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Masterclass

Reappraising entrapment neuropathies – Mechanisms, diagnosis and management☆

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ABSTRACT

The diagnosis of entrapment neuropathies can be difficult because symptoms and signs often do not follow textbook descriptions and vary significantly between patients with the same diagnosis. Signs and symptoms which spread outside of the innervation territory of the affected nerve or nerve root are common. This Masterclass provides insight into relevant mechanisms that may account for this extra-territorial spread in patients with entrapment neuropathies, with an emphasis on neuroinflammation at the level of the dorsal root ganglia and spinal cord, as well as changes in subcortical and cortical regions. Furthermore, we describe how clinical tests and technical investigations may identify these mechanisms if interpreted in the context of gain or loss of function. The management of neuropathies also remains challenging. Common treatment strategies such as joint mobilisation, neurodynamic exercises, education, and medications are discussed in terms of their potential to influence certain mechanisms at the site of nerve injury or in the central nervous system. The mechanism-oriented approach for this Masterclass seems warranted given the limitations in the current evidence for the diagnosis and management of entrapment neuropathies.

1. Introduction

The clinical manifestation of entrapment neuropathies is traditionally considered to be driven by local mechanisms. These local mechanisms may include intraneural ischaemia with subsequent breakdown of the blood–nerve-barrier and intraneural oedema formation (Rydevik and Lundborg, 1977), Schwann cell reaction and demyelination (Mackinnon, 2002; Gupta and Steward, 2003), and ectopic impulse generation as a result of an increased density of ion channels at demyelinated sites (Devor, 2006). If the only relevant mechanisms were at the level of the nerve or nerve root, signs and symptoms should follow a clear anatomical pattern limited to the structures innervated by the affected peripheral nerve, or restricted to the corresponding dermatome, myotome and sclerotome.

In many neuropathies however, widespread symptoms are the norm. For example, two thirds of patients with carpal tunnel syndrome experience pain outside the median nerve territory (Caliandro et al., 2006) (Fig. 1). Similarly, only one third of patients with cervical or lumbar radiculopathy have symptoms in a dermatomal pattern (Murphy et al., 2009). Motor deficits also occur outside the distribution of the affected nerve (Fernandez-de-Las-Penas et al., 2009). Furthermore, a deficit in left/right recognition of the affected body part can be present in patients with entrapment neuropathies (Schmid and Coppieters, 2011).

Considering these widespread and variable manifestations, it is understandable that there are no universally accepted diagnostic criteria for entrapment neuropathies (e.g., cervical radiculopathy (Thoomes et al., 2012), lumbar radiculopathy (Genevay et al., 2010), carpal tunnel syndrome (Bland, 2005)). Also, if the pathological processes were limited to the entrapment site, it would be expected that surgical release would yield excellent results, unless the nerve was irreversibly damaged. However, the mean long-term success rate for carpal tunnel syndrome surgery is 'only' 75% (Bland, 2007). The outcome of surgical decompression for other neuropathies is also suboptimal (e.g., cervical radiculopathy (Nikolaidis et al., 2010), lumbar radiculopathy (Ronnberg et al., 2007)).

☆ This work is attributed to the University of Queensland (for address see a).

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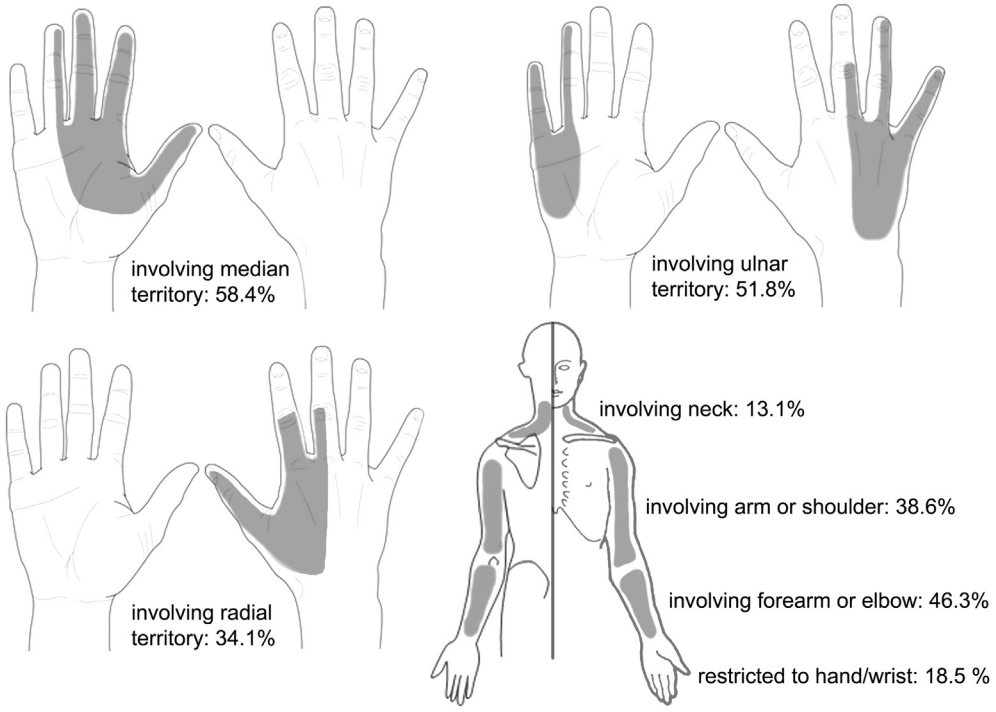

Fig. 1. Frequency of symptoms in median and extramedian territories in patients with carpal tunnel syndrome. Image incorporates data by Nora et al. (2004).

Symptoms outside the innervation area may be referred from associated structural lesions, such as the intervertebral disc or facet joints in radiculopathy, or rheumatoid arthritis in carpal tunnel syndrome. Furthermore, postural changes may strain other musculoskeletal tissues such as the identified forward head posture in patients with carpal tunnel syndrome (De la Llave-Rincon et al., 2009). However, these processes cannot account for all widespread and contralateral symptoms observed in many patients with entrapment neuropathies. Many of these signs and symptoms may be attributed to pathological processes proximal to the lesion site, such as, in the dorsal root ganglion (DRG) or central nervous system. The following section will discuss recent discoveries in this area to better understand the clinical presentation of patients with entrapment neuropathies.

2. Mechanisms – recent discoveries explaining spread of symptoms

Many mechanisms which explain spread of symptoms have been identified in animal models of severe nerve injury (for review see Woolf, 2004). These severe nerve injuries are however not representative for many commonly encountered human entrapment neuropathies, and extrapolations should be made cautiously. Here, we will focus mainly on those mechanisms identified in patients with neuropathies or in animal models that more closely mimic human entrapment neuropathies (Fig. 2).

2.1. Local mechanisms

In the last decade, neuroinflammation has gained considerable interest in the field of neuropathic pain (for review see Moalem and Tracey, 2006; Thacker et al., 2007). There is ample evidence from animal models of peripheral nerve injuries that immune cells, such as macrophages and T-lymphocytes, are recruited to the injury site (Mueller et al., 2003; Moalem et al., 2004) (Table 1, Fig. 3). These cells release inflammatory mediators, such as cytokines, which lower the firing threshold and induce ectopic activity of both mechanosensitive and nociceptive neurons (Sorkin et al., 1997; Grossmann et al., 2009).

Most animal models used to study neuroinflammation cause extensive axonal loss (Basbaum et al., 1991; Hu et al., 2007) and, as mentioned above, are therefore not representative of entrapment neuropathies commonly encountered in the clinic. We have however recently shown that even mild nerve compression is sufficient to induce intraneural inflammation, which is associated with neuropathic pain behaviour (Schmid et al., 2013). Intraneural inflammation is therefore a plausible explanation for the presence of hyperalgesia, both locally and in the affected nerve territory. However, local neuroinflammation may not explain most extraterritorial symptoms.

2.2. Neuroinflammation in the dorsal root ganglia and spinal cord

Following peripheral nerve injury, there is an invasion and activation of macrophages, T-lymphocytes and satellite glial cells in the DRG (Hu and McLachlan, 2002; Hu et al., 2007; Schmid et al., 2013) (Fig. 4). Inflammatory mediators released from these immune cells may result in ectopic activity of DRG neurones (Schafers et al., 2008; Schmid et al., 2013). Given the close proximity of cell bodies from different peripheral nerves within a DRG, neuroinflammation around affected DRG neurons may also alter the firing threshold of adjacent intact neurones originating from different sites. Therefore, neuroinflammation in the dorsal root ganglia (DRGs) is a plausible explanation for the clinically observed spread of symptoms to extraterritorial areas. For example, tarsal tunnel syndrome may induce neuroinflammation in the L4 DRG, which may lower the firing threshold not only of tibial nerve neurones, but also of the fibular and femoral nerve neurones. As a consequence, symptoms and hypersensitivity may occur in other areas than those innervated by the entrapped tibial nerve at the ankle.

Neuroinflammation after severe peripheral nerve injury also occurs at the level of the spinal cord. T-lymphocytes and glial cells

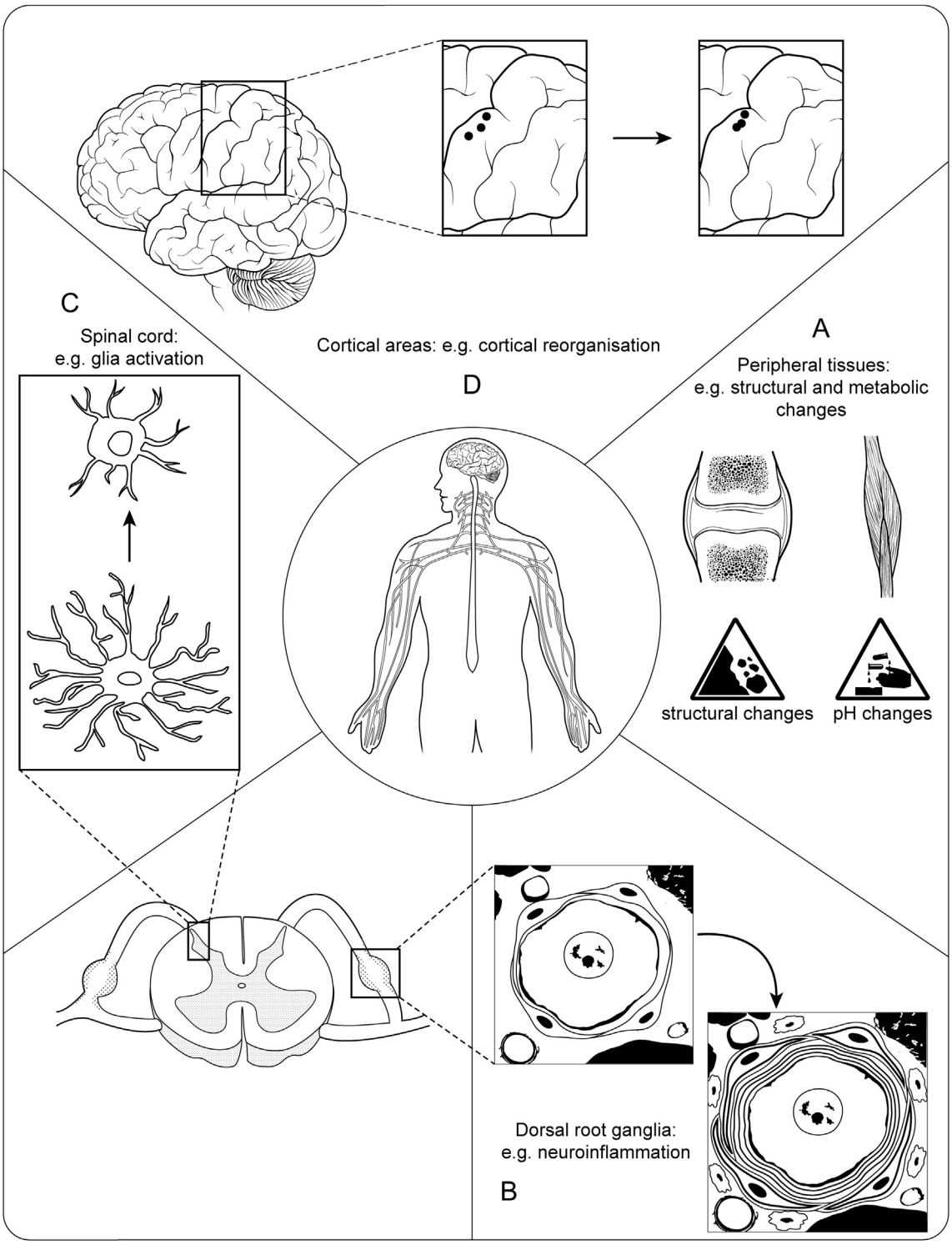

Fig. 2. Mechanisms that may account for widespread signs and symptoms in entrapment neuropathies. (A) Changes in peripheral musculoskeletal structures that contribute to or are initiated by peripheral entrapment neuropathies. Examples are structural changes of facet joints associated with radiculopathies or ischaemic changes in muscles associated with postural changes. (B) Changes at the level of the dorsal root ganglia. These may include proliferation of satellite glial cells, apparent by the formation of multilayer rings around sensory nerve cell bodies. Furthermore, immune cells such as macrophages may become activated and increase in numbers. (C) Changes at the level of the spinal cord. These may include activation of microglial cells apparent by their phenotypic change into larger cell bodies with shortened and thickened processes. (D) Changes in cortical areas. These may include reorganisation of the somatosensory cortex such as the identified shift of finger representation in patients with carpal tunnel syndrome (Napadow et al., 2006).

start to release various inflammatory mediators (for review see Watkins and Maier, 2002). Since incoming primary afferents ascend or descend several segments when entering the spinal cord before they synapse in the dorsal horn (Cervero et al., 1979), an inflammatory response in the spinal cord may lower the firing thresholds of sensory fibres in a multi-segmental manner.

Interestingly, neuroinflammation after severe unilateral peripheral nerve injury also occurs in the DRGs and spinal cord on the

Table 1
Overview of the role of the most common immune cells and immune competent cells after peripheral nerve injury.

	Cell type	Role after peripheral nerve injury
Neutrophils	Leukocytes	Acute local immune response. Phagocytic function and secretion of inflammatory mediators (e.g., TNF, IL-1β, IL-2 and IL-6) that attract other immune cells.
Mast cells		Acute local immune response. Secretion of mediators, which sensitise nociceptors (e.g. histamine, TNF) or directly activate them (e.g. serotonin). Recruitment of other immune cells.
Macrophages	Leukocytes	Acute and chronic immune response. Phagocytosis and antigen presentation to other immune cells. Secretion of mediators that sensitise nociceptors or attract other immune cells (e.g., prostaglandins, IL1β, IL-6, IL12, TNF and reactive oxygen species).
T-lymphocytes	Leukocytes	Acute and chronic immune response. Destruction of pathogens or cells directly or by secreting cytokines (e.g. IL-1β, IL-2 and TNF or IL-4, IL-5, IL-10). Activation of other immune cells (e.g., B-cells, macrophages and other leukocytes).
Schwann cells	Glial cells of the peripheral nervous system	Secretion of nerve growth factors, proinflammatory cytokines (e.g. IL-1, IL-6, IL-8) as well as prostaglandins and ATP which can directly sensitise nociceptors. Recruitment of other immune cells and presentation of antigens.
Satellite glial cells	Glial cells in the DRGs	Secretion of cytokines and chemokines (e.g. IL-1β, TNF) that increase ectopic firing of neurones
Astrocytes	Glial cells in the central nervous system	Release of substances (ATP, nitric oxide, IL-1β, TNF and IL-6), which modulate the firing threshold of neurons. Facilitation of synaptic transmission and communication with other immune cells.
Microglia	Glial cells in the central nervous system	Tissue repair by phagocytosing cellular debris and pathogens. Communication with neurones and immune cells, release of several neuro-active mediators including cytokines, chemokines and growth factors.

TNF: tumour necrosis factor; IL: interleukins; ATP: adenosine triphosphate.

contralateral side (Koltzenburg et al., 1999; Jancalek et al., 2010). This may be one of several factors explaining bilateral symptoms in patients with a unilateral entrapment neuropathy such as carpal tunnel syndrome. However, substantial axonal loss seems necessary to induce such changes (Schmid et al., 2013).

2.3. Mechanisms at subcortical and cortical levels

There is preliminary evidence that severe peripheral nerve injuries induce a glial cell reaction in higher pain centres, such as in the midbrain (Mor et al., 2010) or the thalamus (LeBlanc et al., 2011). Changes at these sensory relay centres could explain widespread symptoms, even in another quadrant. It remains to be explored whether inflammatory changes are present at these higher levels in mild nerve compression.

Functional changes at cortical or subcortical levels have already been demonstrated in patients with entrapment neuropathies. For instance, left/right recognition of the affected body part is impaired in patients with carpal tunnel syndrome (Schmid and Coppieters, 2011) and possibly cervical radiculopathy (Coslett et al., 2010). Since this task activates similar brain areas as imagined and executed movements (Michelon et al., 2006), accurate performance is thought to depend on the integrity of the body's representation in cortical and subcortical areas (Schwoebel et al., 2002). Furthermore, there is emerging evidence for reorganisation of the somatosensory cortex in patients with entrapment neuropathies. In

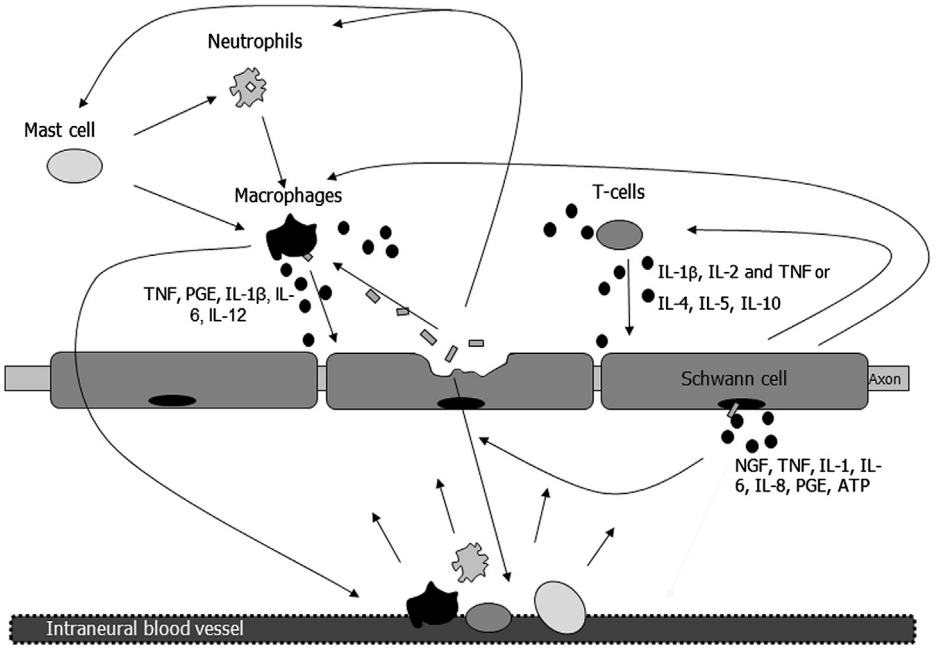

Fig. 3. Activation of immune and inflammatory cells at the site of a peripheral nerve injury. A peripheral nerve lesion leads to an early activation of mast cells and neutrophils, which release chemicals that activate resident macrophages. The macrophages phagocytose axonal or myelin debris and secrete proinflammatory substances that sensitise axons or attract other immune cells. A breakdown of the blood nerve barrier by physical damage or substances released by immune cells leads to an additional influx of blood-borne immune cells. Schwann cells also ingest myelin and subsequently release proinflammatory chemicals. Both Schwann cells and macrophages signal T-cells, some of which will also secrete inflammatory chemicals. This complex cascade with activation of the innate and adaptive immune system leads to a local inflammatory environment that lowers the firing threshold of axons and contributes to neuropathic pain. TNF: tumour necrosis factor; PGE: prostaglandin; IL: interleukin; NGF: nerve growth factor; ATP: adenosine triphosphate.

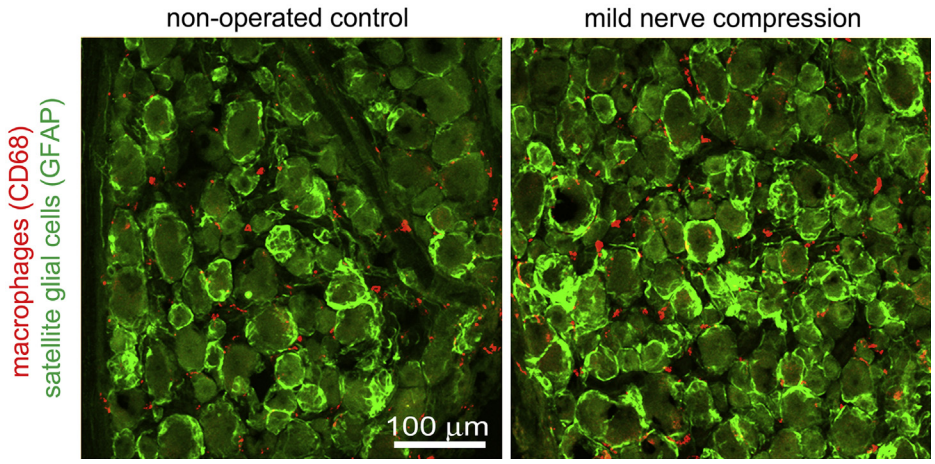

Fig. 4. Neuroinflammation at the level of the dorsal root ganglia (DRGs) in a rat model of mild nerve compression. Longitudinal section through an intact, non-operated (left) DRG at the level L5 and a DRG that receives afferents from a mildly compressed sciatic nerve (right). Satellite glial cells are stained with glial fibrillary acid protein (GFAP) in green. A higher staining intensity and the formation of some $GFAP^{+}$ rings around some neurone cell bodies are visible after mild nerve compression. This indicates activation of satellite glial cells. Macrophages are stained in red with a CD68 antibody. A slight upregulation in numbers of positively stained macrophages is visible in the DRG after mild nerve compression. Calibration applies throughout. Image incorporates findings from Schmid et al. (2013).

carpal tunnel syndrome for instance, both a more extended representation of the fingers innervated by the median nerve (Napadow et al., 2006, 2007), as well as a decreased representation (Druschky et al., 2000) have been reported. Potentially, a differential effect of paraesthesia and pain on cortical reorganisation may explain these conflicting findings (Tecchio et al., 2002). Although further research into the effect of entrapment neuropathies on cortical and subcortical areas is needed, such changes may contribute to extraterritorial or contralateral spread of symptoms.

3. Diagnosis

Considering the various mechanisms mentioned above and that the dominant mechanism is likely to vary between patients, it is logical that there are no universally accepted criteria (or gold) standards to diagnose neuropathies. Diagnostic accuracy studies for neuropathies therefore reflect the strength of the correlation between a test and an imperfect criterion standard, rather than the test's true ability to detect a neuropathy. Consequently, providing an overview of the sensitivity, specificity, and likelihood ratios for tests to diagnose entrapment neuropathies is not within the scope of this Masterclass. Detailed overviews can be found elsewhere (e.g., carpal tunnel syndrome (MacDermid and Wessel, 2004), cervical radiculopathy (Rubinstein et al., 2007), lumbar radiculopathy (van der Windt et al., 2010). Rather, this section will focus on how different diagnostic tests may inform a clinician about potential mechanisms involved in an individual patient.

Symptoms and signs in neuropathies can be classified as gain or loss of function. Gain of function, such as paraesthesia, spontaneous pain, hyperalgesia and allodynia, reflects abnormal excitability or reduced inhibition in the nervous system. Loss of function, such as hypoesthesia or anaesthesia, indicates reduced impulse conduction along the nervous system (Woolf, 2004). Mechanisms already mentioned above that may result in loss of function are axonal loss or demyelination (e.g., numbness). However, demyelination may also induce gain of function (e.g., paraesthesia). Neuroinflammation at various levels in the nervous system is mainly associated with hypersensitivity of neurones, resulting in gain of function.

Interpretation of clinical tests and technical investigations for neuropathies in the context of gain and loss of function may assist in the identification of underlying mechanisms. Electrodiagnostic testing for instance provides important information on loss of function in large myelinated motor neurons and Aβ fibres. Whereas these are believed to be primarily affected in entrapment neuropathies (Mackinnon, 2002), recent evidence suggests that small axon loss is common (e.g., cervical (Chien et al., 2008) and lumbar radiculopathy (Nygaard and Mellgren, 1998) and carpal tunnel syndrome (Lang et al., 1995; Wilder-Smith et al., 2003; Schmid et al., 2012b) and may occur even before dysfunction of large axons becomes apparent (Tsuboya et al., 2007; Tamburin et al., 2010; Schmid et al., 2013)) (Fig. 5). Clinical reliance on electrodiagnostic testing in isolation may however not only be insufficient since it does not provide any information about the integrity of the thinly myelinated or unmyelinated fibres (e.g., Aδ and C-fibres) (Mallik and Weir, 2005) but also since it only tests loss of function.

Quantitative sensory testing (QST) protocols are designed to assess both loss and gain of function, in small and large diameter nerve fibres. Commonly performed protocols include tests to determine a deterioration in thermal and mechanical detection thresholds (loss of function) or lowered pain thresholds (gain of function) (Rolke et al., 2006). Certain loss of function tests may indicate which type of nerve fibre might be involved. For instance, elevated vibration and von Frey monofilament detection thresholds suggest demyelination or dysfunction of the Aβ fibres. Altered cold and warm detection thresholds may indicate Aδ and C-fibre dysfunction, respectively (Rolke et al., 2006). In contrast, the presence of gain of function (lowered pain thresholds) indicates neuronal hyperexcitability. Extraterritorial gain of function (Chien et al., 2008; Schmid et al., 2012b), allodynia upon stimulation with a brush or cotton wool tip (Treede et al., 2004), paradoxical heat sensations and pain exacerbation following repetitive stimuli as compared to a single stimulus (wind-up like pain) (Rolke et al., 2006) are indicative of central mechanisms.

QST has merit in identifying nerve fibre function, but its applicability to individual patients is still limited to those body areas with available reference values (Rolke et al., 2006). QST is often considered too time consuming to be integrated in routine clinical evaluations and the expensive equipment is not widely available to clinicians. Certain tests of the standardised QST battery may however be performed by clinicians without costly equipment. Hypersensitivity to mechanical pin prick (without quantification) and wind-up can be evaluated with a tooth pick. Tests for allodynia

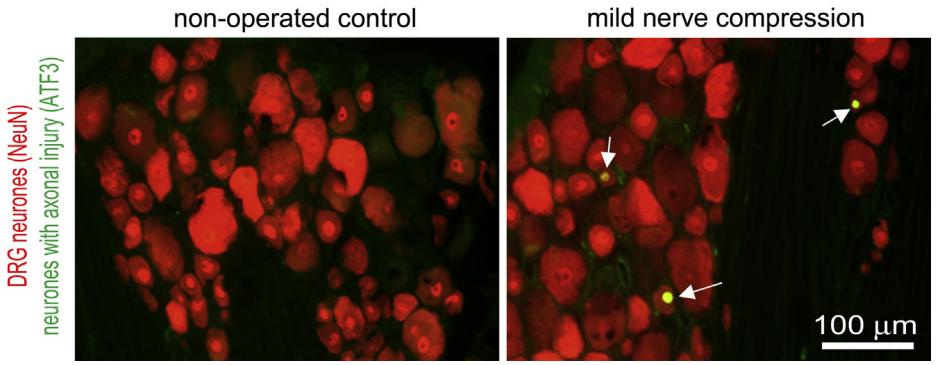

Fig. 5. Preferential small axon damage after mild peripheral nerve compression in rats. The figure shows longitudinal sections through rat L5 DRG. Neuronal cell bodies are stained with neuronal nuclei stain (red). Cell bodies with damaged axons are stained with activating transcription factor 3 (ATF3, green), a marker for axotomised neurones. Whereas no damaged neurones are present in a non-operated control DRG (left), the marker for damaged neurones is preferentially found in neurones with small diameter, most likely representing unmyelinated C-fibres or small myelinated Aδ fibres. Calibration applies throughout. Image incorporates findings from Schmid et al. (2013).

can be mimicked with a paint brush or cotton wool tip. Although not tested in entrapment neuropathies as yet, the pain intensity during ice pack application can identify cold hyperalgesia in patients with whiplash associated disorders (Maxwell and Sterling, 2012).

Traditional clinical tests can also be interpreted in terms of gain and loss of function (see Table 2). Loss of function is detected during the bedside neurological examination (reduced power, reflexes or sensation). Typical signs for gain of function are the provocation of paraesthesia or pain during Tinel's sign (ectopic activity), palpation, neurodynamic tests or Spurling's test. As gain of function is often widespread, clinicians should consider using these tests in extra-territorial areas.

Whereas the tests above focus on the function of the nervous system, its structure can also be examined using standard imaging methods (e.g., ultrasound, magnetic resonance imaging (MRI)) or skin biopsies to quantify nerve fibre density (Myers and Peltier, 2013). Skin biopsies are a valuable technique which can provide a unique insight into the structural integrity of both unmyelinated and myelinated nerve fibres, but is also not yet routinely available clinically and is (minimally) invasive.

A combination of clinical presentation, clinical tests and technical investigations is typically considered the optimal diagnostic approach (Rempel et al., 1998). However, currently identified test clusters (Wainner et al., 2003, 2005) need to be validated and new clusters need to be developed that incorporate items capable of delineating the variety of mechanisms involved in a particular neuropathy. Preliminary attempts have been made to identify signs and symptoms suggestive of peripheral neuropathic pain and central sensitisation (Smart et al., 2010). It is unknown however whether these characteristics accurately reflect the underlying pathobiological mechanisms or simply represent a consensus adopted by clinicians.

4. Management

Several recent reviews summarised the effects of conservative treatments for carpal tunnel syndrome (e.g., Page et al., 2012), cervical radiculopathy (e.g., Thoomes et al., 2013), and lumbar radiculopathy (e.g., Chou et al., 2009). The lack of high-level evidence means that no strong treatment recommendations can be made. In line with the approach of this Masterclass, rather than summarising recommendations based on relatively weak evidence, this section will discuss how various treatments may influence some of the above-mentioned mechanisms involved in entrapment neuropathies. Treatments evaluated in patients with neuropathies or in animal models of neuropathic pain will be emphasised. Obviously, the ability to influence pathological processes alone does not prove clinical efficacy. However, considering the wide variety of treatments suggested for neuropathies and the high cost of clinical trials, an appraisal of how treatments may influence specific mechanisms seems warranted.

Table 2
Clinical tests and technical investigations commonly used in entrapment neuropathies and their main findings in the context of loss and gain of function.

	Gain of function	Loss of function	Structure
Electrodiagnostic tests		Conduction slowing, increased latencies, decreased amplitudes	
Bedside neurological examination	Hyperreflexia, muscle spasm, dystonia, clonus, allodynia, hyperalgesia	Weaker/absent reflexes, muscle weakness, reduced sensation	
Quantitative sensory tests	Lowered pain thresholds: hyperalgesia, wind up, allodynia	Elevated detection thresholds: hypoaesthesia, anaesthesia	
Neurodynamic tests	Increased neural mechanosensitivity and ectopic impulse generation		
Palpation (neural and non-neural structures)	Increased mechanosensitivity		Tissue condition (e.g., swelling, thickening)
Tinel's sign	Increased neural mechanosensitivity and ectopic impulse generation		
Neural compression tests (e.g., Spurling's, Phalens test)	Increased neural mechanosensitivity and ectopic impulse generation		
Imaging methods (ultrasound, MRI, etc)			E.g., increased nerve signal intensity, increased cross sectional area, nerve flattening

Various central nervous system processes, including sensitisation through neuroinflammation, are triggered by aberrant peripheral input (Devor, 2009; Suter et al., 2009). Furthermore, considering the immediate – albeit short term – relief following a local cortisone injection in ~70% of patients with carpal tunnel syndrome (Bland, 2007), attenuation of ongoing peripheral input into the central nervous system is an important goal in the management of entrapment neuropathies in order to prevent or diminish central modulation. Recent practice surveys (Coppieters and Soon, 2013; Nee et al., 2013) revealed the most common modalities used by hand therapists and musculoskeletal physiotherapists to manage carpal tunnel syndrome (Table 3) and cervical radiculopathy (Table 4), respectively. Typical management strategies include explanation and education, postural and ergonomic advice, joint mobilisation, soft tissue techniques, neural mobilisation and exercise.

Accessory and physiological joint mobilisations and manipulations are commonly performed in patients with neuropathies (Coppieters and Soon, 2013; Nee et al., 2013). These techniques may facilitate the descending pain inhibitory system (for review see Vicenzino et al., 2007; Bialosky et al., 2009a). At a peripheral level, mobilisation may disperse and therefore dilute the concentration of chemical mediators that trigger ectopic firing. Following the injection of inflammatory mediators around the L5 DRG in rats, Song et al. (2006) demonstrated that spinal manipulation reduced inflammation and hyperexcitibility of the DRG neurons, which was accompanied by a reduction of thermal and mechanical hyperalgesia. Similarly, peripheral joint mobilisation in rats produced an anti-hyperalgesic effect in conjunction with a normalisation of glia activation in the dorsal horn of the spinal cord (Martins et al., 2011).

Neurodynamic mobilisations (or nerve gliding exercises) are also frequently applied in various neuropathies (Coppieters and Soon, 2013). A recent MRI study in patients with carpal tunnel syndrome revealed a decrease of intraneural oedema (a clinical correlate of neuroinflammation) following one week of nerve and tendon gliding exercises, which was not observed in a control group who received advice to remain active (Schmid et al., 2012a). This study illustrates that gentle mobilisation of a nerve and surrounding structures does not aggravate the inflammatory process, but rather reduces oedema. Although the oedema reduction was not superior to splinting, considering the other benefits of movement, there are various situations when gentle exercises aimed at mobilisation of the nerve and surrounding structures may be preferred over partial immobilisation. Nerve and tendon gliding exercises also resulted in an immediate and substantial reduction in carpal tunnel pressure in a subgroup of patients with carpal tunnel syndrome (Coppieters, 2012; Schmid, 2013).

There is also preliminary evidence that neurodynamic exercises have an effect on central mechanisms. Movements of the wrist in an arm position that elongate the length of the median nerve bedding reduced temporal summation (a clinical correlate of increased excitability of spinal dorsal horn neurones) in patients with carpal tunnel syndrome (Bialosky et al., 2009b). Additionally, a recent study in rats with a severe peripheral nerve injury showed that passive neurodynamic exercises are capable of reducing nociceptive behaviour in combination with a normalisation of the satellite glial cell response in the DRGs and astrocyte response in the spinal cord (Santos et al., 2012).

Table 3
Most frequently employed modalities by hand therapists in the management of carpal tunnel syndrome.

Explanation and advice
Splinting
Ergonomic and postural advice
Nerve gliding exercises
Tendon gliding exercises
Active exercises for wrist and fingers
Stretching of the forearm muscles
Strengthening exercises for the hand muscles
Prescription of home exercise program

Table 4
Most frequently employed modalities by musculoskeletal physiotherapists in the management of cervical radiculopathy (ROM: range of motion).

Explanation and advice
Exercise (motor control, muscle strength & endurance, ROM)
Passive mobilisation (but not manipulation)
Nerve gliding exercises
Stretching (neck and shoulder musculature)
Taping (neck and shoulder)
More heat than cold
Manual traction (but not mechanical or 'home' traction)
Prescription of home exercise program

Although not identified as a common treatment modality in recent physiotherapy practice surveys, animal research suggests that aerobic physical exercise may positively influence neuropathic pain processes. Swimming and treadmill exercise decreased the overproduction of pro-inflammatory cytokines (tumour necrosis factor (TNF) and interleukin 1β (IL-1β)) (Chen et al., 2012), and reduced mechanical and cold allodynia, and thermal hyperalgesia (Kuphal et al., 2007; Shen et al., 2013) in rats with a partial peripheral nerve injury or a constricted sciatic nerve. Future studies are required, but progressive exercise may prove to be a safe and cost-effective therapy in a variety of neuropathic pain states (Shen et al., 2013).

When the clinical reasoning process suggests the predominant involvement of important central processes, many other treatment strategies may be worthwhile to consider. The central mechanisms mentioned above are not unique to patients with entrapment neuropathies. Sensory discrimination training, graded motor imagery (GMI), neuroscience education, and cognitive behavioural therapy (CBT) have been proven beneficial to primarily influence these central mechanisms in other diagnoses and may be plausible interventions for patients with entrapment neuropathies.

Sensory discrimination training can reduce pain in patients with phantom limb pain (Flor et al., 2001) and complex regional pain syndrome (Moseley et al., 2008), and this hypoalgesia is also associated with reductions in cortical reorganisation (Flor et al., 2001; Maihofner et al., 2004).

GMI involves the specific sequence of left/right discrimination training, motor imagery exercises and mirror therapy (Moseley and Flor, 2012) and appears to be effective for patients with phantom limb pain and complex regional pain syndrome (Bowering et al., 2013).

The goals of neuroscience education (i.e., education about the neurophysiological mechanisms related to a patient's pain experience) and CBT are to help the individual gain a sense of control over pain and initiate behaviours that can improve function (Waters et al., 2007; Moseley and Flor, 2012). Theoretically, a better understanding of pain mechanisms and the use of pain-related coping strategies and appropriate pacing to gradually increase activity levels without flare-ups can reduce the threat value of the pain experience and reduce the hypersensitivity of the central nervous system (Moseley, 2003). Neuroscience education (Louw et al., 2011) and CBT (Linton and Ryberg, 2001; Sveinsdottir et al., 2012; Williams et al., 2012) can be effective for persistent pain conditions that are associated with central sensitisation.

Since neuroinflammation seems to be triggered and dependent on the extent of the compression, it may be beneficial to combine interventions that prevent compression and restore

normal movement with anti-inflammatory treatments. However, the evidence for drug treatment in patients with entrapment syndromes is sparse. Whereas corticosteroids and oral or topically applied non-steroidal anti-inflammatory drugs have a beneficial short term effect in neuropathies, there is no evidence for a superior effect over placebo in the long term (Marshall et al., 2007; Benoist et al., 2012). Unfortunately, there is evidence for inefficacy or only slight effectiveness for drugs commonly used to treat neuropathic pain, such as anticonvulsants (e.g. pregabalin), tricyclic antidepressants, opioids and their combination in patients with radiculopathies (Attal et al., 2010). Only recently have drugs that target neuroinflammation been trialled in patients with entrapment syndromes. Whereas a TNF-α blocker does not seem to be superior to placebo (Cohen et al., 2009), Dilmapimod, which is a cytokine suppressive drug, significantly reduced pain in patients with carpal tunnel syndrome, lumbar radiculopathy and neuropathic pain after nerve trauma (Anand et al., 2011). Larger scale trials are needed to confirm beneficial effects of drugs that target neuroinflammation in patients with nerve entrapments.

5. Conclusions

Patients with entrapment neuropathies often present with symptoms outside the innervation area. We have outlined that mechanisms in the DRG or central nervous system may underlie extraterritorial symptoms. The involvement of such remote mechanisms is characterised by the presence of gain of function in a widespread manner. In the clinical examination, tests identifying gain of function in the affected nerve territory but most importantly in extraterritorial areas have therefore the potential to identify these remote mechanisms. A better understanding of the mechanisms involved in each patient may ultimately result in a more targeted therapeutic approach.

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