Editorial: Peripheral nerve anatomy in health and disease

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acetylcholine receptor (AChR), amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth disease (CMT), dorsal root ganglion (DRG), ganglioside, glia, motor neuron, neuromuscular junction (NMJ), node or Ranvier, Schwann cell, sensory neuron.

The nervous system contains some of the most specialised, polarised and rapidly responsive cells in the body. This is best exemplified by the motor and sensory neurons, which possess axons that can reach lengths of over a meter in humans, yet can transmit electrical signals across this distance in only a few hundredths of a second. Having these extreme cellular extensions that can be more than six orders of magnitude longer than their cell bodies, puts a great strain on the neurons of the peripheral nervous system (PNS). Indeed, the efficient and repetitive propagation of unidirectional electrical signals (Purves et al. 2001), the long-range bidirectional delivery of cargoes between the cell body and axon terminals (Sleigh et al. 2019), and the local translation of crucial axonal transcripts (Dalla Costa et al. 2021) are but a few of the cellular processes at particular risk in cells with such extended morphology.

Accordingly, neurons in the somatic division of the PNS are the primary site of pathology in many neurodevelopmental and neurodegenerative conditions, including amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth disease (CMT) and spinal muscular atrophy (SMA). Additionally, given that they predominantly reside outside the central nervous system (CNS) and away from the protection of the blood-brain barrier, motor and sensory nerves are particularly sensitive to toxic substances, such as chemotherapeutics (Boyette-Davis et al. 2018), and they can provide an efficient conduit to the CNS for viruses and neurotoxins (Surana et al. 2018; Tosolini & Sleigh 2020). Moreover, key components of the PNS are targeted in several different autoimmune disorders, including axonal and glial gangliosides in Guillan-Barré syndrome (GBS) (Willison et al. 2016) and neuromuscular synaptic proteins in myasthenia gravis (Lang & Vincent 2009).

Nevertheless, peripheral nerve subtypes are rarely equally impacted by pathology. For instance, large, fast-firing alpha motor neurons are most susceptible to ALS (Nijssen et al. 2017), not all

sensory modalities are necessarily affected in CMT (Gemignani et al. 2004), and SMA patients display greater weakness in proximal than distal muscles (Mercuri et al. 2022). This is almost certainly a product of fundamental morphological, molecular, and cellular distinctions in subclasses of motor and sensory neurons, as well as their supporting glia and target cells/tissues. However, the exact causes for disease-specific vulnerability-resistance axes remain largely unresolved. Fortunately, peripheral nerve diversity is being revealed by careful comparative molecular and anatomical studies in both animal models and humans (Usoskin et al. 2015; Blum et al. 2021; Nguyen et al. 2021; Yadav et al. 2022). Moreover, this is being complemented by neuropathological assessments across an ever-expanding arsenal of disease models (Nair et al. 2019; Devoy et al. 2021).

To showcase some of the breadth and depth in anatomical studies of the PNS, we have compiled this Special Collection of articles on peripheral nerve anatomy in health and disease, concentrating on the somatic nervous system (**Figure 1**). We present 12 publications with a focus on comparative assessment of peripheral nerve development and structure, in order to better understand neuronal homeostasis, as well as dysfunction in disease. We begin with motor neurons and the motor unit, transition into sensory neurons, and conclude with glial cells of the PNS.

The neuromuscular junction (NMJ) is the specialised synaptic contact formed between a distal terminal of a lower motor neuron and a muscle fibre. Action potentials arriving at the motor nerve terminal trigger release of the excitatory neurotransmitter acetylcholine (ACh), which diffuses across the synaptic cleft, binds to post-synaptic ACh receptors (AChRs) in the muscle membrane, ultimately eliciting muscle contraction. When motor neurons begin to deteriorate in peripheral nerve disorders, the NMJ has been identified as an early site of morphological

disruption. This has led to the generation of a “dying-back” hypothesis in ALS, positing that motor neuron degeneration is initiated at the NMJ and progresses in a distal-to-proximal fashion along the axon, prior to cell death (Dadon-Nachum et al. 2011). In this Collection, Alhindi et al. assess the evidence for the temporal disruption of motor neuron health in mouse models of ALS (Alhindi et al. 2022). By evaluating reported motor neuropathologies, it was identified that disturbed NMJ connectivity commonly precedes spinal cord motor neuron loss in mutant *SOD1*, *TARDBP* (TDP-43) and *FUS* mice. Thus, the NMJ is an early site of motor neuron degeneration that could be therapeutically targeted as part of a combinatorial strategy for treating ALS.

While gauging NMJ disruption, Alhindi et al. exposed the breadth of different muscles analysed across ALS mice. Since muscles and their innervating motor neurons can display large differences in neuropathology both in human disease and model mice (Murray et al. 2008; Liu et al. 2013; Sleigh et al. 2014), it is important that comparative morphological studies across several muscles are conducted to get an improved understanding of selective motor neuron vulnerability. This knowledge may then be harnessed to identify therapeutically-targetable contributors to disease (Boyd et al. 2017; Kline et al. 2017; Sleigh et al. 2020a). To aid in this endeavour, Villarroel-Campos et al. provide a step-by-step protocol for the dissection and intravital imaging of the mouse epitrochleoanconeus (ETA) muscle, along with baseline data on fibre type composition (Villarroel-Campos et al. 2022). The ETA is a thin muscle found in the proximal forelimb that can be wholemount processed and imaged, which facilitates accurate and detailed morphological analyses of the neuromuscular system. The simple and rapid ETA dissection method will enable more varied assessments of rodent muscles to elucidate motor neuron vulnerability-resistance spectra in disease.

Much of what we know about the mammalian NMJ has been garnered through analyses of rodent muscles, resulting in part from the prevalence of laboratories working with mice and rats, combined with a relative paucity of large mammalian models due to time, financial and ethical constraints. However, it is becoming evident that, although they function in a similar manner, rodent neuromuscular synapses are not only architecturally distinct from their human counterparts, but they also display more pronounced and rapid age-related changes (Jones et al. 2017; Alhindi et al. 2021). That is not to say that the study of rodent neuromuscular synapses is not of high importance, rather that the identification of mammalian species with morphologically similar NMJs to humans will provide more physiologically-relevant neuromuscular models for testing of pre-clinical therapeutics (Boehm et al. 2020). In a review discussing this important issue, Cahalan et al. present an overview of heterogeneity at the mammalian NMJ and probe evolutionary relationships between key species for similarities and differences in pre- and post-synaptic morphology (Cahalan et al. 2022a). In addition, conditions afflicting the PNS of large mammals are highlighted, as are the translational benefits of scrutinising the NMJ across species.

In light of the importance of examining a range of models, in a second study, Cahalan et al. present techniques for the regional dissection of equine muscles with subsequent immunohistochemical staining to identify and morphologically assess NMJs (Cahalan et al. 2022b). Larger animals generally have larger muscles, which often require sectioning for neuromuscular analyses. Through adapting a fibre-teasing approach, Cahalan et al. (2022b) avoid the necessity for sectioning, thereby reducing potential artefacts caused by muscle cutting. Combined with the ImageJ-based platform NMJ-morph (Jones et al. 2016), the techniques were used on several different distal pelvic-limb muscles from ponies and identified considerable variation in neuronal and endplate morphology between muscles. Furthermore,

pony NMJ architecture was revealed to be similar to that of humans, with endplates displaying a 'nummular' (*i.e.*, coin-shaped) appearance, suggesting that this large mammalian species may provide more relevant insight into the human NMJ than rodents.

During early post-natal development, work primarily performed in rodents indicates that the mammalian NMJ undergoes a well-characterised series of morphological alterations that mould the neuromuscular architecture to better suit the environment experienced after birth (Sanes & Lichtman 1999). For instance, post-synaptic endplates are initially contacted by multiple motor neurons and through a process called synapse elimination they become mono-innervated. Mirroring this maturation, post-synaptic AChR clusters transition from simple, circular structures, often described as being "plaque-like", to more complex, branched, "pretzel-like" assemblies, as the post-synaptic membrane invaginates and the receptors migrate to closely appose the overlying motor neuron (Marques et al. 2000). However, the molecular mechanisms driving these structural alterations at the NMJ have not been fully clarified. In a review of post-synaptic NMJ maturation, Medina-Moreno & Henríquez discuss the importance of local actin re-arrangement in determining areas of low AChR density to aid plaque-to-pretzel endplate transition (Medina-Moreno & Henríquez 2022). Furthermore, small Rho GTPases were highlighted to play a critical role in regulating AChR cluster stability; thus, it is proposed that small Rho GTPases enable assembly of structures akin to actin-rich scaffolds called podosomes to facilitate post-synaptic NMJ maturation.

Neuromuscular morphology not only changes during early post-natal development, but also throughout life in response to environmental triggers. For instance, in muscles, exercise can induce vascular bed expansion, increase fibre size, and alter fibre type proportions, contributing to greater functional capacity (Schiaffino & Reggiani 2011). Electrophysiological and

morphological adaptations must also occur in motor neurons to ensure their properties match the muscle fibres they innervate for performance optimisation (Stifani 2014). To evaluate adaptations in motor neuron size and the abundance of C-boutons, which are neuromodulatory synapses on motor neuron cell bodies that amplify motor output (Deardorff et al. 2014), Kissane et al. used a rat model of functional overload in which removal of tibialis anterior muscle increases demand on the synergistic extensor digitorum longus (EDL) muscle (Kissane et al. 2022). After three weeks of overload, the EDL shifted to a slower, more aerobic identity, determined by having increased fatigue resistance and reduced force output, while the innervating motor neurons mirrored these changes by decreasing cell body area. Contrastingly, C-bouton size and number were unaffected, suggesting that plasticity of these excitatory synapses is not required to alter force output in response to chronic muscle overload.

Dominant intermediate CMT type C (DI-CMTC) is a genetic peripheral neuropathy caused by mutations in the *YARS1* gene, which encodes a tyrosine-charging tRNA synthetase (Jordanova et al. 2006). Patients display muscle weakness and wasting, as well as sensory dysfunction, predominantly in the hands and feet. Mutations in serine palmitoyltransferase-encoding *SPTLC1* cause hereditary sensory and autonomic neuropathy type 1 (HSAN1), which results in loss of pain and temperature sensation usually manifesting in the lower limbs during late adolescence (Bejaoui et al. 2001; Dawkins et al. 2001). To better understand the pathomechanisms underlying DI-CMTC and HSAN1, Hines et al. characterised two new mouse models for inherited peripheral neuropathy – $Yars^{E196K}$ and $Sptlc1^{C133W}$ (Hines et al. 2022). $Yars^{E196K}$ mice precisely recreate the human disease allele, but only displayed CMT-relevant phenotypes as homozygotes (e.g., reduced motor axon calibres), which does not replicate the heterozygous nature of human DI-CMTC. Contrastingly, $Sptlc1^{C133W}$ heterozygotes accurately model human HSAN1 genetics (homozygosity was lethal) and

displayed a relevant biochemical phenotype (*i.e.*, elevated toxic deoxysphingoid bases), but showed no axon loss or dysfunction. Nonetheless, these two mouse models recreate important aspects of their respective conditions, which if harnessed appropriately (Tadenev & Burgess 2019), will ensure that they are valuable additions for neuropathy research.

Sensory neurons represent a population of cells required for detecting and relaying innocuous and noxious external stimuli to the CNS. With cell bodies resident in dorsal root and trigeminal ganglia, pseudo-unipolar axons that project both to the spinal cord and to the periphery, and specialised axon terminals, sensory neurons are highly compartmentalised. Middleton et al. provide a thorough description of this structural organisation of sensory neurons and explain its importance to neuronal function (Middleton et al. 2022). Beginning with distal axon terminals (focusing on cutaneous afferents) and working back to the nodes of Ranvier, cell bodies and, finally, central projections into the spinal cord dorsal horn, key morphological features of each sub-cellular structure and how they drive function are detailed. Moreover, anatomical changes that occur due to nerve injury and their relationship with neuropathic pain (*i.e.*, resulting from nervous system damage or disease) are described.

Continuing the theme of using diverse models to study PNS function and dysfunction, Adalbert et al. describe experiments in which they dissociated and cultured primary sensory neurons from dorsal root ganglia (DRG) of adult horses (Adalbert et al. 2022). Mixed sensory neuronal populations were viable for at least three months and shown to develop long neurites, which were used to study mitochondrial morphology and trafficking. Mitochondria were smaller and transported more quickly in sensory projections than in supporting glial cells. Primary DRG cultures from horses will be a useful tool for studying the impact of several, prevalent equine peripheral nerve diseases (Cahalan et al. 2022a), and can be compared with cultures from

chickens (Powell et al. 2014), mice (Sleigh et al. 2020b) and dogs (Ganchingco et al. 2019), amongst others, to determine whether there are differences in basic cellular processes (e.g., axonal transport) between species.

For many years, neurons have been the primary focus of research on the nervous system, with glial cells being thought of as the sidekick, simply supporting their neuronal partners. However, it is becoming increasingly clear that glia are an equal, reciprocal companion and are essential for the development and function of the nervous system (Allen & Lyons 2018). The roles of glia include, delivery of trophic and metabolic support, provision of physical and electrical insulation, and coordination of the nerve injury response; however, their precise functions are situation- and location-dependent. Highlighting this, Reed et al. provide a comprehensive review of the underappreciated diversity of glial cell subtypes in the PNS (Reed et al. 2022). Through discussion of their developmental origin, morphology and function, a rich heterogeneity of peripheral glia are identified, including myelinating, Remak, and terminal Schwann cells, as well as lesser known counterparts, such as boundary cap-derived, perineurial, and satellite glia. Given that peripheral glial cells are the primary site of pathogenesis in several neurological disorders (e.g., CMT type 1) and contribute to others (e.g., ALS and SMA), it is vital that the complexity of glia-nerve interactions in the PNS becomes increasingly well understood.

Integral to this last point, a plethora of subtype-specific methods are required to elucidate glial cell function, and dysfunction in disease. Unfortunately, several types of peripheral glia are relatively understudied (e.g., perineural), especially compared to PNS neurons; nevertheless, varieties of Schwann cell have been the focus of intensive research since their initial description in the mid 19th century. Demonstrating this, Negro et al. have compiled a thorough review of

the wide-ranging *in vitro* and *in vivo* techniques and models available to study mammalian Schwann cell development, morphology and function (Negro et al. 2022). After outlining the importance of Schwann cells, descriptions of methods to study myelinating, non-myelinating (*i.e.*, Remak), and terminal Schwann cells are provided to guide those entering the Schwann cell field.

Gangliosides are sialic acid-containing glycosphingolipids found throughout the body, predominantly in plasma membranes. They are enriched in the CNS and PNS, both in glia and neurons, and they play important roles in neuronal development and homeostasis (Schnaar 2016). Mutations in ganglioside biosynthesis genes cause complex neurodevelopmental and neurodegenerative disorders (Sandhoff & Harzer 2013), while gangliosides themselves can act as receptors for autoantibodies, including those that cause the severe acute paralytic neuropathy GBS (Willison et al. 2016). In the final article of the Collection, McGonigal & Willison review the importance of gangliosides in the formation and organisation of the mammalian node of Ranvier, the specialised axonal domain found between myelin-forming cells that enables saltatory conduction (McGonigal & Willison 2022). After describing the network of gangliosides and other glycolipids at the node, the ramifications of widespread and tissue-specific ganglioside deficiencies in transgenic mice are examined, both in relation to ganglioside function and to the study of autoimmune-driven injury at the node of Ranvier.

In summary, improving our understanding of peripheral nerve anatomy, along with the temporal progression and selective susceptibility of sub-populations of peripheral nerves in disease models, will undoubtedly help to reveal major pathomechanisms underpinning these devastating disorders. This will require the study not only of motor and sensory neurons, but the wide array of cells essential to PNS development and function, including muscle fibre types

and the assortment of glia. By increasing knowledge of the cellular diversity of the PNS through careful anatomical and molecular work, we will develop a more holistic understanding of the nervous system that will aid the development of more targeted therapeutics for peripheral nerve disorders.

Competing Interests

The author has no competing interest to declare.

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References

Adalbert R, Cahalan SD, Hopkins EL, et al. (2022) Cultured dissociated primary dorsal root ganglion neurons from adult horses enable study of axonal transport. *J Anat.* in press https://doi.org/10.1111/joa.13719

Alhindi A, Boehm I, Forsythe RO, et al. (2021) Terminal Schwann cells at the human neuromuscular junction. *Brain Commun.* 3: fcab081. https://doi.org/10.1093/braincomms/fcab081

Alhindi A, Boehm I & Chaytow H (2022) Small junction, big problems: Neuromuscular junction pathology in mouse models of amyotrophic lateral sclerosis (ALS). *J Anat.* in press https://doi.org/10.1111/joa.13463

Allen NJ & Lyons DA (2018) Glia as architects of central nervous system formation and function. *Science* 362: 181–185. https://doi.org/10.1126/science.aat0473

Bejaoui K, Wu C, Scheffler MD, et al. (2001) *SPTLC1* is mutated in hereditary sensory neuropathy, type 1. *Nat. Genet.* 27: 261–262. https://doi.org/10.1038/85817

Blum JA, Klemm S, Shadrach JL, et al. (2021) Single-cell transcriptomic analysis of the adult mouse spinal cord reveals molecular diversity of autonomic and skeletal motor neurons. *Nat. Neurosci.* 24: 572–583. https://doi.org/10.1038/s41593-020-00795-0

Boehm I, Alhindi A, Leite AS, et al. (2020) Comparative anatomy of the mammalian neuromuscular junction. *J. Anat.* 237: 827–836. https://doi.org/10.1111/joa.13260

Boyd PJ, Tu WY, Shorrock HK, et al. (2017) Bioenergetic status modulates motor neuron vulnerability and pathogenesis in a zebrafish model of spinal muscular atrophy. *PLoS Genet.* 13: e1006744. https://doi.org/10.1371/journal.pgen.1006744

Boyette-Davis JA, Hou S, Abdi S & Dougherty PM (2018) An updated understanding of the mechanisms involved in chemotherapy-induced neuropathy. *Pain Manag*. 8: 363–375. https://doi.org/10.2217/pmt-2018-0020

Cahalan SD, Boehm I, Jones RA & Piercy RJ (2022a) Recognising the potential of large animals for modelling neuromuscular junction physiology and disease. *J Anat.* in press https://doi.org/

Cahalan SD, Perkins JD, Boehm I, Jones RA, Gillingwater TH & Piercy RJ (2022b) A method to identify, dissect and stain equine neuromuscular junctions for morphological analysis. *J Anat.* in press https://doi.org/

Dadon-Nachum M, Melamed E & Offen D (2011) The "dying-back" phenomenon of motor neurons in ALS. *J. Mol. Neurosci.* 43: 470–477. https://doi.org/10.1007/s12031-010-9467-1

Dalla Costa I, Buchanan CN, Zdradzinski MD, et al. (2021) The functional organization of axonal mRNA transport and translation. *Nat. Rev. Neurosci.* 22: 77–91. https://doi.org/10.1038/s41583-020-00407-7

Dawkins JL, Hulme DJ, Brahmbhatt SB, Auer-Grumbach M & Nicholson GA (2001) Mutations in *SPTLC1*, encoding serine palmitoyltransferase, long chain base subunit-1, cause hereditary sensory neuropathy type I. *Nat. Genet.* 27: 309–312. https://doi.org/10.1038/85879

Deardorff AS, Romer SH, Sonner PM & Fyffe RE (2014) Swimming against the tide: investigations of the C-bouton synapse. *Front. Neural Circuits* 8: 106. https://doi.org/10.3389/fncir.2014.00106

Devoy A, Price G, De Giorgio F, et al. (2021) Generation and analysis of innovative genomically humanized knockin *SOD1*, *TARDBP* (TDP-43), and *FUS* mouse models. *iScience* 24: 103463. https://doi.org/10.1016/j.isci.2021.103463

Ganchingco JRC, Fukuyama T, Yoder JA & Bäumer W (2014) Calcium imaging of primary canine sensory neurons: Small-diameter neurons responsive to pruritogens and algogens. *Brain Behav.* 9: e01428. https://doi.org/10.1002/brb3.1428

Gemignani F, Melli G, Alfieri S, Inglese C & Marbini A (2004) Sensory manifestations in Charcot-Marie-Tooth disease. *J. Peripher. Nerv. Syst.* 9: 7–14. https://doi.org/10.1111/j.1085-9489.2004.09103.x

Hines TJ, Tadenev ALD, Lone MA, et al. (2022) Precision mouse models of *Yars*/dominant intermediate Charcot-Marie-Tooth disease type C and *Sptlc1*/hereditary sensory and autonomic neuropathy type 1. *J Anat.* in press https://doi.org/10.1111/joa.13605

Jones RA, Reich CD, Dissanayake KN, et al. (2016) NMJ-morph reveals principal components of synaptic morphology influencing structure-function relationships at the neuromuscular junction. *Open Biol.* 6: 160240. https://doi.org/10.1098/rsob.160240

Jones RA, Harrison C, Eaton SL, et al. (2017) Cellular and molecular anatomy of the human neuromuscular junction. *Cell Rep.* 21: 2348–2356. https://doi.org/10.1016/j.celrep.2017.11.008

Jordanova A, Irobi J, Thomas FP, et al. (2006) Disrupted function and axonal distribution of mutant tyrosyl-tRNA synthetase in dominant intermediate Charcot-Marie-Tooth neuropathy. *Nat. Genet.* 38: 197–202. https://doi.org/10.1038/ng1727

Kissane RWP, Ghaffari-Rafi A, Tickle PG, et al. (2022) C-bouton components on rat extensor digitorum longus motoneurons are resistant to chronic functional overload. *J Anat.* in press https://doi.org/10.1111/joa.13439

Kline RA, Kaifer KA, Osman EY, et al. (2017) Comparison of independent screens on differentially vulnerable motor neurons reveals alpha-synuclein as a common modifier in motor neuron diseases. *PLoS Genet.* 13: e1006680. https://doi.org/10.1371/journal.pgen.1006680

Lang B & Vincent A (2009) Autoimmune disorders of the neuromuscular junction. *Curr. Opin. Pharmacol.* 9: 336–340. https://doi.org/10.1016/j.coph.2009.04.005

Liu JX, Brännström T, Andersen PM & Pedrosa-Domellöf F (2013) Distinct changes in synaptic protein composition at neuromuscular junctions of extraocular muscles versus limb muscles of ALS donors. *PLoS One* 8: e57473. https://doi.org/10.1371/journal.pone.0057473

Marques MJ, Conchello JA & Lichtman JW (2000) From plaque to pretzel: fold formation and acetylcholine receptor loss at the developing neuromuscular junction. *J. Neurosci.* 20: 3663–3675. https://doi.org/10.1523/JNEUROSCI.20-10-03663.2000

McGonigal R & Willison HJ (2022) The role of gangliosides in the organisation of the node of Ranvier examined in glycosyltransferase transgenic mice. *J Anat.* in press https://doi.org/10.1111/joa.13562

Medina-Moreno A & Henríquez JP (2022) Maturation of a postsynaptic domain: Role of small Rho GTPases in organising nicotinic acetylcholine receptor aggregates at the vertebrate neuromuscular junction. *J Anat.* in press https://doi.org/10.1111/joa.13526

Mercuri E, Sumner CJ, Muntoni F, Darras BT & Finkel RS (2022) Spinal muscular atrophy. *Nat Rev Dis Primers* 8: 52. https://doi.org/10.1038/s41572-022-00380-8

Middleton SJ, Perez-Sanchez J & Dawes JM (2022) The structure of sensory afferent compartments in health and disease. *J Anat.* in press https://doi.org/10.1111/joa.13544

Murray LM, Comley LH, Thomson D, Parkinson N, Talbot K & Gillingwater TH (2008) Selective vulnerability of motor neurons and dissociation of pre- and post-synaptic pathology at the neuromuscular junction in mouse models of spinal muscular atrophy. *Hum. Mol. Genet.* 17: 949–962. https://doi.org/10.1093/hmg/ddm367

Nair RR, Corrochano S, Gasco S, et al. (2019) Uses for humanised mouse models in precision medicine for neurodegenerative disease. *Mamm. Genome* 30: 173–191. https://doi.org/10.1007/s00335-019-09807-2

Negro S, Pirazzini M & Rigoni M (2022) Models and methods to study Schwann cells. *J Anat.* in press https://doi.org/10.1111/joa.13606

Nguyen MQ, von Buchholtz LJ, Reker AN, Ryba NJ & Davidson S (2021) Single-nucleus transcriptomic analysis of human dorsal root ganglion neurons. *Elife* 10: e71752. https://doi.org/10.7554/eLife.71752

Nijssen J, Comley LH & Hedlund E (2017) Motor neuron vulnerability and resistance in amyotrophic lateral sclerosis. *Acta Neuropathol.* 133: 863–885. https://doi.org/10.1007/s00401-017-1708-8

Powell S, Vinod A & Lemons ML (2014) Isolation and culture of dissociated sensory neurons from chick embryos. *J. Vis. Exp.* 91: 51991. https://doi.org/10.3791/51991

Purves D, Augustine GJ, Fitzpatrick D, et al. (2001) 'Long-distance signaling by means of action potentials', in Neuroscience (2nd edition), Sinauer Associates, Sunderland, MA, USA.

Reed CB, Feltri ML & Wilson ER (2022) Peripheral glia diversity. *J Anat.* in press https://doi.org/10.1111/joa.13484

Sandhoff K & Harzer K (2013) Gangliosides and gangliosidoses: principles of molecular and metabolic pathogenesis. *J. Neurosci.* 33: 10195–10208. https://doi.org/10.1523/JNEUROSCI.0822-13.2013

Sanes JR & Lichtman JW (1999) Development of the vertebrate neuromuscular junction. *Annu. Rev. Neurosci.* 22: 389–442. https://doi.org/10.1146/annurev.neuro.22.1.389

Schiaffino S & Reggiani C (2011) Fiber types in mammalian skeletal muscles. *Physiol. Rev.* 91: 1447–1531. https://doi.org/10.1152/physrev.00031.2010

Schnaar (2016) Gangliosides of the vertebrate nervous system. *J. Mol. Biol*. 428: 3325–3336. https://doi.org/10.1016/j.jmb.2016.05.020

Sleigh JN, Grice SJ, Burgess RW, Talbot K & Cader MZ (2014) Neuromuscular junction maturation defects precede impaired lower motor neuron connectivity in Charcot-Marie-Tooth type 2D mice. *Hum. Mol. Genet.* 23: 2639–2650. https://doi.org/10.1093/hmg/ddt659

Sleigh JN, Rossor AM, Fellows AD, Tosolini AP & Schiavo G (2019) Axonal transport and neurological disease. *Nat. Rev. Neurol.* 15: 691–703. https://doi.org/10.1038/s41582-019-0257-2

Sleigh JN, Mech AM & Schiavo G (2020a) Developmental demands contribute to early neuromuscular degeneration in CMT2D mice. *Cell Death Dis.* 11: 564. https://doi.org/10.1038/s41419-020-02798-y

Sleigh JN, West SJ & Schiavo G (2020b) A video protocol for rapid dissection of mouse dorsal root ganglia from defined spinal levels. *BMC Res. Notes* 13: 302. https://doi.org/10.1186/s13104-020-05147-6

Stifani N (2014) Motor neurons and the generation of spinal motor neuron diversity. *Front. Cell. Neurosci.* 8: 293. https://doi.org/10.3389/fncel.2014.00293

Surana S, Tosolini AP, Meyer IFG, Fellows AD, Novoselov SS & Schiavo G (2018) The travel diaries of tetanus and botulinum neurotoxins. *Toxicon* 147: 58–67. https://doi.org/10.1016/j.toxicon.2017.10.008

Tadenev ALD & Burgess RW (2019) Model validity for preclinical studies in precision medicine: precisely how precise do we need to be? *Mamm. Genome* 30: 111–122. https://doi.org/10.1007/s00335-019-09798-0

Tosolini AP & Sleigh JN (2020) Intramuscular delivery of gene therapy for targeting the nervous system. *Front. Mol. Neurosci*. 13: 129. https://doi.org/10.3389/fnmol.2020.00129

Usoskin D, Furlan A, Islam S, et al. (2015) Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. *Nat. Neurosci.* 18: 145–153. https://doi.org/10.1038/nn.3881

Villarroel-Campos D, Schiavo G & Sleigh JN (2022) Dissection, *in vivo* imaging and analysis of the mouse epitrochleoanconeus muscle. *J Anat.* in press https://doi.org/10.1111/joa.13478

Willison HJ, Jacobs BC & van Doorn PA (2016) Guillain-Barré syndrome. *Lancet* 388: 717–727. https://doi.org/10.1016/S0140-6736(16)00339-1

Yadav A, Matson JE, Li L, et al. The human motoneuron expression signature is defined by ALS-related genes. *bioRxiv*. https://doi.org/10.1101/2022.03.25.485808

Figure

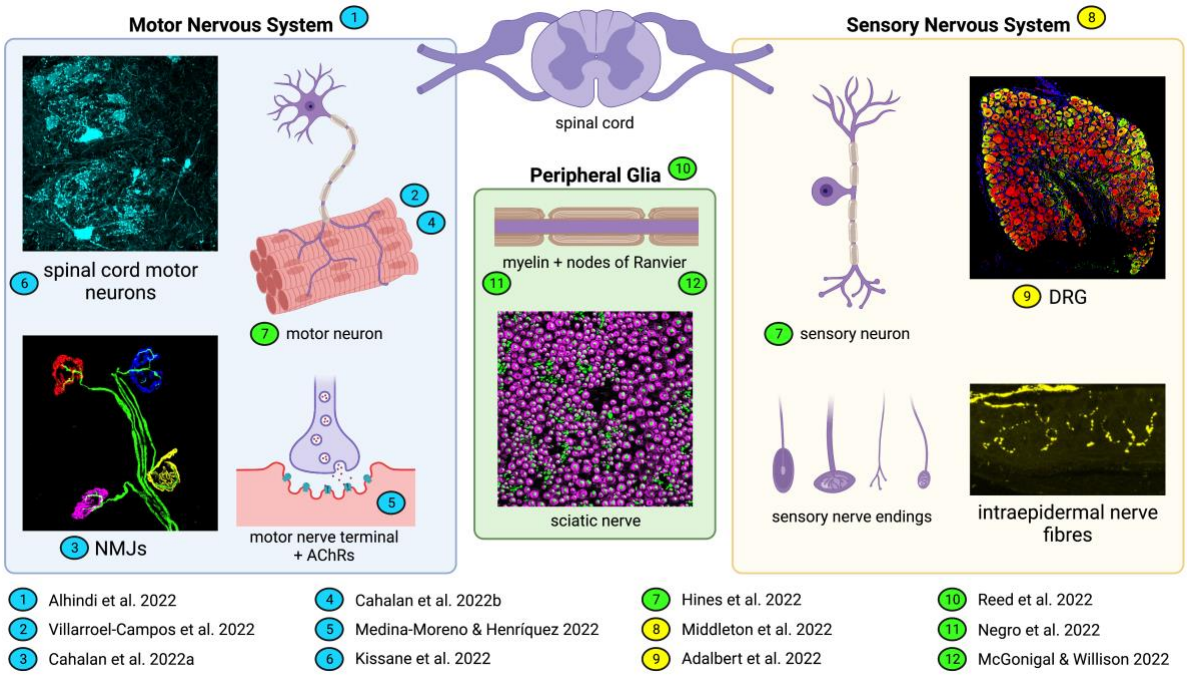

Figure 1. Peripheral nerve anatomy in health and disease. In this Special Collection, we present 12 articles that showcase important anatomical work on the somatic nervous system, focusing on motor neurons (Articles 1 to 7), sensory neurons (Articles 7 to 9) and peripheral glia (Articles 10 to 12). *AChRs*, acetylcholine receptors; *DRG*, dorsal root ganglion; *NMJs*, neuromuscular junctions. Created with BioRender (https://Biorender.com).