Clinical and research applications of peripheral nerve MRI

Abstract
The non-invasive exploration of the peripheral nervous system using magnetic resonance imaging (MRI) has recently gained momentum. The use of basic and advanced MRI protocols has allowed for both qualitative and quantitative assessment of the peripheral nerves (PN), enabling the structural and functional changes of peripheral pathology to be increasingly investigated. From a clinical perspective, this has impacted diagnosis, treatment and monitoring across a variety of conditions. This review will provide an overview of the current MRI protocols used for PN evaluation, the application of this in the clinical setting, and the expanding techniques within the research field.

Introduction
Peripheral nerves (PN) are involved in a myriad of pathologies and represent a significant burden of disease. Gold standard evaluation currently relies on both clinical and electrodiagnostic testing, but this bestows certain challenges, particularly in early stages of disease when signs and symptoms may be insidious.1 As such, neuromuscular medicine is not uncommonly marred by diagnostic uncertainty, complicating management and treatment decisions.

Although magnetic resonance imaging (MRI) commands a pivotal role in the clinical assessment of neurological disorders, early analysis focused on the central nervous system leaving peripheral nerve techniques relatively unsophisticated. Since MR visualisation of the peripheral nerve was eventually pioneered in 1992,2 developments in this field have now accelerated this tool into the clinical spotlight.3 This review provides an overview of the MRI techniques to assess peripheral nerves, and will outline current clinical applications. Emerging research in this field will also be summarised.

Peripheral nerve MR techniques
Peripheral nerves can now be directly visualised using basic and advanced MRI protocols, allowing differentiation of various pathologies at a structural and functional level (Table 1).

Conventional MRI
MRI provides important information about the structural integrity of the nerve. Understanding the microstructural organisation of this pathway is a crucial step for accurate interpretation of imaging findings (Figure 1).4 Briefly, the axon is encased by the endoneurium and surrounded by endoneurial fluid. This fluid is a main determinant of signal characteristics on non-contrast T2 scans, appearing moderately hyperintense in the absence of pathology. The nerve fascicle is the smallest unit that can be visualised on MRI, sheathed by the perineurium. This layer acts as a blood-nerve-barrier, and thus no gadolinium contrast enhancement should be seen in healthy nerves.1,3

MR neurography (MRN) is a specifically designed PN protocol that delivers a higher level of anatomic detail. This usually incorporates a T1-weighted image that highlights the fascicular ultrastructure of the nerve, often combined with a T2-weighted image that is modified to suppress non-neural structures (e.g. fat and vasculature). The latter sequence enhances water-based pathology, such as oedema and nerve inflammation.5 High resolution phased-array coils can also be used to increase anatomical detail, making fascicles appear more hyperintense and nerve characteristics (including calibre, course and size) easier to identify.1

Advanced MRI techniques
Quantitative assessment of PN pathology is possible through advanced MRI sequences, providing valuable pathophysiological information regarding the functional integrity of the nerve. Currently, techniques for the PN are largely based on diffusion imaging, which measures a wide range of nerve properties.5

Diffusion imaging
MR diffusion imaging is based on the concept that water molecules are highly directional (anisotropic), effectively restricted to move along the...
linear nerve pathways, hindered by intact cell membranes and macromolecules (Figure 2A).5-7 Any damage to this microstructural integrity results in less restriction of water diffusion along this path and a loss of this directionality (Figure 2B).6 MR diffusion tensor imaging (DTI) provides metrics to interpret directionality using diffusion tensor tractography to give a 3D representation of nerve fibre orientation and has been related to changes in myelin pathology.8 These DTI datasets can also be reconstructed to give a 3D representation of nerve fibre orientation using diffusion tensor tractography (DTT) (Figure 3).7,10

Clinical application of peripheral nerve MRI

Although clinical and electrodiagnostic testing remain at the core of PN evaluation and diagnosis, false negative results can be common, particularly during the early phase of disease, in very proximal nerves, or when nerve injury is mild.11 Neurophysiological assessment can also be invasive and uncomfortable, and may be impacted by technical issues and heterogeneous disease pathology. Such factors can lead to a failure to localise pathology to a specific nerve segment and may hinder treatment decisions.

MRI is a particularly useful tool in these settings, with techniques increasingly applied to a wide range of PN pathologies including traumatic nerve injuries, non-traumatic neuropathies (such as inherited and immune-mediated disorders) and nerve tumours.7,12-14 Practically, PN imaging is usually performed on three Tesla (3T) MRI field strength scanners. Standard protocols (such as MRN) can be performed with basic MRI facilities, while DTI protocols often require technical expertise. The growing use of MRI in practice is allowing crucial clinical questions to be more accurately addressed, such as (i) localisation of disease pathology, (ii) measurement of injury severity and (iii) monitoring of nerve recovery.

(i) Localising pathology

Basic MRI can localise structural pathology, such as focal nerve swelling at sites of conduction block in inflammatory polyneuropathies.15 Locating the lesion in carpal tunnel syndrome (CTS), the most common form of entrapment neuropathy (caused by median nerve compression at the wrist), may also require MRI when limited by normal electrophysiological tests in early disease.11,16 In this clinical setting, T2 hyperintense signal changes are seen 24 hours post-injury at (and distal to) the site of pathology. Three main signs subsequently evolve on imaging to confirm entrapment neuropathy: (i) intraneural oedema, (ii) nerve enlargement, and (iii) gadolinium enhancement (in some instances). MRI can also explore the specific level and aetiology of compression, indirectly aided by the presence

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Table 1: Typical peripheral nerve features using MRI

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR Neurography</td>
<td>Distally decrementing, similar to vessel diameter</td>
<td>Enlarged or flattened (diffuse or focal): &gt; vessel diameter</td>
</tr>
<tr>
<td></td>
<td>T1: isointense to muscle; T2FS isointense = mild ↑</td>
<td>T2: hyperintense, similar to adjacent veins</td>
</tr>
<tr>
<td></td>
<td>Anatomically consistent, perineural fat outline</td>
<td>Abnormal to anatomical path; focal or diffuse deviations</td>
</tr>
<tr>
<td></td>
<td>Present on T1 and T2-weighted images</td>
<td>Loss or disruption of pattern on T2 (esp. T2FS)</td>
</tr>
<tr>
<td></td>
<td>Hyperintense</td>
<td>Loss of contrast resolution</td>
</tr>
<tr>
<td></td>
<td>T1: no significant enhancement (due to bnb)</td>
<td>T1: moderate contrast enhancement; muscle enhancement</td>
</tr>
<tr>
<td></td>
<td>No significant changes in muscle size and intensity</td>
<td>Changes seen distally to nerve lesion</td>
</tr>
</tbody>
</table>

- SI = signal intensity; CT = connective tissue; > greater than; ↑ increased; ↓ decreased; bnb = blood neuronal barrier of the perineurium; T2FS = T2-weighted fat-suppressed imaging; DTI values taken from Kronlage et al [28], with normal values given in mean [range]. The mean is of all nerves tested (sciatic, tibial, ulnar, median, radial).

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Figure 2: Principles of DTI.
A. In a normal PN with preserved axonal integrity, water molecules diffuse along one main direction (red arrows) and have low perpendicular movement (yellow arrow) due to the physiological barriers of the intact nerve. B. An injured PN demonstrates a loss of fibre organisation (dashed black lines), with subsequent loss of directionality of water molecule movement (red arrows). Loss of perpendicular barrier integrity (i.e. myelin sheath) increases movement in this direction (yellow arrows).
and distribution of muscle denervation around the nerve(s) involved (Table 1).16

The location of PN tumours involving the nerve sheath can also be identified on basic MRI by way of a 'fat-split' sign, which occurs around the intersomatic or neurovascular bundle. Characteristic MRI features have also been described to differentiate between malignant and benign nerve tumour forms, such as a large size and perilesional oedema (causing indistinct margins and peripheral enhancement) in the case of the former.17

(ii) Measuring disease severity
Identifying the severity of nerve injury is essential to determine the most efficacious treatment and the likelihood of recovery.7 Nerve injury grading systems, established by Seddon and adapted by Sunderland (Table 2),18,19 represent a continuum ranging from mild damage involving focal nerve demyelination with no axonal involvement (neuropraxia/stage I), to complete nerve tears with a focal loss of axons (neurotmesis/stage V) (Table 2). Although electrophysiology remains the mainstay of such assessment, these changes can be challenging to resolve in the first six weeks and MRI may be of additional benefit by identifying early disruption to nerve ultrastructure. MRI can also facilitate distinction between the very severe levels of injury that are identical on electrophysiological testing, as in the case of axonotmesis (i.e. focal loss of axons with preservation of nerve connective tissue) versus neuromatosis (i.e. focal loss of axons and nerve connective tissue elements) (Table 2). Although axonotmesis may recover spontaneously, neuromatosis requires early surgical intervention. As such, clinical distinction is paramount in order to guide treatment.20

(iii) Monitoring nerve recovery
MR modalities can, in theory, also offer a non-invasive alternative for routine monitoring of nerve recovery post-injury, particularly when repeating electrophysiology may not be practical. In some cases, early normalisation of MRN changes has been reported prior to neurophysiological evidence of recovery, and may be useful in relapsing inflammatory conditions or if infiltrative lesions are of concern.18 MRI measurement of axonal degeneration has also been reported in conditions such as amyotrophic lateral sclerosis (ALS), a rare and progressive terminal disorder, with correlation between disease progression and increased brachial plexus signal on T2-weighted sequences described.21

Ultimately however, these dynamic nerve changes can take months to resolve on MRN, and as such this has not been adopted for routine use in clinical practice.

Future developments
The growth of MRI technology continues to promote experimental techniques for PN imaging, which are currently being developed within the research spectrum. With each technique offering their own strengths and weaknesses (Table 3), the combined use of quantitative and qualitative assessments is particularly beneficial, providing unique clinical advantages to PN characterisation that include insights into the dynamics of nerve injury and regeneration.

Table 2: Nerve injury findings

<table>
<thead>
<tr>
<th>Category</th>
<th>Neural Structure Affected</th>
<th>MRN changes</th>
<th>DTI changes</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunderland</td>
<td>Seddon</td>
<td>Myelin</td>
<td>Axon</td>
<td>Endo</td>
</tr>
<tr>
<td>I</td>
<td>Neuropraxia</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>II</td>
<td>Axonotmesis</td>
<td>✓/X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>III</td>
<td>–</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>IV</td>
<td>–</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>V</td>
<td>Neurotmesis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓ affected; X not affected; Endo = endoneurium; Peri = perineurium; Epi = epineurium; ↑ enlargement; Δ change; > greater than; N/A = not assessed; FA = functional anisotropy; RD = radial diffusivity; AD = axial diffusivity. *Traumatic neuroma is the non-neoplastic mass of focal nerve enlargement with an effaced fascicular pattern, formed from entangled regenerating Schwann cells and axons, proliferation of fibroblasts and fibrosis. Colour gradients for DTI: darker colour indicates a higher value; a lighter colour indicates a lower value.
pilot study involving three healthy volunteers. This demonstrated 7T MRI imaging of the PN has only recently been attempted in a small clinical setting. and the need for different receiver coils have limited the immediate use of this protocol in the clinical setting.

7T MRI

7T MRI imaging of the PN has only recently been attempted in a small pilot study involving three healthy volunteers. This demonstrated much clearer visualisation of nerve fascicles in comparison to 3T imaging (Figure 4A-D). Although feasible, the availability of 7T scanners, a longer scan time, potentially increased sensitivity to side-effects, and the need for different receiver coils have limited the immediate use of this protocol in the clinical setting.

Figure 4: Peripheral nerve imaging using 7T MRI.
Tibial nerve fascicles are depicted on high resolution images acquired at 3T and 7T. A and B show full images at 3T and 7T, respectively. C. Enlarged version within the outlined yellow box in A. showing tibial nerve fascicles in detail at 3T. D. Enlarged version within the outlined yellow box in B. showing the same nerve image at 7T. The yellow dotted line (C,D) outlines the tibial nerve fascicles, and a single fascicle is seen marked by the linear line in C and D (as highlighted by the blue and green arrow, respectively). Overall, the fascicular structure has a clearer definition on 7T (D). Reproduced with permission [22].

**DTI**

DTI can specify pathophysiological changes affecting nerve fibre integrity (such as loss of myelin, presence of oedema, or axonal loss), which is particularly useful in circumstances where structural changes are subtle and difficult to identify using standard MRI. In CTS, a reduction of FA correlates with electrodagnostic studies and has been reported to hold a diagnostic sensitivity and specificity of 82.2% and 77.8%, respectively. Non-invasive localisation and differentiation between benign and malignant nerve tumours may also be facilitated with DTI, with a relatively lower FA and higher MD seen in cases of malignancy. 3D nerve reconstructions with DTI have been particularly useful for pre-operative planning in this regard, depicting the relationship of the tumour to the remaining nerve fibre (with a mapping sensitivity of 95.7% and specificity of 66.7%). The use of this technique has resulted in a changed surgical strategy in 25% of reported cases.

The dynamic change of DTI parameters (particularly FA) during the functional stages of recovery has been demonstrated as a marker of PN regenreation and an indicator of treatment efficacy. This has mainly been evaluated after traumatic nerve injury, with a gradual increase of FA occurring between six weeks to six months in patients who show clinical improvement. 3D nerve reconstruction has also had a role in the post-injury phase and can visualise axonal regeneration. These findings correlate with electrophysiological studies and probably reflect PN axonal growth and regeneration, restoring the nerve towards a normal (anisotropic) structure. Equally, axonal degeneration can be identified by a gradual decline in FA and AD metrics in the lower limb of ALS patients, demonstrated over a six-month period. In such conditions where robust biomarkers are truly lacking, these parameters may offer an important indication of disease progression.

**Conclusion**

The use of non-invasive, novel MRI techniques has enhanced understanding of the structural and functional architecture of PN pathology. The evolution of these techniques for the PN has provided multifaceted information to pilot diagnosis and clinical decision making and has allowed objective monitoring of treatment efficacy. A consensus between the protean MRI protocols are now well poised to be validated in larger cohorts, which will hopefully verify robustness and repeatability of technique. This will be essential for successful translation into the routine clinical and diagnostic rhetoric of PN assessment, and for reliable interpretation of pathology. Ultimately, the current exponential growth of peripheral MRI techniques may soon enable dynamic disease characterisation at an individual patient level, inline with a modern era of personalised medicine.

<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>Strengths</th>
<th>Weakness</th>
<th>What clinical questions can be answered?</th>
<th>Clinical utility</th>
</tr>
</thead>
</table>
| MR neurography    | o Provides anatomical information  
                   o May localise nerve pathology  
                   o Visualises superficial and deep nerves  
                   o Accessible technique | o Only provides structural information  
                   o Field of view is limited  
                   o Not possible if MRI contraindications | o Location of nerve injury (if structural damage is present)  
                   o The visual extent of structural damage  
                   o In some instances, aetiology | o Usually 3rd line investigation (after clinical exam and electrophysiology if localisation remains unclear) |
| Diffusion tensor imaging | o Additionally provides information about nerve fibre integrity  
                   o Quantitative and qualitative  
                   o 3D nerve reconstructions provide structural and functional information  
                   o Useful for monitoring progression and/or recovery of the nerve | o Technique is not readily accessible (needs expertise)  
                   o Wide range of normal values make standardisation difficult  
                   o Values are subject to age-related Δ (FA ↑, AD ↓, RD ↑ with increasing age)  
                   o Small diameter of PN (≥10mm) makes spatial resolution difficult  
                   o Proximity of surrounding vessels may make contrast resolution poor | o What nerve structures are compromised (axon, myelin, collagen support etc)  
                   o Aetiology of nerve pathology  
                   o Severity of nerve injury  
                   o Recovery of nerve function (e.g. postsurgical intervention) | o Developing research tool  
                   o Not yet routinely implemented in clinical practice |
REFERENCES


Rhoton’s Atlas of Head, Neck and Brain

First heard the name Rhoton when assisting in an operation to secure a ruptured brain aneurysm as a junior surgical registrar. The instruments which bear his name are used for microsurgical techniques in neurosurgery, helping to carefully dissect the brain to its deepest structures and secrets. After this operation, neurosurgery was the career I wanted to follow, and Rhoton was a name I have heard a lot more of since.

Known to some as the father of microscopic neurosurgery, Rhoton’s reputation as an anatomist, surgeon and teacher became more apparent when I was learning more about the brain. This book encompasses not only the art and scientific detail of the dissections Rhoton was famous for, but also the way in which they are presented, conducive to learning anatomy, and sharing this knowledge with others.

In 624 figures arranged in 28 sections over four parts Dr. Peris-Celda and Prof. Martinez-Soriano lay out the head, neck and brain in stunning detail, with meticulous labelling by Prof. Valverde and Prof. Marti.

Part one covers the osteolology of the head and neck. One can spend many hours searching for well annotated plates such as these. Holding a 3D model of a skull in your hand whilst examining the images can be recommended, to fully appreciate the grooves, foramina and prominences.

The face and neck is covered in part two. The nerves, blood supply and muscles which give humans expression, function, and movement are discussed, with relevant knowledge of their components.

Part three includes all the structures which bear his name are used for microsurgical techniques in neurosurgery, helping to carefully dissect the brain to its deepest structures and secrets. After this operation, neurosurgery was the career I wanted to follow, and Rhoton was a name I have heard a lot more of since.

Part four goes into intricate detail of the brain. These dissections help visualise the approaches used to different areas of the brain, and tie in the deficit which would be experienced in disease. Understanding of neuroanatomy in this anatomy enables the most complex of neurosurgical operations to be undertaken. Dissections rather than illustrations or diagrammatic figures serve this purpose to a greater extent when laid out well, as they are in this volume.

The book is large and heavy, reminiscent of coffee table hardbacks, and is not something to be carried round on a day to day basis. The price tag is equally hefty, more suitable for a departmental purchase than pocket money. That being said, it is a pleasure to use and would be a great addition to any neurosurgeon’s library. Perhaps the icing on the cake is that the plates are also available online. With the use of the 3D glasses provided, the dissections come to life. The view down the glasses is very similar to that of the operative microscope and helps further appreciate the relationship of the structures shown.

This book serves as a worthy tribute to the work of Rhoton, laying out beautifully dissections which help impart his skills and knowledge to the next generation of surgeons, and will help them to do the same to the following generation.