;72(3):381-384. https://doi.org/10.1212/NXI.0000000000200064
21. Tremlett H, Zhao Y. Primary and secondary progressive MS have a similar age at onset of progression - NO. Multiple Sclerosis. 2017;23(5)640-642. https://doi.org/10.1177/1352458516684559
22. Mawer C. Data show big rise in deaths of people with neurological disorders - Rapid Response. BMJ. 2018.
23. Rollot F et al. Effects of Age and Disease Duration on Excess Mortality in Patients With Multiple Sclerosis From a French Nationwide Cohort. Neurology. 2021;97(4) https://doi.org/10.1212/WNL.0000000000012224
24. Willumsen JS, Grytten N, Aarseth J, Myklebust TÅ, Myhr KM, Midgard R, Mortality and cause of death in multiple sclerosis in western Norway 1950-2021: a registry-based linkage study. J Neurol Neurosurg Psychiatry. 2022;93(11):1154-1161. https://doi.org/10.1136/jnnp-2022-329169
25. Lunde HMB, Assmus J, Myhr KM, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psychiatry. 2017;88(8):621-625. https://doi.org/10.1136/jnnp-2016-315238
26. Leadbetter R, MacAskill M, Myall DJ, Taylor BV, Joshi P, Mason DF. Multiple sclerosis mortality in New Zealand: a nationwide prospective study. J Neurol Neurosurg Psychiatry. 2023;94(7)511-517. https://doi.org/10.1136/jnnp-2022-330582
27. Lebrun C, Rocher F. Cancer Risk in Patients with Multiple Sclerosis: Potential Impact of Disease-Modifying Drugs. CNS Drugs.Springer International Publishing. 2018:32(10):939-949. https://doi.org/10.1007/s40263-018-0564-y
28. Grebenciucova E, Pruitt A. Infections in Patients Receiving Multiple Sclerosis Disease-Modifying Therapies. Curr Neurol Neurosci Rep. 2017;17(11):88. https://doi.org/10.1007/s11910-017-0800-8
29. Förster M et al. Managing Risks with Immune Therapies in Multiple Sclerosis. Drug Saf. 2019;42(5):633-647. https://doi.org/10.1007/s40264-018-0782-8
30. Schweitzer F et al. Age and the risks of high-efficacy disease modifying drugs in multiple sclerosis. Current Opinion in Neurology.Lippincott Williams and Wilkins 2019;32(3):305-312. https://doi.org/10.1097/WCO.0000000000000701
31. Solana R, Tarazona R, Gayoso I, Lesur O, Dupuis G, Fulop T. Innate immunosenescence: Effect of aging on cells and receptors of the innate immune system in humans. Semin Immunol. 2012;24(5):331-341. https://doi.org/10.1016/j.smim.2012.04.008

32. Cancer Research UK. Cancer Incidence by Age. https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero.
33. Gheuens S, Pierone G, Peeters P, Koralnik IJ. Progressive multifocal leukoencephalopathy in individuals with minimal or occult immunosuppression. J Neurol Neurosurg Psychiatry. 2010;81(3):247-254. https://doi.org/10.1136/jnnp.2009.187666
34. Cortese I, Reich DS, Nath A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. Nat Rev Neurol. 2021;17(1):37-51. https://doi.org/10.1038/s41582-020-00427-y
35. Kingston A, Robinson L, Booth H, Knapp M, Jagger C. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. Age Ageing. 2018;47(3):374-380. https://doi.org/10.1093/ageing/afx201
36. NICE. Beta interferons and glatiramer acetate for treating multiple sclerosis Technology appraisal guidance [TA527]. https://www.nice.org.uk/guidance/ta527/chapter/1-Recommendations. 2018.
37. Calabresi PA et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13(7)657-667. https://doi.org/10.1016/S1474-4422(14)70068-7
38. Hu X et al. COMPARE: Pharmacokinetic profiles of subcutaneous peginterferon beta-1a and subcutaneous interferon beta-1a over 2 weeks in healthy subjects. Br J Clin Pharmacol. 2016;82(2):380-8. https://doi.org/10.1111/bcp.12968
39. Hu X et al. A Novel PEGylated Interferon Beta-1a for Multiple Sclerosis: Safety, Pharmacology, and Biology. The Journal of Clinical Pharmacology. 2012;52(6):798-808. https://doi.org/10.1177/0091270011407068
40. Kingwell E, Evans C, Zhu F, Oger J, Hashimoto S, Tremlett H. Assessment of cancer risk with β-interferon treatment for multiple sclerosis. J Neurol Neurosurg Psychiatry. 2014;85(10):1096-1102. https://doi.org/10.1136/jnnp-2013-307238
41. Luna G et al. Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. JAMA Neurol.2020;77(2):184. https://doi.org/10.1001/jamaneurol.2019.3365
42. Winkelmann A, Loebermann M, Reisinger EC, Hartung H-P, Zettl UK. Disease-modifying therapies and infectious risks in multiple sclerosis. Nat Rev Neurol. 2016;12(4):217-233.https://doi.org/10.1038/nrneurol.2016.21
43. Lehmann HC, Krüger K, Fink GR, Schroeter M. Progressive multifocal leukoencephalopathy after interferon beta-1a monotherapy. J Neurol. 2015;262(3):771-773. https://doi.org/10.1007/s00415-014-7620-4
44. Lebrun C et al. Cancer and multiple sclerosis in the era of disease-modifying treatments. J Neurol. 2011;258(7):1304-1311. https://doi.org/10.1007/s00415-011-5929-9
45. Safran J. Assessment of malignancy risk in patients with multiple sclerosis treated with intramuscular interferon beta-1a: retrospective evaluation using a health insurance claims database and postmarketing surveillance data. Ther Clin Risk Manag. 2012:313 https://doi.org/10.2147/TCRM.S31347
46. Sandberg-Wollheim M, Kornmann G, Bischof D, Moraga MS, Hennessy B, Alteri E. The risk of malignancy is not increased in patients with multiple sclerosis treated with subcutaneous interferon beta-1a: analysis of data from clinical trial and post-marketing surveillance settings. Multiple Sclerosis Journal. 2011;17(4):431-440. https://doi.org/10.1177/1352458511403642
47. Zanghì A, D'amico E, Patti F, Avolio C. Stopping Interferon Beta 1b Does Not Influence the Risk of Disability Accrual in Non-Active SPMS: Results from an Italian Real-World Study. Int J Environ Res Public Health. 2022;19(10). https://doi.org/10.3390/ijerph19106069
48. Sabsabi S, Mikhael E, Jalkh G, Macaron G, Rensel M. Clinical Evaluation of Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Pathophysiology, Efficacy, Safety, Patient Acceptability and Adherence. Patient Preference and Adherence. Dove Medical Press Ltd. 2022;16:1307-1319. https://doi.org/10.2147/PPA.S221882
49. Chaudhry BZ, Cohen JA, Conway DS. Sphingosine 1-Phosphate Receptor Modulators for the Treatment of Multiple Sclerosis. Neurotherapeutics. 2017;14(4)859-873. https://doi.org/10.1007/s13311-017-0565-4
50. Regner-Nelke L et al. Real-world evidence on siponimod treatment in patients with secondary progressive multiple sclerosis. Neurol Res Pract. 2022;4(1). https://doi.org/10.1186/s42466-022-00219-3
51. Kappos L, Bar-Or A, Cree BAC. 'Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 stud Lancet. 2018;391(10127):1263-1273.
52. Electronic Medicines Compendium. Mayzent - Summary of Product Characteristics. Accessed 06/2023.
53. Marra F, Parhar K, Huang B, Vadlamudi N. Risk Factors for Herpes Zoster Infection: A Meta-Analysis. Open Forum Infect Dis. 2020;7(1). https://doi.org/10.1093/ofid/ofaa005
54. Sullivan R et al. COVID-19 Infection in Fingolimod- or Siponimod-Treated Patients. Neurology - Neuroimmunology Neuroinflammation. 2022;9(1) p.e1092. https://doi.org/10.1212/NXI.0000000000001092
55. Tallantyre EC et al. COVID-19 Vaccine Response in People with Multiple Sclerosis. Ann Neurol. 2022;91(1):89-100. https://doi.org/10.1002/ana.26251
56. Krbot Skorić M, Rogić D, Lapić I, Šegulja D, Habek M, Humoral immune response to COVID-19 vaccines in people with secondary progressive multiple sclerosis treated with siponimod. Mult Scler Relat Disord. 2022;57:p.103435. https://doi.org/10.1016/j.msard.2021.103435
57. Novartis. Novartis PML Siponimod Report. Accessed: Jun. 19, 2023. [Online]. Available: http://siponimodinfo.com
58. Stamatellos VP, Rigas A, Stamoula E, Lallas A, Papadopoulou A, Papazisis G. S1P receptor modulators in Multiple Sclerosis: Detecting a potential skin cancer safety signal. Mult Scler Relat Disord. 2022;59. https://doi.org/10.1016/j.msard.2022.103681
59. Hoffmann O, Schreiber H, Klotz L, Weber M, Weiss C, Ziemssen T. AMASIA study: Real world insights on the impact of early siponimod treatment on SPMS patients in Germany (P8-3.013). in Tuesday, April 25, Lippincott Williams & Wilkins, 2023:4390. https://doi.org/10.1212/WNL.0000000000203952
60. CADTH. CADTH Canadian Drug Expert Committee Recommendation: Siponimod (Mayzent - Novartis Pharmaceuticals Canada Inc.)/ Ottawa (ON):2020.
61. NICE. Hypertension in adults: diagnosis and management. https://www.nice.org.uk/guidance/ng136.
62. Mulero P, Midaglia L, Montalban X. Ocrelizumab: a new milestone in multiple sclerosis therapy. Therapeutic Advances in Neurological Disorders. 2018;11. SAGE Publications Ltd. https://doi.org/10.1177/1756286418773025
63. Montalban X, Hauser SL, Kappos L. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med. 2017;376(3)209-220. https://doi.org/10.1056/NEJMoa1606468
64. NICE. Ocrelizumab for treating primary progressive multiple sclerosis. 2019.
65. Cannon L, Pan A, Kovalick L, Sarkissian A, Wu EY. Secondary immunodeficiencies and infectious considerations of biologic immunomodulatory therapies. Annals of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. 2023 Jun. 01. https://doi.org/10.1016/j.anai.2023.02.010
66. Athni TS, Barmettler S. Hypogammaglobulinemia, late-onset neutropenia, and infections following rituximab. Annals of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology, Jun. 01, 2023.https://doi.org/10.1016/j.anai.2023.01.018
67. Tallantyre EC et al. Secondary antibody deficiency: a complication of anti-CD20 therapy for neuroinflammation. J Neurol. 2018;265(5):1115-1122. https://doi.org/10.1007/s00415-018-8812-0
68. Sacco KA, Abraham RS. Consequences of B-cell-depleting therapy: Hypogammaglobulinemia and impaired B-cell reconstitution. Immunotherapy. Future Medicine Ltd. 2018;10(8):713-728. https://doi.org/10.2217/imt-2017-0178
69. Electronics Medicine Compendium, Ocrevus - Summary of Product Characteristics. 2023.
70. Rapisarda L et al. Varicella zoster immunity loss in multiple sclerosis patient treated with ocrelizumab. Clinical Immunology. 2021. https://doi.org/10.1016/j.clim.2020.108554
71. Simpson-Yap S et al. Associations of Disease-Modifying Therapies With COVID-19 Severity in Multiple Sclerosis. Neurology. 2021;97(19):e1870-e1885 https://doi.org/10.1212/WNL.0000000000012753
72. Sormani MP et al. Disease-Modifying Therapies and Coronavirus Disease 2019 Severity in Multiple Sclerosis. Ann Neurol. 2021;89(4):780-789. https://doi.org/10.1002/ana.26028
73. Tortorella C et al. Humoral- and T-Cell-Specific Immune Responses to SARS-CoV-2 mRNA Vaccination in Patients With MS Using Different Disease-Modifying Therapies. Neurology. 2022;98(5):e541-e554. https://doi.org/10.1212/WNL.0000000000013108
74. Genetech. Genetech Prescribing Information: Ocrelizumab.
75. Genetech. Genentech data on file: March 31, 2022, post-marketing experience; March 2022, clinical trials data cut-off. https://www.ocrelizumabinfo.com/index.html. Accessed August 2023.
76. Electronic Medicines Compendium, 'Product Specifications: Ocrelizumab (Ocrevus)', vol. 06, 2023.
77. Dirks P et al. Design of a non-interventional post-marketing study to assess the long-term safety and effectiveness of ocrelizumab in German real world multiple sclerosis cohorts - The CONFIDENCE study protocol', BMC Neurol. 2020;20(1) https://doi.org/10.1186/s12883-020-01667-7
78. MS Society. Disease Modifying Treatments for Multiple Sclerosis. Accessed September 2023. https://nms2cdn.azureedge.net/cmssite/nationalmssociety/media/msnationalfiles/brochures/brochure-the-ms-disease-modifying-medications.pdf.
79. Federal Drug Authority (FDA). FDA Ofatumumab Prescribing Data. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125326s070lbl.pdf. 2020.
80. Hauser SL et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. New England Journal of Medicine. 2020;383(6):546-557. https://doi.org/10.1056/NEJMoa1917246
81. Bar-Or A et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis. Neurology. 2018;90(20):e1805-e1814. https://doi.org/10.1212/WNL.0000000000005516
82. Hauser SL et al. Safety experience with continued exposure to ofatumumab in patients with relapsing forms of multiple sclerosis for up to 3.5 years. Multiple Sclerosis Journal. 2022;28(10):1576-1590. https://doi.org/10.1177/13524585221079731
83. Cohen J et al. Five-Year Safety of Ofatumumab in People Living With Relapsing Multiple Sclerosis (P8-3.004)', in Tuesday, April 25, Lippincott Williams & Wilkins. 2023:2942. https://doi.org/10.1212/WNL.0000000000202906
84. Krämer J, Bar-Or A, Turner TJ, Wiendl H. Bruton tyrosine kinase inhibitors for multiple sclerosis. Nat Rev Neurol. 2023;19(5):289-304. https://doi.org/10.1038/s41582-023-00800-7
85. Williams T et al. 007 The MS-STAT2 trial in secondary progressive MS - study design and update. J Neurol Neurosurg Psychiatry. 2022;93(6):A16.1-A16. https://doi.org/10.1136/jnnp-2022-ABN.46
86. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. Nat Rev Immunol. 2006;6(5):358-370. https://doi.org/10.1038/nri1839
87. Williams T et al. Cardiovascular risk factors in Secondary Progressive Multiple Sclerosis: a cross-sectional analysis from the MS-STAT2 randomised controlled trial. Eur J Neurol. 2023. https://doi.org/10.1111/ene.15924
88. Talreja O, Kerndt CC, Cassagnol M. Simvastatin. 2023.
89. Chataway J, Schuerer N, Alsanousi A. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. Lancet. 2014:383(9936):2213-2221. https://doi.org/10.1016/S0140-6736(13)62242-4
90. Chataway J, Williams T, Li V, Marrie RA, Ontaneda D, Fox RJ. Clinical trials for progressive multiple sclerosis: progress, new lessons learned, and remaining challenges. Lancet Neurol. 2024;23(3):277-301. https://doi.org/10.1016/S1474-4422(24)00027-9
91. Public Health England. Immunisation against infectious disease (The Green Book). The Stationery Office: London. 2017.
92. Reyes S, Ramsay M, Ladhani S et al. Protecting people with multiple sclerosis through vaccination. Pract Neurol. 2020:435-445. https://doi.org/10.1136/practneurol-2020-002527
93. Bar-Or A et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis. Neurology. 2020;95(14):e1999-e2008. https://doi.org/10.1212/WNL.0000000000010380

# The Brain: Discover the Way Your Mind Works

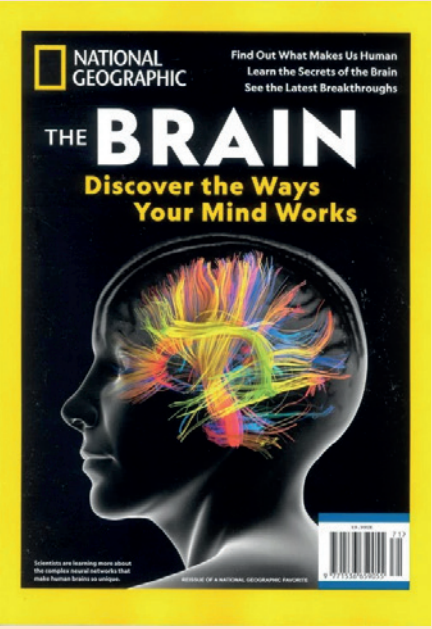
**Author:** Julia Sklar
**Published by:** National Geographic Partners Washington DC, 2022. Re issue 2024.
**Pages:** 96
**Reviewed by:** Rhys Davies, Neurologist, The Walton Centre, Liverpool, UK.

The Brain, a special edition of National Geographic compiled by Julia Skylar is an hour's read from cover to cover and has four sections which encompass Neurodiversity, Perception, Neural Injury and Consciousness. Of course, this is not core reading for neurologists, although UK Neurology gets a mention, with Sanjay Manohar. Furthermore, the content inclines very much towards Human Brain and Systems Neuroscience topics likely to be of interest to us, rather than neural Cell Biology.

As you'd expect, the journalistic style of writing is very clear and engaging. The images are glossy, and err somewhat on the attention-seeking side. Having picked it up as the least unpromising of the options in an airport bookshop, I expected nothing less. By contrast, however, I was pleasantly surprised by the text, and its measured turn of phrase.

There are some very clever decisions as to content and presentation. The easily misrepresented subject of Neurodiversity, rather than the more obvious, is represented by developmental prosopagnosia. The potentially controversial topic of traumatic encephalopathy is framed by being presented alongside congenital insensitivity to pain. The vexed topics of consciousness, responsiveness and identity are described with reference both to Neuroscience and Philosophy.

We are fortunate to have the British Neuroscience Association visiting Liverpool for its annual conference in 2025, a few weeks before the ABN is here. I must say, this slim volume is as efficient a re-primer on fundamental Neuroscience as a clinician of the nervous system is likely to get hold of, whether the intention is to attend a Neuroscience meeting or otherwise. With the 2024 work experience season for 6th formers well under way, I think it is also a good recommendation for our colleagues of the future, alongside Sacks, Marsh, O'Sullivan and others.



# Innovative delivery of specialist neurological rehabilitation in virtual beds: 7 years' experience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**Abstract**

One of the main priorities of the Integrated Care Systems (ICS) is to expand the number of 'virtual wards' and deliver multidisciplinary care for patients closer to home. We present to you the Specialist Neurological Rehabilitation Service (SNRS) which has demonstrated over the last 7 years that intensive neurological rehabilitation can be delivered successfully in the patients' own homes.

A novel commissioning model has been used in partnership with different NHS trusts to provide a unified neurorehabilitation service with both inpatient hospital beds and virtual beds in the patients' own homes. While patients are on the virtual bed pathway, they remain under the care of the Consultant in Rehabilitation Medicine with support from the Clinical Nurse Specialist and have access to diagnostics/interventions and clinic reviews. The patients get daily intensive MDT therapy input from the skilled community team who provide the same frequency of therapy sessions at home (as they would get in a level 2 inpatient neurorehabilitation unit). This pathway is supporting the earlier discharge of patients from hospital. Additionally, the analysis of data from the virtual bed pathway shows that rehabilitation outcomes in patients' own homes are similar to those of bedded units for this subset of patients with complex neurological needs. This illustrates that the virtual ward model can be successfully implemented in neurorehabilitation.


## Introduction

One of the main priorities of the Integrated Care Systems (ICS) in 2022/23 was to expand the number of 'virtual wards' and deliver multidisciplinary care for patients closer to home [1]. The main focus was on preventing hospital admissions and facilitating early discharge. During the pandemic, there was considerable success in implementing virtual wards for managing 'acute respiratory infections' and 'frailty' [1]. However, we would like to demonstrate that the virtual ward / 'Hospital at Home' model also works well in


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neurological rehabilitation and can have the same benefits of reducing hospital admissions while providing patients with specialist rehabilitation in their own home. The Specialist Neurological Rehabilitation Service (SNRS) has been running a virtual ward successfully for the past 7 years. The service has demonstrated that by drawing on the expertise of the whole system, intensive neurological rehabilitation can be delivered effectively in the community.

The total number of neurological cases in England was around 16.5 million in 2019 [2]. The Neurological Alliance estimates that at least 1 in 6 people live with one or more neurological condition(s) [3]. This figure will continue to rise in part due to the impact of an ageing population. Specialist rehabilitation has been proven to be highly cost-effective for all neurological conditions, producing substantial savings in ongoing care costs, especially in the most dependent patients [4]. Current issues highlighted by the ICS include long waiting lists particularly to get into level 1 rehabilitation units. In addition to this, there is a disparity in the provision of community rehabilitation across the UK. The lack of availability of community rehabilitation is often a key reason given by clinicians for their reluctance to discharge patients earlier from inpatient beds.

In 2015 the Tri-borough Clinical Commissioning Group (CCG) Commissioners of 'Hammersmith and Fulham', 'Kensington and Chelsea' and 'Westminster' together with clinicians designed the innovative virtual bed model to help with the issue of poor access to community rehabilitation. The Specialist Neurological Rehabilitation Service (SNRS) model was crafted so that the inpatient service and the virtual beds would be integrated as part of the same service. The SNRS service is made up of 19 beds in total. There are 15 hospital-based beds in Charing Cross Neurological Rehabilitation Unit (CNRU) where rehabilitation is provided to patients on the premises as in-patients. There are also a further 4 virtual beds where rehabilitation is provided to patients in their own homes. The virtual bed service is called the **Specialist Neurological Rehabilitation Outreach Service (SNROS)**. The host provider for the SNRS is the Acute Trust which operationally manages the service via a series of service level agreements (SLA) with the other partners in the community to support the therapy input to the virtual beds.

Several patients during their inpatient rehabilitation will reach a stage where their medical and nursing needs can be managed safely at home. However, they continue to have complex rehabilitation needs with multi-disciplinary therapy goals. These patients can be discharged into the virtual beds with a package of care (if required) and additionally get the same frequency of therapy sessions as in the level 2 inpatient unit at home. Patients in the virtual neurological rehabilitation beds remain under the care of the Consultant in Rehabilitation Medicine, Clinical Nurse Specialist (CNS) and Multi-Disciplinary-Team

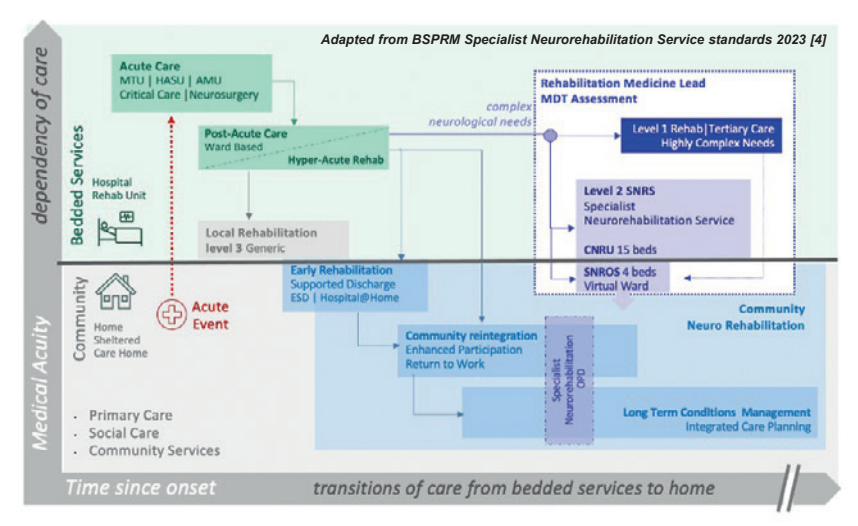


Figure 1: Figure adapted from BSPRM Specialist Neurorehabilitation Service standards 2023 [4] to illustrate the relationship between level 2 bedded and virtual ward neurorehabilitation services, as a means of providing specialist neurorehabilitation to patients with complex needs, directly from acute inpatient services into the community, as well as supporting the transition from level 1 and 2 bedded neurorehabilitation services back into their homes with a seamless transition of care into community neurorehabilitation pathways and long-term condition management. Ongoing specialist support is offered via multi-disciplinary-meetings/clinics/home visits on an outpatient basis to support long-term conditions e.g. spasticity management.

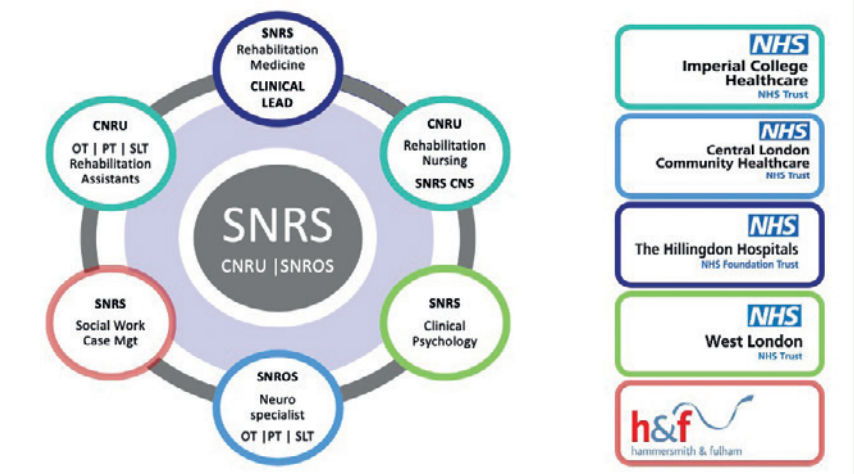


Figure 2: SNRS is led by the Consultant in Rehabilitation Medicine, substantively employed by Hillingdon Hospitals NHS trust. The wider multi-disciplinary team (MDT) is established through an integrated workforce model with partner NHS trusts representing discipline specific expertise. Charing Cross Neurorehabilitation Unit (CNRU) is a 15 bedded in-patient unit based in Charing Cross Hospital and is hosted by Imperial College Healthcare NHS Trust. The virtual ward, which consists of 4 beds, and is referred to as the Specialist Neurorehabilitation Outreach Service (SNROS) is hosted by Central London Community Healthcare NHS Trust which delivers other community neurorehabilitation pathways including Early Support Discharge (ESD) for stroke. The original model of SNRS (pictured here) included a dedicated case manager / specialist social worker employed by Adult Social Care, which is not part of the current model. The current provision is through hospital-based and borough-based social workers.

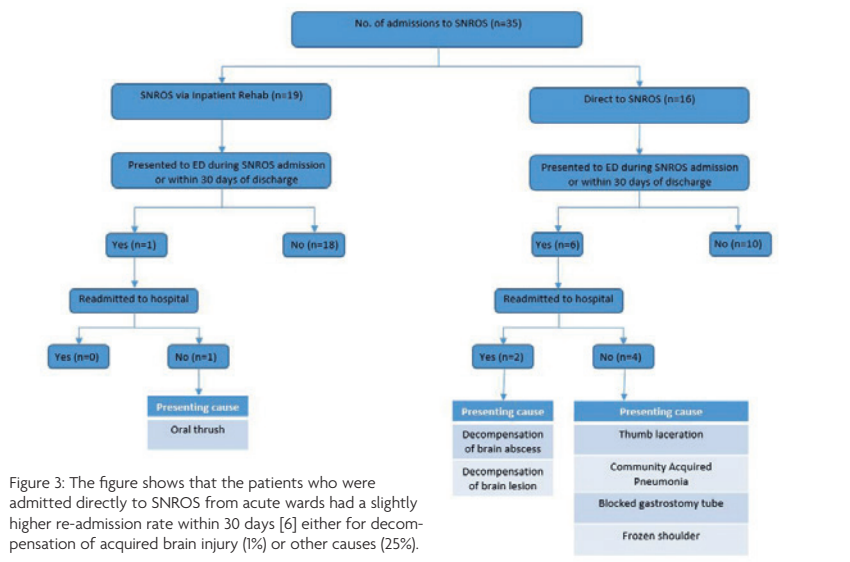


Figure 3: The figure shows that the patients who were admitted directly to SNROS from acute wards had a slightly higher re-admission rate within 30 days [6] either for decompensation of acquired brain injury (1%) or other causes (25%).

(MDT) in the community.

**The SNROS virtual beds improve things in four key ways:**

1. Direct transfer to the community setting for intensive rehabilitation: patients who are waiting for inpatient rehabilitation beds while on acute wards (for e.g. major trauma unit, neurology/neurosurgery services) can be discharged directly to the virtual beds, where their medical/nursing and therapy needs can be supported at home.

2. Optimising flow in the whole system: patients can be discharged from the inpatient rehabilitation unit or directly from acute wards to the virtual beds hence optimising flow in the whole system. Patients continue to have high intensity of therapy on discharge and no delay in waiting for community therapy.

3. Rehabilitation at home: patients are discharged into their own homes and get intensive rehabilitation (the same intensity as level 2 rehabilitation unit) at home. This allows patients to receive specific functional task training and enables problem solving in a familiar setting.

4. Continuity of care: the patient remains under the care of the Consultant in Rehabilitation Medicine who is in charge of the inpatient beds in the specialist neuro-rehabilitation unit. The SNROS therapists are also part of the wider Community Neurological Rehabilitation Service (CNRS). Hence when stepped down from the SNROS service, the same therapists will continue to treat the patient on the less intensive CNRS pathways. Unlike patients that receive Early Supported Discharge (ESD) care, patients on the SNROS pathway can access diagnostics/blood tests/clinic reviews etc more rapidly and, if necessary, via the Consultant and Clinical Nurse Specialist.

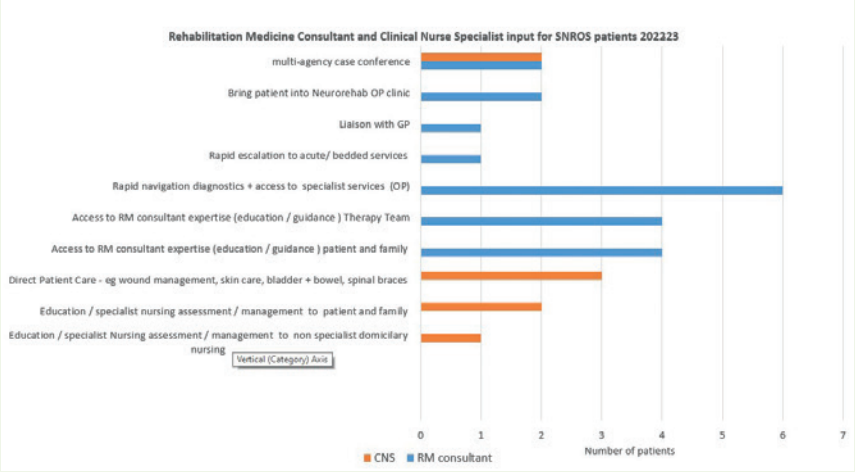


Figure 4: Input/intervention required from the Consultant in Rehabilitation Medicine and the Clinical Nurse Specialist varied from arranging rapid diagnostics (MRI, nerve conduction studies) to liaising with other specialties: Neurology/Neurosurgery/Stroke/Psychiatry/Neuroradiology (e.g. Anti-epileptic-medication optimisation). Education and guidance of both therapy teams/patients and families as well as wound management, bladder and bowel care and bringing into Neurorehabilitation clinics for spasticity interventions. All of the above input/intervention makes this pathway different to other community rehabilitation services such as Early Supported Discharge (ESD).

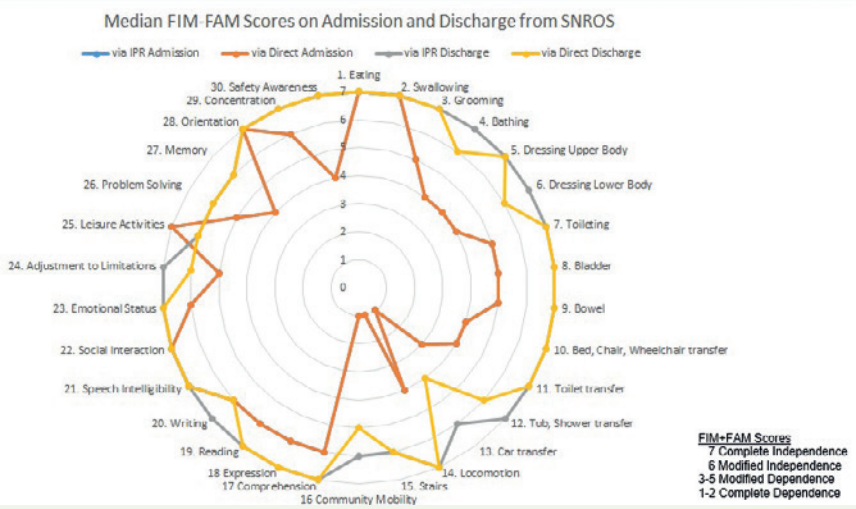


Figure 5 shows the median FIM-FAM scores of patients admitted to SNROS on admission and discharge. FIM-FAM is the principle outcome measure used by UK specialist rehabilitation centres to quantify functional gains across 30 domains. The scores range from 1-7, where 1-2 equals "complete dependence" and 7 equals "complete independence" [8].

**Innovative Commissioning – Sharing the expertise from where it already exists**

As previously mentioned, the SNRS service is comprised of hospital-based beds in CNRU and virtual beds in the patient's own home (SNROS). The design of the SNRS service is novel. It is formed through partnerships between different organisations in order to obtain the expertise from where it already exists. The host partner is Imperial College Healthcare Trust where the inpatient CNRU beds are based. Imperial College Healthcare Trust employs the staff including the nursing and therapy team. The Rehabilitation Medicine consultant input comes from The Hillingdon Hospital Trust where there has been an established inpatient rehabilitation unit for over 25 years. Clinical psychology input for CNRU is provided through the West London Trust. The therapy input for the virtual beds is provided by the Central London Community Healthcare Trust (CLCH) which manages a flexible caseload covering services for Early Supported Discharge (ESD) for stroke, CNRS pathways (including less intensive MDT neurorehabilitation, disability management and rapidly progressive pathways) as well as our SNROS service.

Everyone at SNRS works through a Service Level Agreement (SLA) with Imperial College Health Care Trust. The staffing is based on British Society of Physical and Rehabilitation Medicine (BSPRM) 'Specialised Neurorehabilitation Service Standands' for level 2 rehabilitation unit [4].

**The day to day running of the service**

The SNRS service provides intensive level 2 neurorehabilitation through the inpatient beds CNRU and virtual beds in SNROS. The SNROS patients have complex (Category A+B needs) on The Patient Categorisation Tool (PCAT) [11] and have therapists going into their homes to deliver sessions. The SNROS team have a weekly multi-disciplinary team meeting with the Consultant in Rehabilitation Medicine, Clinical Nurse Specialist (CNS) and community therapy team from CLCH. All referrals to SNROS and every patient who is currently on the SNROS pathway is discussed. If there are medical and/or nursing issues arising, the team will consider the following options:

1. Liaise with the GP (e.g. to start medications for neuropathic pain)

2. Liaise with other specialties and diagnostics - Neurology/Neurosurgery/Stroke/Psychiatry/Neuroradiology (e.g. Anti-epileptic medication optimisation)

3. Bring patient into Rehabilitation Medicine Outpatient clinic (e.g. to review spasticity)

4. Arrange home visits (e.g. to review bladder and bowel complications)

5. Rapid escalation to acute/bedded services

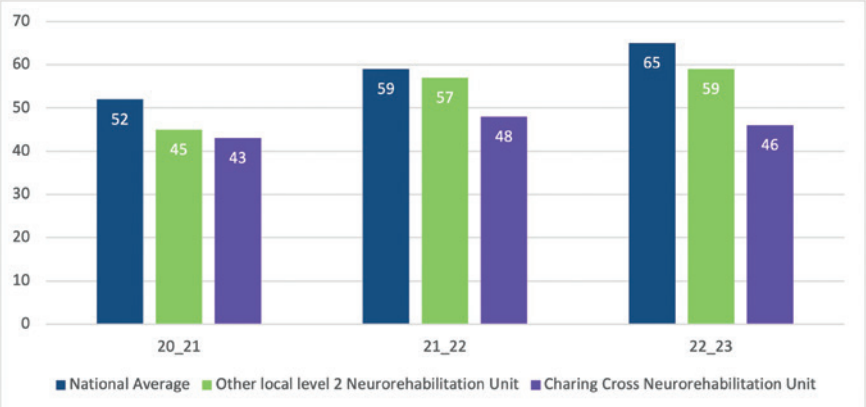


Figure 6: Illustrates the impact of the SNROS team on the average length of stay (days) for bedded neurorehabilitation episodes against the national average and when compared with other local level 2 neurorehabilitation services who don't have access to the virtual beds. This trend has changed over time and is reflected in increased SNROS activity (see Figure 4)

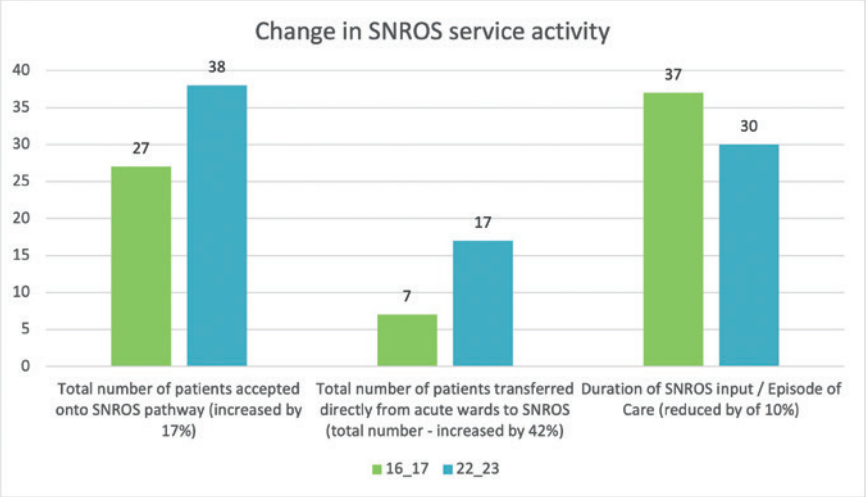


Figure 7: SNROS service has built up capacity over the past 7 years with increasing referrals onto the pathway particularly directly from acute wards (directly to SNROS). The SNROS team have also reduced the average duration of input by 7 days meaning patients can be stepped down to the Community Neuro Rehabilitation Therapy (CNRT) sooner helping more patients to get access to SNROS quickly.

There are also in-reach visits from the SNROS team into CNRU for joint sessions to help patients get to know their community therapists. This ensures that a thorough handover takes place and that there is a clear plan for rehabilitation prior to discharge. Referrals to the SNRS service are received through the London-wide referral management system 'Badgernet'. Outcome measures for both inpatient and virtual beds are collected and submitted to the national database, which collates case episodes for rehabilitation: UK Rehabilitation Outcomes Collaborative (UKROC) [5]. Through the years, there has also been a trend of increasing referrals for stepping up to SNROS beds in patients already in the community. Hence preventing an inpatient rehabilitation admission.

**Staffing**

NHS staffing trends have shown that it is difficult to recruit to certain disciplines and there is poor retention and high attrition [7]. To help with this, the SNRS service has created rotational posts for physiotherapists, occupational therapists and speech and language therapists through the hospital and community. This variety in exposure has proven to be highly attractive for the retention of staff. In addition, the team becomes familiar with the whole pathway having worked in different sections of it. Other initiatives to educate and empower staff include SNRS networking and educational meetings.

**Patient experience**

CLCH uses patient stories to gain rich narrative feedback from patients. The following are quotes from patients on the SNROS pathway describing their experience of participating in level 2 specialist neurorehabilitation at home.

*John was transferred directly to SNROS from Major trauma having sustained a traumatic brain injury secondary to a fall: 'in hospital I dunno, not for me. Home was a better environment to do my rehab without a doubt'.*

*Mary, who sustained a brain injury on holiday and was repatriated back to CNRU to commence goal focused rehab fed back on the seamlessness of transfer between CNRU and SNROS: 'I was impressed with the care I got. When I got discharged from Charing Cross, they said I would have therapy in the community but I didn't expect it to be taken up so quickly.'*

**Benefits and outcomes**

One of the primary outcomes of the SNROS pathway has been reducing Length of Stay (LOS) in inpatient rehabilitation. Data over the last 3 years demonstrates that our inpatient rehabilitation unit (CNRU) has a lower length of stay than the national average and another specialist level 2 unit in the same sector in London (Figure 3). This is largely due to having a seamless SNROS community service that patients can be discharged into.

The Patient Categorisation Tool (PCAT) is a wide-ranging tool for identifying patients with complex (category A and B) needs requiring rehabilitation in a Level 1 or 2 inpatient rehabilitation service [9]. The SNROS patients have a mean PCAT score of 28 which are category B needs [11]. This illustrates moderate complexity in the SNROS pathway comparable with level 2 inpatient neurorehabilitation services. However, complexity scores for patients on SNROS are greater for psychosocial, communication, mental capacity, vocational rehabilitation, rather than domains associated with medical risk and acuity.

Figure 5 demonstrates that on admission to SNROS; the patients have the same level of functional dependence regardless of whether they are admitted via an inpatient level 2 rehabilitation service or directly from an acute ward. On the diagram this is shown by dark orange (admitted from acute ward) being directly on top of blue (admitted from level 2 unit) as the admission scores for both groups were the same (hence only the dark orange line is visible). On discharge from SNROS patients made functional improvements across all domains with the majority achieving either scores of 6 or 7 (i.e. modified or complete independence), suggesting that the SNROS pathway is both supporting earlier discharge from bedded services and delivering the functional benefits expected from a high-intensity neurorehabilitation service.

**Summary**

A model and pathway for home-based care which enables rapid step down from bedded acute and rehabilitation services for people with complex (category A and B) neurological rehabilitation needs, has been developed and tested within this specialist neurorehabilitation service. By creating SNROS and integrating it with the inpatient bedded service; we have

demonstrated the ability to streamline transitions of care and deliver intensive therapy, similar to that provided within an inpatient unit, at home. With access to skilled community therapy teams, Consultant in Rehabilitation Medicine assessments/reviews, monitoring and Clinical Nurse specialist (CNS) support, the outcomes for rehabilitation in the patient's own home are comparable to bedded units for this subset of patients with complex neurological needs.

We would advocate for enhancing integrated specialist neurorehabilitation services with both acute and community teams to provide a flexible and responsive service for our patients who require neurological rehabilitation. This model is aligned with strategic objectives within the ICS, reducing demand on bedded services and increasing integration between services while providing access to specialist care.

**References**


1. NHS England and NHS Improvement (NHSE/I) 2022/23 operational planning guidance
2. National Neuro Advisory Group Impact Report 2019
3. "Neuro Numbers 2019"- A report by the Neurological Alliance - March 2019
4. British Society of Physical and Rehabilitation Medicine (BSPRM) Specialist neuro-rehabilitation services: providing for patients with complex rehabilitation needs 2010 (latest update May 2023)
5. UK Rehabilitation Outcomes Collaborative - www.ukroc.org
6. NHS England Digital 3.2 Emergency readmissions within 30 days of discharge from hospital - Specification version 1.4 March 2020.
7. A critical moment: NHS staffing trends, retention and attrition 2019.The Health Foundation 2019
8. Nayar M,Vanderstay R, Siegert RJ,Turner-Stokes L.The UK Functional Assessment Measure (UK FIM+FAM): Psychometric Evaluation in Patients Undergoing Specialist Rehabilitation following a Stroke from the National UK Clinical Dataset. PLoS One. 2016 Jan 29;11(1):e0147288. PMID: 26824696; PMCID: PMC4732596. https://doi.org/10.1371/journal.pone.0147288
9. https://www.england.nhs.uk/virtual-wards/what-is-a-virtual-ward/
10. A new community rehabilitation and reablement model Good practice guidance for integrated care boards (commissioners and providers NHS England September 2023
11. Siegert RJ, Medvedev O,Turner-Stokes L. Dimensionality and scaling properties of the Patient Categorisation Tool in patients with complex rehabilitation needs following acquired brain injury.J Rehabil Med. 2018 May 8;50(5):435-443. PMID: 29582901. https://doi.org/10.2340/16501977-2327

# RCPsych Faculty of Neuropsychiatry Annual Conference 12-13 September 2024 RCPsych London/ Live streamed

Following on from the success of our 2023 meeting we are able to confirm the 2024 RCPsych Faculty of Neuropsychiatry annual conference.
This will take place 12-13 September at our HQ in London.
The conference will also be live steamed.

*Delegates will also be able to attend workshops on day 1.*

**Confirmed Topics**

1. Recent developments in unravelling mysteries of causation of Functional Neurological Disorders (FND).
2. The neuropsychiatry of 'organic' psychotic syndromes.
3. Paediatric Neuropsychiatry: taking a developmental perspective through the lens of Developmental Regression and Intense Imagery Movements (IIM).
4. The placebo effect in neuropsychiatric conditions: implications for clinical trials and disorder mechanisms.
5. Neuropsychiatry in print: what do neurologists need to know.
6. Trainee awards presentations.

Visit rcpsych.ac.uk/events for further details and to register online.
Contact: Rukiyat Babajide on Rukiyat.babajide@rcpsych.ac.uk or 0208 618 4288

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# John Hughlings Jackson (1835-1911): an addition to his published writings?

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**Abstract**
Attempts made hitherto to document the complete published oeuvre of John Hughlings Jackson have included the rider that more may yet be found amongst the multiplicity of journals serving the medical profession during Jackson's lifetime. Here I suggest a further item, a case of "treadler's cramp", previously noted indirectly in reports of the meeting at which it was presented but not in its original form which appeared in the *Transactions of the Medical Society of London* in 1891.

In his biography of John Hughlings Jackson, Samuel Grenblatt noted, in the context of the bibliography of Jackson's published papers, numbering more than 500, that "Doubtless there are still more out there" [1]. Briefly, I thought I had found one, and after further investigation this may still be the case. The story is as follows: In the *Transactions of the Medical Society of London* for 1891, under the heading "CASE OF TREADLER'S CRAMP. By J. HUGHLINGS JACKSON, M.D., F.R.S.", this brief note appeared:

> Dr. RIVERS showed for Dr. Hughlings Jackson a case of treadler's cramp occurring in a man who, after having been a hand-loom weaver for thirty years, began to make mistakes in his work owing to defective treadling with his right leg (the one principally used); later the right leg became lame, and after using the left leg for some years this became weak, rendering him unable to follow his occupation. The spasm occurred at the commencement of the flexion movement which accompanied the upward motion of the treadle, the extension or downward movement being well performed. The spasm was of the combined movement of the hip and knee, each joint being moved freely by itself. The difficulty was referred by the patient to the gluteal region, and both the gluteal and hamstring muscles on the right side showed decided diminution of faradic and galvanic irritability. The right leg was held stiffly in walking, the case thus agreeing with other occupation spasms in which large movements were concerned, and in which the affected limb was more or less generally disabled [2] [capitals in original].

As Greenblatt points out, most of Hughlings Jackson's papers "were originally given at meetings of medical organizations" [1] of which there were many in late nineteenth-century London. These oral papers were then reported in the weekly medical press, sometimes two, three or even four versions appearing in the different journals, not only the *Lancet* and the *British Medical Journal* but also the *Medical Times* and *Gazette* and the *Medical Press and Circular*. This appears to be borne out for the case of treadler's cramp.

There are two substantial published bibliographies of Hughlings Jackson's work: the Catalogue Raisonné of York & Steinberg (2006) and Greenblatt's "Published writings of John Hughlings Jackson" (2022). Consulting these sources for the year 1891 [3,4], one finds that the case of treadler's cramp was reported in the *Lancet* and in *Brain* (York & Steinberg items [91-01] and [91-06]). The *Lancet* report (identical wording to that given above) related to a meeting which took place at the Medical Society of London on 16th February [5]. However, the original publication in the *Transactions of the Medical Society of London* appears in neither bibliography.

Why this oversight? Why did these distinguished authors not think to access the original presentation, rather than simply report thereof? One possible explanation might be that these authors were unaware of this relatively obscure journal, but more likely, I think, the journal may have been inaccessible rather than unknown to them. (I saw this journal on a pre-arranged visit to the Medical Society of London, although it is available through Internet Archive.)

What can one make of the actual case report? Irrespective of the well-recognised shortcomings of attempted retrospective diagnosis, I suspect that many neurologists will want to venture a diagnostic or differential diagnostic opinion, notwithstanding the paucity of clinical information (no examination!). My reading, for what it is worth, is that the 30-year history of repetitive flexion-extension movement might make compressive lumbosacral radiculopathies in the context of degenerative spinal disease the most likely diagnosis; this might also perhaps account for the "diminution of faradic and galvanic irritability" in the gluteal and hamstring muscles. However, the mention of spasm and of stiffness in the leg may perhaps suggest a more proximally located (i.e. central) disorder: is this a form of occupational or task-specific dystonia, *avant le nom*?

Luckily, as in any typical grand round presentation, further clinical information is available! Unlike the *Lancet* report, which is identical to the

References

1. Greenblatt SH. John Hughlings Jackson. Clinical neurology, evolution, and Victorian brain science. Oxford: Oxford University Press. 2022:7. https://doi.org/10.1093/med/9780192897640.001.0001
2. Jackson JH. Case of treadler's cramp. Trans Med Soc Lond. 1891;14:439.
3. York GK, Steinberg DA. An introduction to the life and work of John Hughlings Jackson with a catalogue raisonné of his writings. Med Hist Suppl 2006;26:121.
4. Op. cit., ref. 1: 496-7.
5. Medical Society of London. Lancet 1891; 1(3521): 433-5 (21st February) [case at 434]. https://doi.org/10.1016/S0140-6736(02)17948-7
6. Rivers WHR. A case of treadler's cramp. Brain. 1891;14(1):110-1. https://doi.org/10.1093/brain/14.1.110
7. Shorvon S, Compston A. Queen Square. A history of the National Hospital and its Institute of Neurology. Cambridge: Cambridge University Press, 2019: 342. https://doi.org/10.1017/9781316181430
8. Jacyna LS. Medicine and modernism: A biography of Henry Head. Pittsburgh: University of Pittsburgh Press, 2016: 125-30.

*Transactions of the Medical Society of London* account, the *Brain* report is quite different. Indeed, it is related to a different meeting, that of the Neurological Society (of London) held on 5th March 1891, and Jackson's name does not appear on the by-line [6]. Now we are given details of the man's age (56) and initials (J.M.), and some examination findings: "The tendon jerks are equal and not exaggerated" and the right glutei and hamstring muscles are wasted compared to the left. Moreover:

> the flexion of the limb when treadling is performed with great difficulty, as if some resistance were being overcome, the thigh becoming inverted during the process.

Could this resistance be involuntary co-contraction of agonist and antagonist muscles? Could the thigh inversion be dystonic posturing?

> The spasm can be lessened by supporting the lower end of the thigh, and especially when any pressure is exerted on the popliteal space. … whether in the present case the improvement is due to any pressure on the nerve I have not been able to determine, but am inclined to attribute it solely to support of the limb.

Could this be a sensory trick which relieves a dystonic posture?

> The patient walks leaning forward and using the right leg very stiffly. He goes upstairs with difficulty; downstairs easily. That the gait should be affected is in accordance with … [the] observation that, while in an occupation spasm, like writer's cramp, in which the movements concerned are fine, the affection is usually, though not invariably, limited to the act of writing; in those in which the movements are large … the limb suffers for modes of action other than that of the occupation. Since both walking and going upstairs involve flexion of the limb similar to that which occurs in treadling, it might be expected that they would suffer in this case.

The comparison here with writer's cramp, another "occupation spasm", is of note, although the appearance of symptoms when walking as well as when treadling may be more in keeping with a task-specific dystonia. Rivers reported Hughlings Jackson's view of these cases as follows:

> He considers that the affections known as occupation spasms are due to defective action of some elements of the spinal centres, or their homologues higher up.

Whatever the diagnosis in this patient may have been, the attempted formulation presented here may illustrate how the clinical approach to cases changes over time, not merely in terms of investigations available but conceptually.

York & Steinberg stated that the "Dr. Rivers" by whom the case was presented on behalf of Hughlings Jackson, at both the Medical Society of London and the Neurological Society, was W.H.R. Rivers (1864-1922). Indeed, this is the name which appears on the by-line of the *Brain* paper [6]. Rivers is perhaps best known to posterity for his work with patients suffering from shell-shock during the First World War, but at this early stage in his career he was house physician at the National Hospital for the Paralysed and Epileptic at Queen Square (although mentioned only in passing in this capacity in Shorvon & Compston's history of the National [7]). It was apparently at this time that Rivers also met and became friends with another physician from the London Hospital, Henry Head, with whom he later (1903-1907) collaborated in a famous experiment on the consequences of nerve division, Head being the experimental subject [8].

**Acknowledgement**
Thanks to Dr Sundus Alusi for her insights into the clinical formulation of the case history. Any remaining errors are solely those of the author.

REGULARS - AWARDS

## Professor Mary Reilly wins the 2024 Peripheral Nerve Society Alan J Gebhart Prize

Congratulations to Professor Mary Reilly (Neuromuscular Diseases, UCL Queen Square Institute of Neurology) who was been awarded the prestigious Alan J Gebhart Prize for Excellence in Peripheral Nerve Research at the Peripheral Nerve Society in Montreal.

PNS award the prestigious Alan J Gebhart Prize for Excellence in Peripheral Nerve Research each year during their awards ceremony at the PNS Annual Meeting.This award recognises an Active PNS Member's ongoing contributions to their mission of "improving the lives of people with peripheral neuropathies." The unrestricted cash prize is awarded to an established researcher (or researchers) in the peripheral nerve field.

More information about this award can be found at: www.ucl.ac.uk/ion/news/2024/jul/professor-mary-reilly-wins-2024-peripheral-nerve-society-pns-alan-j-gebhart-prize

Dr David Cornblath, Professor Mary Reilly, Dr. Charlotte Sumner

## 2024 World Federation of Neurorehabilitation (WFNR) Franz Gerstenbrand Award

Dr Christian Endisch, a physician with a neurology residency at the department of Neurology and Experimental Neurology Charité Universitätsmedizin in Berlin, Germany, is the winner of the 2024 World Federation of Neurorehabilitation (WFNR) Franz Gerstenbrand Award.

Dr Endisch's team conducted a retrospective, international, multicentre study of 706 comatose cardiac arrest (CA) patients and looked at their cortical somatosensory evoked potential (SSEP) amplitudes using a standardised evaluation pathway.

The results of Dr Endisch's study, published last year [1], showed that bilaterally absent and cortical SSEP amplitudes below 0.5 µV reliably predicted a poor outcome and high cortical SSEP amplitudes were likely to indicate the absence of severe brain injury.

As a result of Dr Endisch's findings comatose CA patients will benefit from either the continuation of treatment and neurorehabilitation in the absence of severe brain injury, or the withdrawal of futile therapy for those with severe brain injury and no long-term prospect of regaining consciousness.

For more information about the World Federation of Neurorehabilitation (WFNR) Franz Gerstenbrand Award please visit https://www.wfnr.co.uk/awards/award

WFNR
World Federation for Neurorehabilitation

References

1. Aalberts N, Westhall E, Johnsen B, Hahn K, Kenda M, Cronberg T, Friberg H, Preuß S, Ploner CJ, Storm C, Nee J, Leithner C, Endisch C. Cortical somatosensory evoked potential amplitudes and clinical outcome after cardiac arrest: a retrospective multicenter study. J Neurol. 2023. Dec;270(12):5999-6009. https://www.doi.org/10.1007/s00415-023-11951-4. Epub 2023 Aug 28. PMID: 37639017; PMCID: PMC10632270.

# Narcolepsy: origins and insertions

My first encounter with narcolepsy was memorable. As a visiting medical student in Aarhus, Denmark, I was astonished to see a fellow student suddenly fall asleep standing upright in a doorway when awaiting the arrival of a minibus to take us to the hospital. He quickly regained his senses and told us of his affliction. This was clearly different from the physiological post–prandial or ethanolic dozing of middle–aged and elderly people, and from Dickens' account of Joe, the fat boy in The Pickwick Papers:

> *On the box sat a fat and red-faced boy, in a state of somnolency… the fat boy waddled to the same perch, and fell fast asleep instantly. "Damn that boy, he's gone to sleep again. … Sleep!" said the old gentleman, "he's always asleep. Goes on errands fast asleep, and snores as he waits at table. How very odd!" said Mr. Pickwick.*

The obesity, daytime sleepiness, snoring, and possible sleep apnoea are now labelled the "obesity hypoventilation syndrome" or "Pickwickian syndrome."

Narcolepsy derives from the Greek ναρκωστς (narkē, numbness or stupor, and lepsis, seizure); cataplexy is from the Greek καταπληκτικός being stricken down. It is often called Gélineau's syndrome, after the French physician and naval surgeon Jean Baptiste Edouard Gélineau (1828–1906) who in 1880 described both cataplexy and narcolepsy triggered by sudden emotions. He said: "Therefore, I feel justified in designating narcolepsy as a specific neurosis, little known until now," in a 38-year-old man with frequent narcoleptic sleep attacks, up to two hundred daily:

> *When laughing out loud or when anticipating a good business deal in his profession, he would feel weakness in his legs, which would buckle under him. Later, when playing cards, if he was dealt a good hand he would freeze, unable to move his arms. His head would nod forward and he would fall asleep. He would wake up a minute later [1,9].*

Gélineau briefly described cataplexy as "astasia", the sudden muscle weakness initiated by surprise, laughter or unexpected emotions. He reported sleep paralysis but not hypnagogic/hypnopompic hallucinations. Years later he was awarded the Chevalier de la Légion d' Honneur, and in his retirement was a prize–winning wine producer.

An earlier probable portrayal is that of Thomas Willis who noted that it was not just an embarrassing somnolence but a humoral disease in which the body produced its own narcotic substances [2]. He described patients with:

> *A sleepy disposition—they eat and drink well, go abroad, take care well enough of their domestick affairs, yet whilst talking or walking, or eating, yea their mouthes being full of meat, they shall nod, and unless roused by others, fall fast asleep [3].*

Gowers stressed the importance of separating narcolepsy (NT1)* from other neurological disorders associated with somnolence. WJ Adie at Queen Square described six of his patients with cataplexy and fifteen from the literature:

> *THE disease I am about to describe is characterized by the occurrence of attacks of irresistible sleep without apparent cause, and curious attacks on emotion in which the muscles relax suddenly, so that the victim sinks to the ground fully conscious but unable to move. As a rule the attacks occur independently ; occasionally an attack on emotion ends in sleep [4].*

Kinnier Wilson added more examples in a masterly review and coined the term "sleep paralysis [5]." Daniels [6], Yoss and Daly [7] drew attention to the concurrence of narcolepsy, cataplexy sleep paralysis, and hypnagogic hallucinations, although the complete tetrad is observed in only about twenty per cent of narcolepsy cases.

Episodes of both narcolepsy and cataplexy last for about two minutes with widely varying frequency, accompanied by excessive daytime sleepiness. Sleep paralysis and hypnagogic hallucinations can occur in normal subjects during the twilight states as well as in narcolepsy. In sleep paralysis, the terrified patient lies wide awake unable to move for seconds or a few minutes. Hypnagogic (on falling sleep) and hypnopompic (on awakening) hallucinations may be isolated or accompany sleep paralysis. Patients describe frightening hallucinations of kaleidoscopic shapes, animals or people, sometimes as a terrifying incubus squashing the chest.

**Westphal, narcolepsy and cataplexy**

Carl Friedrich Otto Westphal (1833-90) provided an earlier but often overlooked account and described both narcolepsy—"peculiar attacks associated with falling asleep"—and cataplexy. In July 1876 three years before Gélineau's paper he presented two patients, a bookbinder and a cooper to the Berlin Medical and Psychological Society, published in 1877 [8].

Schenck and colleagues drew attention to English translations of Westphal's report: He described narcolepsy associated with cataplexy:

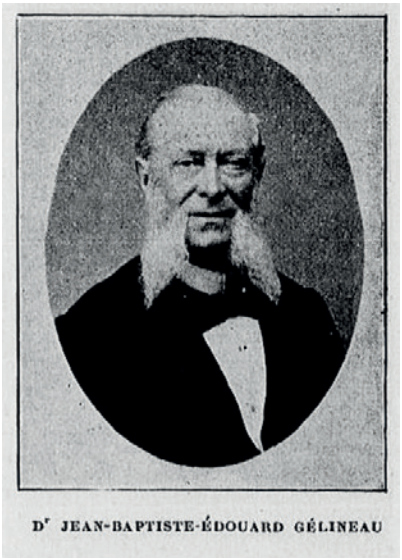


Figure 1. Jean Baptiste Edouard Gélineau

> *At times…these attacks [of cataplexy] do cause the patient to fall asleep. The falling asleep appears, as it were, to be an extension or increase of the attack…while "strolling around quietly and aimlessly.*

In the sleep attacks:

> *His upper eyelids lowered gradually like those of a person falling asleep (during which the eyes roll upward). Then they opened again once or twice, seemingly with great effort, until they finally shut completely, whereupon the patient stopped speaking after murmuring something incomprehensible. His head sank down to his chest, and his brow seemed forcefully knit… he hears and understands what is said to him during the attack [9].*

He emphasised that he did not lose consciousness. He was also the first to describe familial cataplexy: the mother of his 36-year old patient also suffered from recurrent episodes of cataplexy.

Westphal made many important neurological contributions and is remembered eponymously for the Edinger Westphal nucleus and for introducing tendon reflex examination into routine clinical practice. He trained Arnold Pick, Hermann Oppenheim and Carl Wernicke.

Löwenfeld in 1902 recognised narcolepsy with cataplexy as a "disease sui generis, and gave cataplexy its name [10]. Von Economo in 1930 with prescience proposed "narcolepsy has its primary cause in an yet unknown disease of that region"— the posterior hypothalamus.

> *"On the box sat a fat and red-faced boy, in a state of somnolency… the fat boy waddled to the same perch, and fell fast asleep instantly. "Damn that boy, he's gone to sleep again. … Sleep!" said the old gentleman, "he's always asleep. Goes on errands fast asleep, and snores as he waits at table. How very odd!" said Mr. Pickwick.*

Narcolepsy has a prevalence of about 25–50 per 100,000. The onset is usually in the second or third decade, succeeded by lifelong attacks of falling asleep during the day, often with disturbed sleep at night. It is usually clinically distinguishable from obesity hypoventilation sleep apnoea and other causes of hypersomnolence. Polysomnography and a mean latency sleep test (MLST) are common aids to diagnosis [11].

**Recent advances**

In 1963 narcolepsy was related to sleep onset rapid eye movements (REM) [12]. Normal sleep is accompanied by dreaming and loss of muscle tone; in narcoleptics these features occur when the subject is awake, resulting in attacks of daytime sleep often accompanied by cataplexy, nocturnal hypnagogic hallucinations, and sleep paralysis which are pathological manifestation of REM sleep.

Although human narcolepsy is not a simple genetic disorder [13], first-degree relatives of a narcoleptic patient, have a risk estimated at 1–2 per cent, some 10 to 40 times higher than in the general population. The concordance rate in monozygotic twins is approximately 20–30 per cent.

Most narcoleptics carry a HLA-DR or DQ haplotype. The DQB1 alleles are haplotypes associated with narcolepsy, suggesting an autoimmune basis; but this is unproven [14]. HLA gene variations may increase susceptibility to a putative immune attack on hypocretin cells. However, 30 per cent of families have no association with HLA DQB1∗0602, which suggests other environmental or immune factors. Emmanuel Mignot and others have shown that neurons that secrete hypocretin (orexin) are depleted in the brain and cerebrospinal fluid in the narcoleptic syndrome [15]. Two hypocretin neuropeptides are produced in the lateral hypothalamus and act on specific receptors, which modulate sleep, arousal, feeding, anxiety and cognition. Narcolepsy patients also show loss of hypothalamic corticotrophin-releasing hormone producing neurons, which suggests mechanisms other than a cell-specific autoimmune attack.

Modafinil and low sodium oxybates are the mainstays of treatment. The current development of orexin receptor agonists promises the possibility of better symptomatic control.

**Narcolepsy type 2 (NT2) is a poorly understood variant without cataplexy and with normal orexin levels.*

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References

1. Gélineau JBE. De la narcolepsie. Gazette des Hôpitaux. 1880;53:626-8. 54:635-7.
2. Pearce JMS. Willis on narcolepsy. Journal of Neurology, Neurosurgery & Psychiatry. 2003;74:76. https://doi.org/10.1136/jnnp.74.1.76
3. Willis T. cited by Lennox WC. Thomas Willis on narcolepsy. Archives of Neurology and Psychiatry. 1939;41:348-51. https://doi.org/10.1001/archneurpsyc.1939.02270140134010
4. Adie WJ. Idiopathic narcolepsy: a disease sui generis: With remarks on the mechanism of sleep. Brain. 1926;49: 275-306. https://doi.org/10.1093/brain/49.3.257
5. Wilson SAK. The narcolepsies. Brain. 1928;51:63-109. https://doi.org/10.1093/brain/51.1.63
6. Daniels LE. Narcolepsy. Medicine 1934;13:1-122.https://doi.org/10.1097/00005792-193413010-00001
7. Yoss RE, Daly DD. Criteria for the diagnosis of the narcoleptic syndrome. Mayo Clin Proc. 1957;32:320-328.
8. Westphal C. Eigentümliche mit Einschlafen verbundene Anfälle. Archiv für Psychiatrie und Nervenkrankheiten. 1877;7:631-5.https://doi.org/10.1007/BF02041879
9. Schenck CH, Bassetti CL, Arnulf I, Mignot E. English translations of the first clinical reports on narcolepsy and cataplexy by Westphal and Gélineau in the late 19th century, with commentary. J Clin Sleep Med. 2007 Apr 15;3(3);301-11. https://doi.org/10.5664/jcsm.26804
10. Löwenfeld L. Ueber Narkolepsie. München Medizinische Wochenschrift. 1902;49:1041-5.
11. Reading P.Recent advances in narcolepsy. Advances in Clinical Neuroscience and Rehabilitation 2016.
12. Rechtschaffen A, Wolpert EA, Dement WC, Mitchell SA, Fisher C. Nocturnal sleep of narcoleptics. Electroencephalog Clin Neurophysiol. 1963;15:599-609. https://doi.org/10.1016/0013-4694(63)90032-4
13. Miyagawa T, Tokunaga K. Genetics of narcolepsy. Hum Genome Var 6, 4 (2019). https://doi.org/10.1038/s41439-018-0033-7
14. Parkes JD, Lock C B. Genetic factors in sleep disorders. J Neurol Neurosurg Psychiat. Special Supplement1989:101-108 https://doi.org/10.1136/jnnp.52.Suppl.101
15. Dauvilliers Y, Mignot E, del Río Villegas R, Du Yeting, Hanson E et al. Oral Orexin Receptor 2 Agonist in Narcolepsy Type 1. New England Journal of Medicine 2023;389(4):309-321.https://doi.org/10.1056/NEJMoa2301940

# Obituary: Dr Jenny Rosemary Vaughan OBE
# Neurologist, campaigner, mum, wife and special friend

*Dr Chinar Osman pays tribute to her friend and colleague, Dr Jenny Vaughan OBE.*

Dr Jenny Vaughan, OBE needs no introduction to the neurology audience as she achieved legendary status both as a brilliantly gifted neurologist and a fearless advocate for justice in the wider medical profession. Her premature death from metastatic breast cancer in March makes all the things she achieved in her 55 years even more remarkable.

Born in Bristol on 25th June 1968 to Elizabeth, a nurse, and Leslie, a schoolteacher, it became apparent from her early years that Jenny was not only exceptionally intelligent (she perfectly recited a monologue from Shakespeare's Hamlet aged 3!) but was also gifted with a passion to help others. Jenny initially had dreams of bringing clean water to Africa as a civil engineer, but her mother's nursing experience and other influences led her to apply to medical school, gaining a place at Nottingham University. Jenny excelled in her studies, graduating with a First Class honours degree, and also had a fun-filled social life with her ever-present smile and cheeky humour. She even found time to learn to fly, gaining a Private Pilot's Licence in 1992!

After moving to London and marrying Matt, her medical interests began to focus on neurology, influenced by the tragic premature death of her stepfather from glioblastoma multiforme and encouraged by Professor Newsom-Davies and many others. It soon became clear that neurology perfectly suited Jenny's meticulous and logical thinking. She particularly loved the detective work involved in tracking down a diagnosis. Jenny's subspecialty interest in movement disorders led her to take up a PhD in the neurogenetics of Parkinson's Disease under Professor Nick Wood at the Institute of Neurology, arriving just at a time when the genetic basis for some forms of the disease were being discovered. As always Jenny threw herself into her research,

Jenny and her sons at their Coronation street party June 2023

Jenny and family at the OBE ceremony in Windsor Castle March 2023

tracking down a particularly intriguing family with a high incidence of PD, whizzing around the country to collect samples of DNA from sibling pairs. This led her to team up for the first time with Dr David Nicholl who happened to be doing his PhD in Birmingham on a similar family. Not only that, David also turned out to be a kindred spirit as a bold human rights campaigner, leading to a lifelong friendship.

Jenny was appointed as a full time Consultant Neurologist at Imperial College (Charing Cross) and Ealing Hospital in 2003, continuing her academic interests with monthly neurogenetics and movement disorders clinics as well as plenty of general neurology. Even though she loved neurology, Jenny always wanted to follow her core instincts to campaign for justice and social improvement. This was to bring her into increasing national prominence in the coming years.

**Campaigner and a warrior**

Jenny had always had a remarkable ability to use the power of a persuasive argument to convince others to see sense and had demonstrated her abilities as a campaigner as the chair of the BMA Junior Members Forum. In 1998, she decided to stand as a Labour councillor in Hammersmith & Fulham, overturning a significant Conservative majority and going on to make a major contribution to health & social care policies in the Borough. This not only equipped Jenny for her key role in preventing the closure of the A&E Department at Ealing Hospital but brought her into contact with Catherine Sellu, Ealing's A&E matron. She became aware that Catherine's husband, David, a Consultant Colorectal Surgeon at Ealing had been charged and then surprisingly convicted of gross negligence manslaughter (GNM). Little did the Sellu family know that they had encountered the person who would not only rescue David from a wrongful conviction but also transform the UK law on GNM in healthcare.

Jenny became convinced that key evidence had not been presented at David's original trial and that his conviction was unsafe. Despite being told that the chances of a successful appeal was almost zero, she worked tirelessly over the next three years to take an appeal to the High Court, spending hours with expert witnesses and barristers to construct a case. Against all odds, in November 2016, David's conviction was quashed by three appeal court judges. Such was the impact of this decision that Jenny pledged to continue campaigning against the criminalisation of healthcare professionals and for a "Learn Not Blame" culture in the NHS. This led her into contact with the paediatrician Dr Hadiza Bawa-Garba, who had also been convicted of GNM and given a 2-year suspended sentence. Having examined the circumstances, Jenny and many others were appalled at this decision and fought for Dr Bawa-Garba to be restored to the GMC medical register. As with David Sellu, Jenny's determination and collaboration with like-minded campaigners brought success at the court of appeal. Other cases came her way for advice and support and Jenny joined with like-minded doctors to set up the Doctors Association UK and lead its 'Learn Not Blame' campaign with the aim to achieve a 'just culture' in healthcare. She was invited by then Health Secretary Jeremy Hunt to contribute to a rapid policy review conducted by Professor Sir Norman Williams, establishing recommendations as to what defines an 'exceptionally bad performance' by a doctor. The Doctors' Association proved to be a powerful voice during the Covid-19 pandemic, especially speaking up for

the provision of widespread, effective PPE for frontline healthcare workers. For all of this, Jenny was recognised in the 2023 New Year Honours list by the award of an OBE.

**Loyal friend and shared struggles**

Personally, our friendship began at Ealing Hospital in 2010. It was a wonderful place to work because everyone was so close and united. I was the medical SHO on call and contacted Jenny for a neurology review as I was concerned that a "psychiatric patient" about to be discharged may actually have undiagnosed auto-immune encephalitis. Jenny was already on her Vespa motorbike in the car park but immediately came to see the patient with me. She reviewed the patient, spoke to the family with me, and agreed that this patient needed to stay for further investigations, which diagnosed NMDA encephalitis. Our conversation then turned to my Kurdish origins and I was so impressed that that she knew so much about my people, saying 'I am sorry for all the suffering the Kurds have faced'. I knew from then that Jenny was a uniquely humble and special human being and even though I was "just an SHO" it was the start of a wonderful friendship.

We went on to organise the Ealing Neurology/Ophthalmology PACES course together, having enormous fun in the process. She recruited her patients who were always happy to give up those weekends, often telling me "We are here as there is no doctor like Dr Vaughan". The course was mainly attended by international doctors who were new to the NHS and often struggling to pass PACES. As well as preparing them for their exam Jenny really made them feel at ease but also offered her help to guide them in their wider roles, especially if they faced concerns.

The first time I went to her home, I had no idea of her love for reptiles and she had no idea about my fear of reptiles. She couldn't understand why I leaped on to her kitchen table as a huge iguana and an ancient tortoise ambled across the floor! Our friendship became closer when I was diagnosed with breast cancer. She was always there for me or at the end of the phone. Our roles reversed 7 months later when she received the same devastating diagnosis and our late-night calls and research about best treatments for breast cancer became a common topic. We also shared the same surgeon and oncologist, who saw how determined we were to beat the disease. Jenny and I encouraged each other to stay positive and I know that I couldn't have done any of it without Jenny. Although we were no longer working in the same hospital, we would try to book the same annual neurology meetings together to catch-up, explore beautiful cities and have a heart to heart. We created wonderful memories when Jenny and her family came to our wedding in 2019 in Puglia, Italy, all of us dancing well into the night.

Unfortunately, Jenny's cancer relapsed in 2020 and her life returned to further rounds of treatment and the stress of scans. Her positive spirit, strong Christian faith and sheer determination made sure that she still made the most

Jenny and me at the ABN, Liverpool May 2017

of life. She was my inspiration not only for my neurology career but also with all the selfless work she was involved in. As she always said, "I did it because it was the right thing to do".

Jenny was an extraordinary human being as well as a fantastic clinician, loved by colleagues and patients. She was a dedicated wife, a mother to two special boys and a unique friend in her own beautiful ways. The world was truly a better place with Jenny in it and she undoubtedly leaves the legacy of a better, fairer NHS.

Rest in peace my friend.
Chinar

# Obituary: Richard Orrell, Consultant Neurologist

*Lionel Ginsberg pays tribute to Richard Orrell.*

Richard Orrell died unexpectedly on 26th May 2024, while travelling in South Korea. He was 64 years old and had worked for more than 25 years as consultant neurologist at the Royal Free Hospital, the National Hospital for Neurology and Neurosurgery, and Queen Elizabeth II Hospital, Welwyn Garden City. He was Associate Professor of the UCL Queen Square Institute of Neurology and President of the Clinical Neurosciences Section of the Royal Society of Medicine.

Richard grew up in Worsley, west of Manchester. At school, he excelled in all areas, including sports and music, playing the piano and clarinet to a high standard. His academic prowess was such that he jumped a year in primary school and then again in secondary school, resulting in him starting medical school at Manchester University a few days after his seventeenth birthday. On completing his medical degree, and a degree in Physiology, Richard gained experience in many physicianly specialties and in General Practice and Paediatrics.

Settling on a career in Neurology, he migrated to London and began his MD research work at Charing Cross Hospital, on the genetics of motor neurone disease, focusing on superoxide dismutase mutations. A lifelong interest in MND was sparked and Richard continued to research in this area, with an emphasis on neurogenetics and clinical trials. He wrote well over 100 research papers, review articles and book chapters. Richard's MND research paralleled his commitment to patient care. He was successful in marshalling the resources of a general hospital to this end, including collaborating with respiratory and gastroenterological teams, nutritionists and therapists.

Richard's skill in neuromuscular diseases extended beyond contributions to MND research and care. He spent a year as a fellow in Rochester, New York, as foundation for an enduring concern for adult patients with muscular dystrophies. He also co-led the Royal Free peripheral nerve service, performing nerve and muscle biopsies on his patients, and conducting a neurophysiology clinic in Hertfordshire. An insightful researcher, Richard was a fluent scientific writer and an authoritative speaker and teacher. Within and beyond the neuromuscular diseases, he provided expert clinical opinion – reliable and clear-sighted.

Richard had many interests outside Medicine. He took advantage of living in central London, going to the theatre, ballet and opera, and visiting art galleries, particularly to view modern art. Perhaps reflecting his professional inquiries into genetics, he was fascinated by his own family history and the genealogy of the Orrell family name. Richard was gregarious, with a circle of close friends and a loving family, who all benefitted from the same good nature, generosity and endearing character as was evident at work. He was also an intrepid voyager to exotic locations and it is poignant that his death occurred so far from home. His extensive travels may have been a factor leading to him recently becoming a member of the Reform Club, emulating the protagonist of "Around the World in Eighty Days."

At the funeral service, the priest likened the sudden loss of Richard to the felling of a tree by night. This metaphor holds, in terms of the gap in the neurological landscape, and in Richard's circle of family and friends, left by his absence. But it also speaks of the shelter and nourishment provided by a tree's branches and roots, comparable to Richard's kindness and expertise, experienced by patients, students and colleagues alike. Thank you, Richard.

# BSPRM Insights from The TOXINS 2024 Conference

***Conference details:*** 17th to 20th January 2024 Berlin, Germany. ***Report by:*** Ece Yilmaz-Kara, Consultant in Physical & Rehabilitation Medicine at Oxford University Hospitals NHS Foundation Trust, UK. ***Conflict of interest:*** None declared.


The TOXINS 2024 conference, which brought together experts from around the world who utilise botulinum toxin in their clinical practice and research, took place in Berlin, Germany from January 17th to 20th. The beautiful city of Berlin, covered in a pristine layer of snow, provided an inspiring backdrop for this gathering of minds, fostering an environment of collaboration and growth.

The first day of TOXINS marked the commencement of the conference with poster setup, a warm welcome, and opening remarks.

The second day of the conference was lively and began with a warm greeting from David Simpson, President of the International Neurotoxin Association, to the foremost experts in botulinum toxin. This was followed by Nils Brose of Germany discussing the molecular aspects of presynaptic nerve signalling. Preeti Raghavan from Johns Hopkins, USA, then shared intriguing findings on muscle physiology, focusing on the role of intramuscular hyaluronidase in managing fibrosis. Professor Robert Brownstone from University College London, both a neurosurgeon and neuroscientist, presented an engaging lecture on dystonia, eliciting numerous inquiries from the audience. Juan Pablo Henriques from Chile examined the prolonged effects at the neuromuscular junction. Additionally, the esteemed Barbara Karp from Maryland, USA, reviewed the latest advancements in using ultrasound and electromyography for guiding botulinum toxin injections, highlighting the criticality of injection depth.

The third day's plenary session, chaired by Giampietro Schiavi, conference co-chair, featured Professor Peter McCaughan, King's College London discussing somatosensory perception of pain and temperature in relation to botulinum toxin. Prof Bahman Jabbari, Yale Medical School, explored the role of toxin in cancer patients, while Sara Marinelli, Italy piqued thoughts when discussing the actions of the toxin beyond neurons. Mandar Jog of Canada shared their innovative system for assessing and treating tremors with Botulinum Toxin, showcasing videos from their case studies.

Both Thursday and Friday afternoons included parallel streams covering topics such as Spasticity, Dystonia, Dysphonia, Aesthetics, Basic Science, Migraine, and hands-on injections and ultrasound workshops. With numerous options to choose from, I focused on my primary interests, spasticity, and dystonia, to gain insights from around the world. Professor Alberto Esquenazi of the USA chaired the thought-provoking Thursday session on Adult Spasticity. Professor Tony Ward, a lifetime member of the BSPRM and 'founder' of RM in the UK, chaired the Friday Adult spasticity session and discussed the predictive value of diagnostic nerve blocks, skilfully fielding questions from the attentive audience.

During breaks, attendees had the opportunity to explore the poster hall and interact with presenters across the world.

The conference served as an outstanding venue for idea-sharing and establishing connections with global and UK-based colleagues, including Klemen Grabljevec, President of ESPRM, Serdar Kocer from Fribourg, Switzerland, and Professor Belgin Erhan from Istanbul, Turkey. From the UK, I had the opportunity to meet with esteemed professionals like Bhaskar Basu from Manchester, Rachel Farrell from UCL, Anton Pick from Oxford, Damon Hoad from Warwick, Sohail Salam and Revin Thomas from Newcastle as well as Eleonora Bradaschia and Ruairi Connolly of King's College, London. These individuals are not only authorities in their respective f ields but also inspiring figures with unique and thought-provoking perspectives.

On Saturday, I carefully packed not only my bag but also a treasure trove of innovative ideas, thoughts, and cherished memories, as I prepared to catch the flight to London and embrace reality, again. With a sense of readiness to apply these insights into my professional journey, I look forward to future conferences with anticipation.

# The South of England Neurosciences Association Meeting

***Conference details:*** 26th April, London, UK. ***Report by:*** Johnson Ja, Neurology Registrar, Royal Free Hospital, London, UK. ***Conflict of interest:*** None declared.

The South of England Neurosciences Association (SENA) Meeting occurred on Friday 26th April 2024 and was hosted by the Royal Free Hospital, London. The meeting was held at the historic Stationers' Hall in central London. The programme featured world-renowned speakers covering topics from cross-disciplinary specialities.

The day consisted of engaging talks with speakers generously sharing their personal and clinical experience with the audience. It was inspirational to hear about the cutting-edge research and translational medicine led by our esteemed speakers.

The morning commenced with a fascinating talk from Dr Rebecca Liu, Neurologist, detailing her experience helping to look after the first patient treated for Ebola in the UK. Dr Liu offered a glimpse into the incredible teamwork which went on behind the scenes across the country to deliver monoclonal antibody therapeutics and experimental treatment in record time.

Dr Jane Macnaughtan, Hepatologist, spoke about the neurological presentations of hepatic disease. We were given a refresher on hepatic encephalopathy, hepatic myelopathy and Wilson's disease, all important diagnoses with treatments available and not to be overlooked on the ward.

Amyloid expert, Prof Julian Gilmore provided an update on ATTR transthyretin amyloidosis. We were given an overview of the exciting gene editing and disease modifying treatments which will revolutionise the treatment of this condition. We were reminded to consider amyloid as a differential in the patient without diabetes, presenting with neuropathy and autonomic symptoms.

The afternoon session kicked off with brilliant cases presented by neurology trainees across South and South East England, all of whom shared interesting and unusual cases from the wards. The cases included a communicating hydrocephalus caused by normal pressure hydrocephalus and vestibular schwannoma; facial nerve baroparesis on board a flight; cavernous sinus haemangioma presenting with multiple cranial neuropathies during pregnancy; bilateral opercular syndrome diagnosed with a bedside dad's joke (!); "triple M" syndrome (myasthenia, myositis, myocarditis) and CNS lymphoma, the mimicker.


Dr Ann Donnelly, Neurologist, provided an update on best practice management of spasticity, an often-overlooked symptom which afflicts many of our patients. The important practice points were to ensure antispasticity drugs are trialled at maximally-tolerated doses and early referral to specialists for consideration of parenteral therapies.

Prof Anthony Schipara, Neurologist, provided an overview of the familial and genetic Parkinson syndromes and the work he has been leading in phase two trials on LRKK2 inhibitor and GLP1 agonist therapy. This was an exciting look into the field of disease modifying therapy for patients with Parkinson syndromes.

Prof Huw Morris, Neurologist, detailed his work on biomarkers, both current and emerging, which will help to standardise diagnosis of Parkinson-plus syndromes. These biomarkers will undoubtedly have a role to play in the monitoring of progression and treatment response.

Dr Jonathan Kennedy, Neurologist, provided an important update on the disease modifying therapies which will revolutionise the treatment of people living with Alzheimer's and dementia. This area is dynamic, with the addition of new therapies to our armamentarium hopefully imminent in the UK.

We were treated to an entertaining debate between Neurologists, Dr Ben Turner and Dr Adrian Wills, who argued for and against neurologists managing acute neurology in the emergency department, respectively. Both speakers presented masterful arguments on the merits of specialism versus generalism.

The day concluded with a special talk from Prof Steve Powis, National Director of NHS England. Prof Powis provided a "state-of-the-NHS" address post-COVID19 and emphasised the importance of primary prevention, the backbone of our health care system.

Overall, the day provided a stimulating and informative discussion of many "hot topics" in neurology. The advent of gene editing, disease modifying treatments and personalised medicine are the future for neurology - watch this space!

Many thanks to Royal Free Hospital Neurologists, Dr Ann Donnelly, Prof Huw Morris and Dr Bob Brenner for putting on this fantastic programme.

**Rachael Hansford, Publisher**

# COMING SOON... Join ACNR's Community!

Where do you find peer support and engagement in your professional life? Social media platforms appear to be losing users and credibility, and suffer from trust and privacy issues. Unpredictable algorithms mean that we don't always see the content we want to. There's such a vast amount of information available that it's often difficult to know where to focus our attention.

To help address these issues, ACNR is launching a secure online community for neurological specialists, moderated by our team. The community will be collaborative, allowing members to share work with peers and learn from each other in a safe environment. We have lots of ideas about how the community can help you, but ultimately it will develop to fit the needs of users.

Please join our wait list to be notified when we're accepting members. Simply email your details to Rachael@acnr.co.uk

If you'd like to see how the community looks, or to discuss any aspects of it, please do get in touch with me – I'm keen to hear your views.

The free network for sharing of information, knowledge and research in neurology.

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