One Nervous System: Critical Links Between Central and Peripheral Nervous System Health and Implications for Obesity and Diabetes

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There are key differences between the central nervous system (CNS) (brain and spinal cord) and peripheral nervous system (PNS), such as glial cell types, whether there is protection by the blood-brain barrier, modes of synaptic connections, etc. However, there are many more similarities between these two arms of the nervous system, including neuronal structure and function, neuroimmune and neurovascular interactions, and, perhaps most essentially, the balance between neural plasticity (including processes like neuron survival, neurite outgrowth, synapse formation, gliogenesis) and neurodegeneration (neuronal death, peripheral neuropathies like axonopathy and demyelination). This article brings together current research evidence on shared mechanisms of nervous system health and disease between the CNS and PNS, particularly with metabolic diseases like obesity and diabetes. This evidence supports the claim that the two arms of the nervous system are critically linked and that previously understudied conditions of central neurodegeneration or peripheral neurodegeneration may actually be manifesting across the entire nervous system at the same time, through shared genetic and cellular mechanisms. This topic has been critically underexplored due to the research silos between studies of the brain and studies of peripheral nerves and an overemphasis on the brain in neuroscience as a field of study. There are likely shared and linked mechanisms for how neurons stay healthy versus undergo damage and disease among this one nervous system in the body—providing new opportunities for understanding neurological disease etiology and future development of neuroprotective therapeutics.

ARTICLE HIGHLIGHTS

- The central nervous system (CNS) (brain and spinal cord) and peripheral nervous system (PNS) exhibit numerous structural and functional similarities but also key differences. The PNS is relatively understudied compared with the brain.
- In numerous neurological diseases, symptoms and mechanistic involvement across both the CNS and PNS arms of the nervous system are seen.
- The PNS provides key bidirectional neural communication between the brain and tissues/organs, including numerous tissues and organs involved in metabolism (adipose, liver, muscle, heart, etc.)
- The PNS and CNS both undergo neurodegeneration, but peripheral neuropathy is the number one manifestation of neurodegenerative disease in humans.

As someone trained with a PhD in Neuroscience who has taught undergraduate and graduate courses in this field, I know firsthand how singularly focused we (neurologists, neuroscientists, psychiatrists, and neurological surgeons) are on the brain and how little we acknowledge an integral role of the peripheral nervous system (PNS) in neurological health and disease. The seminal neuroscience textbook by Kandel, Schwartz, Jessell, and colleagues, *Principles of Neural Science* (1), covers the neuromuscular junction and somatosensation but devotes zero chapters to the rest of the PNS, as one key example of overlooking the PNS in the neuroscience field. Similarly, the largest scientific conference in the world, hosted by the Society for Neuroscience, features mostly research on the brain with relatively little representation of findings in the PNS. We have known about the existence of a PNS since the third century BCE,

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when physician-philosopher Herophilus of Chalcedon demonstrated that nerves connected the brain to the interior of organs, and not just the vasculature, as was the common thought at that time (2). He also used a holistic approach to the treatment of neurological disorders that included the whole nervous system and distinguished between sensory and motor nerves as subtypes in the PNS. As I will lay out in this article, emerging evidence increasingly indicates that neurological diseases and disorders that impact the central nervous system (CNS) (brain and spinal cord) tend to also have effects in the PNS and vice versa. We can no longer think of brain disorders as solely brain disorders when we have not investigated PNS involvement—because when we do look, both arms of the nervous system tend to be implicated (as outlined in the examples in Table 1). This is especially important for studies of neurometabolism, or the system- and cellular-level cross talk between the nervous system and metabolic regulation, especially since the orchestration of neurometabolism underlies much of the study of energy balance homeostasis and diseases like obesity and diabetes.

CNS AND PNS: SIMILARITIES AND DIFFERENCES

Essentially all the same cell types that are important for brain function (neurons; immune cells including brain macrophages, microglia, and more; blood and lymphatic/glymphatic vasculature; and glial cells like astrocytes and oligodendrocytes) are also cell types important for peripheral nerve function (where neurons and their long axons extend into tissues and organs, with support from vasculature, neuroimmune cells, and glial support cells, including numerous types of Schwann cells) (3) (Fig. 1). The same neuropeptides we investigate in the hypothalamic control of appetite and energy expenditure pathways (e.g., neuropeptide Y [NPY], pituitary adenylate cyclase–activating polypeptide [PACAP], calcitonin gene–related peptide [CGRP], and many more) are also expressed in the peripheral nerves that innervate our adipose

Table 1—Examples of neurological diseases that impact both the brain/CNS and PNS arms of the body's one nervous system

Disease/condition	Brain/CNS impacts	PNS impacts
Multiple sclerosis	The most common cause of neurological disability in young adults	Demyelination, changes to nerve conductance (34,35)
Parkinson disease	Cognitive impairment (36)	Prevalence of peripheral neuropathy reported at 4.8%–55.0%, GI issues; small fiber damage from α-synuclein, potential involvement in gait/motor symptoms (37)
Alzheimer/APOE variants	Numerous CNS effects (38)	APOE and neuromuscular disease (39), tau in peripheral tissues (40), amyloid roles in peripheral nerves (41)
Long COVID	"Brain fog," cognitive dysfunction, lethargy (42)	Dysautonomia, peripheral neuropathy (43)
Diabetes	Changes to brain structure, cognitive dysfunction (44)	Diabetic peripheral neuropathy (45)
Chemotherapy	Brain fog; deficits in attention, memory, and executive functioning; fatigue (46)	CIPN (47)
Obesity	Increased dementia (48–52)	Peripheral neuropathy (53), including adipose neuropathy (54,55)
Aging	Cognitive dysfunction, increased risk for neurological disease, memory impairment (56)	Peripheral neuropathy, prevalence of which is estimated to be 7% among elderly (57)
Epilepsy	Cognitive impairment (58)	Neuropathy implicated (59)
Mental illness	Brain neuroplasticity and mental health (60)	Anxiety and depression with small fiber neuropathy (61), emotional impacts of neuropathic pain (62), ANS dysfunction with schizophrenia (63)
Huntington disease	Neurodegeneration (64)	Involvement of sensory DRG neurons (65)
TBI, SCI	Cognitive impairment (66)	TBI and peripheral nerve impacts (67,68), SCI and peripheral nerve impacts (69,70)
ALS	Brain involvement (71)	Motor neuron involvement and destruction of peripheral nerve terminals (72)
Stroke	Central neurodegeneration and role of adult brain stem cells (73)	Neuropathy symptoms (74)

ALS, anterior lateral sclerosis; ANS, autonomic nervous system; CIPN, chemotherapy-induced peripheral neuropathy; DRG, dorsal root ganglia; GI, gastrointestinal; SCI, spinal cord injury; TBI, traumatic brain injury.

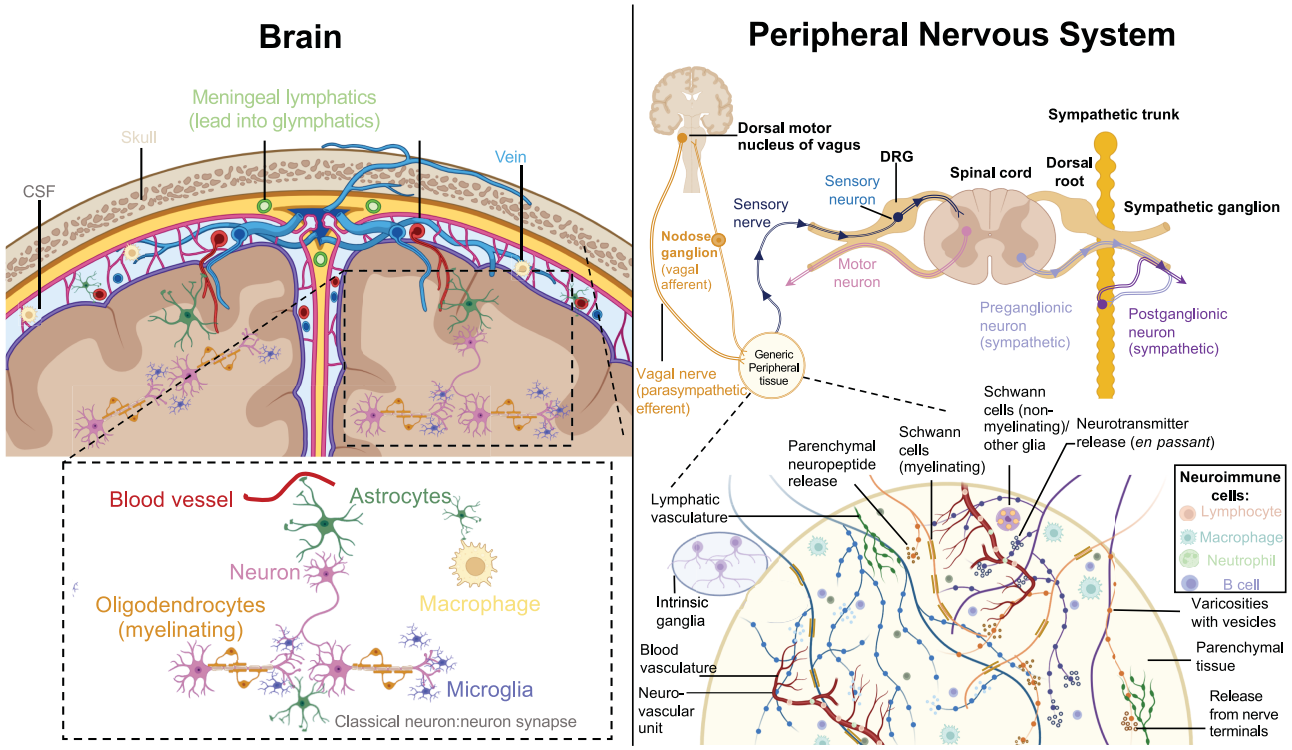

Figure 1—Comparison of nervous system components between brain and PNS. The brain and PNS have many similarities as well as several differences in cellular components, axonal length, protection by the blood-brain barrier versus a less restrictive endoneurium blood-nerve barrier in PNS, and more. CSF, cerebrospinal fluid; DRG, dorsal root ganglia.

tissues, but are vastly understudied there despite the likelihood that they exert metabolic effects across multiple tissues outside the brain (4,5) (Fig. 2). In support of this idea, numerous human genes have been implicated through genome-wide association studies for metabolic diseases like obesity and diabetes as clearly important for the nervous system and neuronal functions (6), implicating dysregulation of the nervous system's energy balance homeostasis in the development of obesity. However, it is glaring that mechanistic investigations of these genes have almost solely been focused on their involvement in brain processes, with potential functions in peripheral nerves ignored, despite similar expression of these genes in the PNS. For example, brain-derived neurotrophic factor (BDNF), its receptor TrkB, Calca, and many more genes associated with human obesity are expressed in both the brain and in peripheral nerves, but have almost exclusively been studied in the brain. Relatedly, results of several studies with investigation of proteins that can act as axon outgrowth signals (Sema7a and Slit2 as prime examples) have implicated their importance in adipose tissue functions, but in these studies measurements of tissue innervation, neurite density, or nerve function, that likely were contributing to the adipose phenotypes, were completely ignored (7,8).

As similar as the structure-function relationships are between the CNS and PNS, important differences remain as well. One difference is the relative lack of protection in the PNS, without the blood-brain and blood–cerebrospinal fluid interfaces/barriers in the CNS, leaving the PNS with less protection from peripheral toxins, inflammatory signals, and damaging metabolites that can lead to glucotoxicity or lipotoxicity with diabetes or obesity. Similarly, the PNS is also directly exposed to the circulating hormones, nutrients, immune cells, and many more blood and lymphatic components that allow interorgan communication and a more diverse fuel supply. Another distinction is that the neuronal cell bodies in the PNS are housed in specialized structures called ganglia that are synaptically connected to the CNS, where nearby Schwann cells, other glial cells, and immune cells reside. Some are "intrinsic" ganglia that sit directly on top of organs like the intestine, heart, and pancreas (Fig. 2), while other neuronal cell bodies are in spinal ganglia (e.g., dorsal root ganglia or sympathetic chain ganglia), which are sometimes at long distances from their axon terminals in tissues like skin and muscle (of note, the longest axon in the human body is the sciatic nerve, which can measure >1 m in length) (9). This creates long distances for cell survival signals that originate at the cell body to reach the termini of PNS axons, a challenge not faced by neurons in the brain. In the brain, axons, dendrites, and cell bodies are housed in relatively close proximity, forming shorter neural circuits that are nearby to support cells like glia. Furthermore, myelin chemistry is largely similar between the CNS and PNS, but there are differences in composition (10).

Finally, the brain's synapses are nearly all classical synapses (presynaptic neuron to postsynaptic neuron), whereas in the PNS we know too little about specialized nerve terminals

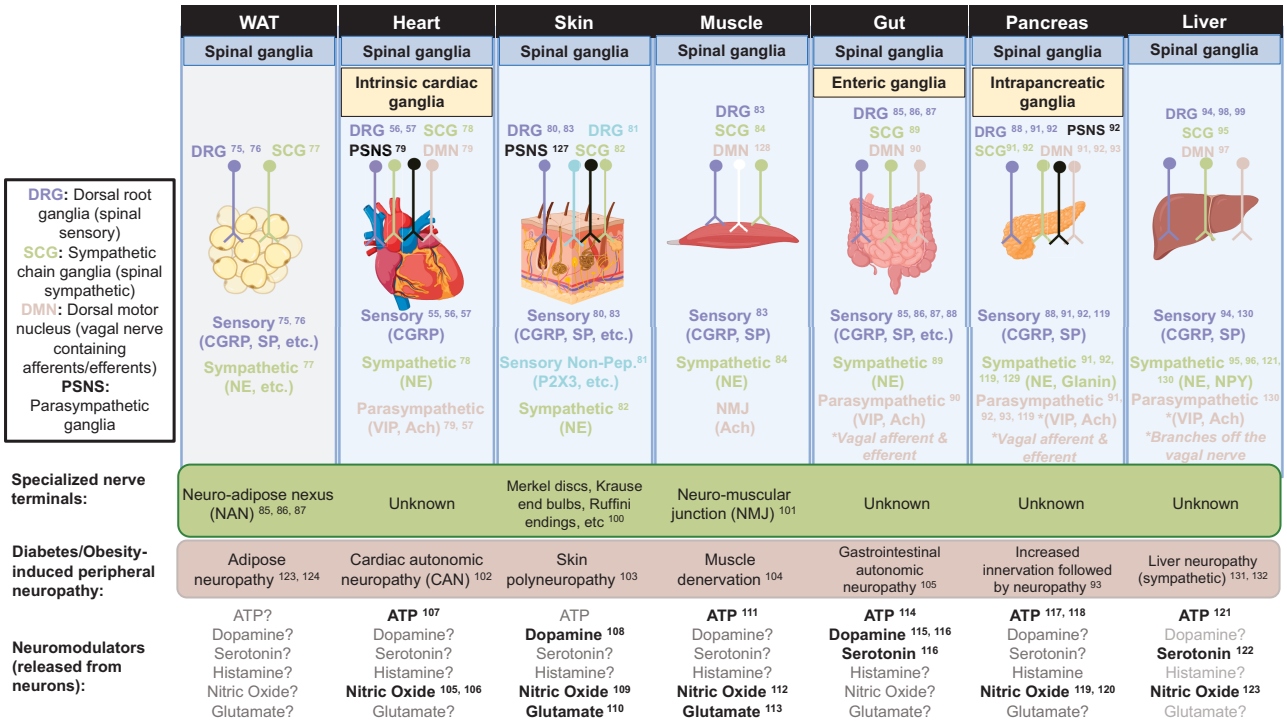

Figure 2—Innervation of metabolic tissues and organs and impacts of metabolic disease–associated peripheral neuropathy: white adipose tissue (brown adipose is similar but not shown), heart, skin (where thermal sensation begins for cold-stimulated thermogenesis), muscle, gut/intestine, pancreas, and liver are all metabolically important innervated organs. These tissues and organs have a diverse nerve supply that enables bidirectional neural communication with the brain and results in release of numerous neurotransmitters, neuropeptides, and neuromodulators. Many of these tissues have been implicated in peripheral neuropathy related to diabetes and obesity, but many tissues have not yet been investigated, and for some tissues little is still known about the PNS. (Note that signs of neuropathy could include altered nerve electrical activity, reduced nerve product levels, reduced neurotrophic factors, quantities of nerve terminals or axon counts/density, axon growth cone/outgrowth markers, synaptic markers, demyelination, altered Schwann cell phenotype with axonopathy, etc. [11–13,54,55,75–132.]) Ach, acetylcholine; Non-Pep, non-peptide; NMJ, neuromuscular junction; SP, substance P; VIP, vasoactive intestinal peptide; WAT, white adipose tissue.

and junctions, aside from the well-characterized skin nerve ending structures and the neuromuscular junction (Fig. 2). Only recently was a synaptic structure first described in adipose tissues, the neuro-adipose nexus (NAN) (11–13) for example, despite the critical role of adipose nerves in the control of metabolic health and adipose tissue functions (14,15). Nerve terminal structures are far better characterized in muscle and skin (Fig. 2). The NAN features axon terminals with presynaptic protein markers and synaptic vesicle markers and is comprised of both tyrosine hydroxylase–expressing fibers and calcitonin gene–related peptide (CGRP) fibers, indicating that NANs may be a mix of sensory and sympathetic nerve endings. Similar to the neuromuscular junction, the NANs are myelinated leading up to the start of the terminal structure. NANs are relatively infrequent in the tissue, and typically appear at the tissue surface, but are found in nearly all mouse adipose depots. They increase in number with obesity and aging, as we demonstrated recently, potentially in response to inflammation in the tissue (14,15).

OPPORTUNITIES FOR NEW WORK IN THE PNS

Many who conduct biomedical research focused on peripheral tissues and organs tend to ignore the presence of a peripheral nerve supply that may impact tissue functions. For example, individuals in my laboratory continue to meet colleagues who are surprised that adipose tissues are innervated, and not just clusters of lipid-laden adipocytes that communicate with the brain solely through the hormone leptin or other adipokines, when we know from surgical, chemical, genetic, and viral denervation experiments that adipose nerves are important for the tissue's function and provide bidirectional neural communication with the brain. Unlike circulating factors, a peripheral nerve–mediated communication route is swift and directed and can impact a single tissue or organ without systemic effects.

Now that advanced tissue clearing and microscopy techniques have evolved, antibodies have improved, and more nerve reporter mouse lines are available for experiments, investigation of tissue and organ innervation patterns has revealed a robust network of vagal and spinal afferents and efferents that enable bidirectional neural communication between the brain and peripheral tissues, including those important for metabolic health (Fig. 2). The broad categorization of nerve subtypes (e.g., vagal and spinal sensory, motor, autonomic/sympathetic) likely underrepresents even more subdivisions of axonal subtypes, with their own orchestration of neurotransmitter

and neuropeptide signals, or individualized responses to the plasticity-inducing cues from axon outgrowth signals and neurotrophic factors. Newer single-cell -omics studies of ganglia are revealing some of this neuronal diversity in the PNS (16–18). With emphasis more recently, the function of sensory nerves is an important new horizon for neuroscience research because we know that the body's interoceptive and exteroceptive sensations of chemical, mechanical, heat, and other signals are integral for our cognitive experience of the world, and there is strong evidence that PNS function impacts brain health, including mental health (19,20). For example, patients with peripheral neuropathy report cognitive impairment and depression (Table 1).

Neuropeptides are likely understudied due to their small size and short half-life and because of the difficulty in capturing them with use of traditional methods like Western blots or proteomics. Other challenges include the persistent lack of reliable antibodies for G-protein–coupled receptors, such as the adrenergic receptors that respond to catecholamines like norepinephrine (NE). Lastly, an important research and gene therapy goal is the targeting of viral vectors to the PNS while avoiding off target transduction in the brain and spinal cord, which our group has been optimizing for adipose nerves and others have optimized for gut and pancreatic nerves.

THE PNS: RELEVANCE IN OBESITY AND DIABETES

Diabetes and obesity are prime examples of diseases with whole nervous system involvement. For example, body weight homeostasis is regulated by a complex interplay among nutrients, circulating neuroendocrine hormones that are released from peripheral tissues to act in the brain and other tissues, and coordination by the peripheral nerves innervating the gut, adipose, pancreas, and more. Even the release of hormonal signals from endocrine tissues is largely under PNS control; as a recent example, the release of intestinal incretin hormones was found to be under sympathetic nerve control (21), and the question of whether obesity-associated peripheral neuropathy may impede these neuroendocrine signals in the gut remains unexplored. Glucose regulation is also not a purely cell-autonomous process of glucose-stimulated insulin release from β-cells in the pancreas. It involves neuronal sensors of nutrient status, pancreatic nerves that control glucose homeostasis, and the action of intestinal incretin hormones that improve diabetes and whole-body metabolic health.

The most effective treatments for human obesity have consistently impacted the nervous system, from bariatric surgery to appetite suppressants and the newer broad-acting glucagon-like peptide 1 (GLP-1) and GIP dual agonists. Indeed, GLP-1 and GIP receptors are expressed both in the brain and in peripheral nerves (22,23). By contrast, treatments for metabolic disease that prompt rapid weight loss can have unintended negative consequences on the peripheral nerves, causing neuropathies instead of preventing them (24).

For decades investigators have worked to capitalize on the antiobesity and antidiabetes functions of thermogenic brown adipocytes, e.g., increasing their number or activity to drive more energy expenditure and clearance of glucose and lipids from the circulation. To maintain this caloric drive, brown adipocytes expressing uncoupling protein 1 (UCP1) need neuronal stimulation (primarily via NE), and without these nerve signals they can revert back to a less energetically active state ("whitening"). Recent work focused on human-derived brown adipocytes as a cell-based therapy underscored the importance of peripheral nerves for metabolic health. The researchers demonstrated that human preadipocytes treated with forskolin (a sympathomimetic) increased UCP1 expression and maintained this UCP1 thermogenic activity when transplanted into the body because the stimulated cells released neurotrophic factors like BDNF to promote the cell transplant's neural innervation (25–28). Brown adipose therapies are often critiqued because of this need for sympathetic drive, which can be detrimental if stimulated at a whole-body level (29) but targeted to a tissue transplant is likely to be less problematic, since this mimics physiological sympathetic drive to brown fat. The next nervous system challenge will be overcoming the compensatory appetite increase that can result when the body goes into a state of negative energy balance, regardless of the body's need to dispense of excess adipose for health reasons. Again, this cross talk between the brain and peripheral tissues and organs is bidirectional: changes in the periphery can drive afferent neural activity to the brain, which can then trigger stimulation of efferent nerve signals back out to the periphery. Losing weight drives increased appetite, at any body weight, potentially via these afferent signals. This neural cross talk has also repeatedly been observed in studies with denervation of adipose depots, for example. Denervation of one depot tends to lead to compensatory changes to innervation of another depot in the body (or increased activity of remaining nerves in the denervated tissue), underscoring the redundant coordination that ensures our brain can continuously communicate with our fat storage organs through peripheral nerves, and utilize those stored lipids (14).

Taken together, the PNS is an integral, yet often overlooked, component of metabolically relevant organs including the heart, intestine, liver, adipose, pancreas, muscle, and many more (Fig. 2). While autonomic and motor nerves in the PNS are better understood, as evidenced by our deep understanding of NE-releasing sympathetic nerves in adipose tissue, we know far less about the afferent sensory nerves—those involved in interoception, somatosensation, and nociception in the body. It is laudable that the National Institutes of Health (NIH) has prioritized work in pain conditions (30) and interoception (as part of the Blueprint for Neuroscience Research [31]) to help close this gap in knowledge about peripheral nerve functions, but more still needs to be done. As a country we have devoted enormous

resources to brain research (e.g., the NIH Brain Research through Advancing Innovative Neurotechnologies [BRAIN] Initiative [32]) and Alzheimer disease (at NIH alone, more than $3.7 billion in expenditures for research on this disease annually, according to the Alzheimer's Association [www.alz.org/]). However, peripheral neuropathy is the number one manifestation of neurodegenerative disease in humans (33), and despite impacting 30 million Americans or more, work in peripheral neuropathy is relatively underfunded across all agencies and foundations. Since neuropathy overall has been understudied, we are still learning which tissues are impacted in the number one cause (diabetes/obesity) (Fig. 2)—not to mention the dozens of other neuropathy causes, including long COVID, aging, chemotherapy, and more.

PERSPECTIVE: ONE NERVOUS SYSTEM

When you are attuned to it, there is clear evidence underscoring the interconnectedness in our one nervous system: the brain, brainstem, spinal cord, ganglia, cranial nerves, peripheral nerves, and tissue nerve terminals that work in a single coordinated physiological system. Data on neurological diseases and disorders are revealing that those conditions formerly considered "brain only" also involve the PNS and vice versa (Table 1). Similarly, have we overlooked treatments and therapies that target the spinal cord, such as neuromodulation with spinal cord stimulation, that may also impact the brain and peripheral nerves? Or have we neglected investigating drugs for brain disorders (antidepressants, seizure medications) that may also improve PNS function and neuropathy? My guess is, yes, we have—if we are not concertedly looking for PNS effects, we certainly will not find them.

SUMMARY: KEY UNANSWERED QUESTIONS

As covered in this article, mounting evidence now encourages neuroscientists to consider both arms of the nervous system in investigations of diseases and treatments. The nervous system is a single, interconnected physiological system that responds to internal and external signals to regulate numerous metabolically relevant processes in many tissues and organs that are important for obesity, diabetes, aging, and cardiometabolic health. Myriad areas of biomedical investigation remain to be fully explored related to the PNS and the interconnectedness of the nervous system in health and disease, including the nerve subtypes present in tissues/organs and their responses to local neurotrophic factors, the actions of various nerve products on different cell types in the tissue, the cross talk between arms of the PNS at the tissue or ganglia/spinal levels, the impact of peripheral neuropathy on tissues beyond the skin, and the structure/function relationships for nerve terminal structures in different tissues/organs.

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References

1. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ, Mack S. *Principles of Neural Science.* 5th ed. McGraw-Hill Education, 2014
2. Panegyres KP, Panegyres PK. The Ancient Greek discovery of the nervous system: Alcmaeon, Praxagoras and Herophilus. J Clin Neurosci 2016;29:21–24
3. Gunsch G, Paradie E, Townsend KL. Peripheral nervous system glia in support of metabolic tissue functions. Trends Endocrinol Metab 2023;34:622–639
4. Mishra G, Townsend KL. The metabolic and functional roles of sensory nerves in adipose tissues. Nat Metab 2023;5:1461–1474
5. Mishra G, Townsend KL. Sensory nerve and neuropeptide diversity in adipose tissues. Mol Cells 2024;47:100030
6. Yeo GSH, O'Rahilly S. Finding genes that control body weight. Science 2021;373:30–31
7. Lu Q, Liu Z, Zhao L, et al. Sema7A protects against high-fat diet-induced obesity and hepatic steatosis by regulating adipo/lipogenesis. Mol Metab 2023;70:101698
8. Svensson KJ, Long JZ, Jedrychowski MP, et al. A secreted Slit2 fragment regulates adipose tissue thermogenesis and metabolic function. Cell Metab 2016;23:454–466
9. Muzio MR, Adegbenro O, Cascella M. Histology, Axon. In StatPearls. Treasure Island, FL, StatPearls Publishing, 2024
10. Morell P, Quarles RH. Characteristic Composition of Myelin. In *Basic Neurochemistry: Molecular, Cellular and Medical Aspects.* 6th ed. Siegel GJ, Agranoff BW, Albers RW, Eds. Lippincott-Raven, 1999
11. Willows JW, Blaszkiewicz M, Lamore A, et al. Visualization and analysis of whole depot adipose tissue neural innervation. iScience 2021;24:103127
12. Willows JW, Gunsch G, Paradie E, et al. Schwann cells contribute to demyelinating diabetic neuropathy and nerve terminal structures in white adipose tissue. iScience 2023;26:106189
13. Blaszkiewicz M, Tao T, Mensah-Arhin K, et al. Gene therapy approaches for obesity-induced adipose neuropathy: device-targeted AAV-mediated neurotrophic factor delivery to adipocytes in subcutaneous adipose. Mol Ther 2024;32:1407–1424
14. Willows JW, Blaszkiewicz M, Townsend KL. The sympathetic innervation of adipose tissues: regulation, functions, and plasticity. Compr Physiol 2023;13:4985–5021
15. Blaszkiewicz M, Willows JW, Johnson CP, Townsend KL. The importance of peripheral nerves in adipose tissue for the regulation of energy balance. Biology (Basel) 2019;8:10
16. Qi L, Iskols M, Shi D, et al. A mouse DRG genetic toolkit reveals morphological and physiological diversity of somatosensory neuron subtypes. Cell 2024;187:1508–1526.e16
17. Nguyen MQ, von Buchholtz LJ, Reker AN, Ryba NJ, Davidson S. Single-nucleus transcriptomic analysis of human dorsal root ganglion neurons. Elife 2021;10:e71752

18. Tavares-Ferreira D, Shiers S, Ray PR, et al. Spatial transcriptomics of dorsal root ganglia identifies molecular signatures of human nociceptors. Sci Transl Med 2022;14:eabj8186
19. Schmitt CM, Schoen S. Interoception: a multi-sensory foundation of participation in daily life. Front Neurosci 2022;16:875200
20. Khalsa SS, Adolphs R, Cameron OG, et al.; Interoception Summit 2016 participants. Interoception and mental health: a roadmap. Biol Psychiatry Cogn Neurosci Neuroimaging 2018;3:501–513
21. Ren W, Chen J, Wang W, et al. Sympathetic nerve-enteroendocrine L cell communication modulates GLP-1 release, brain glucose utilization, and cognitive function. Neuron 2024;112:972–990.e8
22. Muscogiuri G, DeFronzo RA, Gastaldelli A, Holst JJ. Glucagon-like peptide-1 and the central/peripheral nervous system: crosstalk in diabetes. Trends Endocrinol Metab 2017;28:88–103
23. Fukuda M. The role of GIP receptor in the CNS for the pathogenesis of obesity. Diabetes 2021;70:1929–1937
24. Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. Ann Neurol 2010;67:534–541
25. Min SY, Kady J, Nam M, et al. Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. Nat Med 2016;22:312–318
26. Tsagkaraki E, Nicoloro SM, DeSouza T, et al. CRISPR-enhanced human adipocyte browning as cell therapy for metabolic disease. Nat Commun 2021;12:6931
27. Yang Loureiro Z, Solivan-Rivera J, Corvera S. Adipocyte heterogeneity underlying adipose tissue functions. Endocrinology 2022;163:bqab138
28. Yang Loureiro Z, Joyce S, DeSouza T, et al. Wnt signaling preserves progenitor cell multipotency during adipose tissue development. Nat Metab 2023;5:1014–1028
29. Liu X, Zhang Z, Song Y, Xie H, Dong M. An update on brown adipose tissue and obesity intervention: function, regulation and therapeutic implications. Front Endocrinol (Lausanne) 2023;13:1065263
30. The Helping to End Addiction Long-term Initiative. National Institutes of Health, 2023. Accessed 30 September 2024. Available from https://heal.nih.gov/
31. NIH Research Projects on Interoception to Improve Understanding of Brain-Body Function. National Institutes of Health, 2021. Accessed 30 September 2024. Available from https://www.nih.gov/news-events/news-releases/nih-research-projects-interoception-improve-understanding-brain-body-function
32. The Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative. Available from https://braininitiative.nih.gov/
33. DiAntonio A. Axon degeneration: mechanistic insights lead to therapeutic opportunities for the prevention and treatment of peripheral neuropathy. Pain 2019;160(Suppl. 1):S17–S22
34. Oudejans E, Luchicchi A, Strijbis EMM, Geurts JJG, van Dam A-M. Is MS affecting the CNS only? Lessons from clinic to myelin pathophysiology. Neurol Neuroimmunol Neuroinflamm 2020;8:e914
35. Poser CM. The peripheral nervous system in multiple sclerosis. A review and pathogenetic hypothesis. J Neurol Sci 1987;79:83–90
36. Aarsland D, Batzu L, Halliday GM, et al. Parkinson disease-associated cognitive impairment. Nat Rev Dis Primers 2021;7:47
37. Corrà MF, Vila-Chã N, Sardoeira A, et al. Peripheral neuropathy in Parkinson's disease: prevalence and functional impact on gait and balance. Brain 2023;146:225–236
38. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. Molecules 2020;25:5789
39. Bedlack RS, Strittmatter WJ, Morgenlander JC. Apolipoprotein E and neuromuscular disease: a critical review of the literature. Arch Neurol 2000;57:1561–1565
40. Dugger BN, Whiteside CM, Maarouf CL, et al. The presence of select tau species in human peripheral tissues and their relation to Alzheimer's disease. J Alzheimers Dis 2016;51:345–356
41. Caldwell JH, Klevanski M, Saar M, Müller UC. Roles of the amyloid precursor protein family in the peripheral nervous system. Mech Dev 2013;130:433–446
42. Al-Aly Z, Rosen CJ. Long Covid and impaired cognition - more evidence and more work to do. N Engl J Med 2024;390:858–860
43. Dani M, Dirksen A, Taraborrelli P, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med (Lond) 2021;21:e63–e67
44. Seaquist ER. The final frontier: how does diabetes affect the brain? Diabetes 2010;59:4–5
45. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers 2019;5:41
46. Vichaya EG, Chiu GS, Krukowski K, et al. Mechanisms of chemotherapy-induced behavioral toxicities. Front Neurosci 2015;9:131
47. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: a current review. Ann Neurol 2017;81:772–781
48. Callaghan BC, Reynolds EL, Banerjee M, et al. The prevalence and determinants of cognitive deficits and traditional diabetic complications in the severely obese. Diabetes Care 2020;43:683–690
49. Mulhauser K, Reynolds EL, Callaghan BC, Fierro C, Giordani B, Votruba K. Executive functioning in extreme obesity: contributions from metabolic status, medical comorbidities, and psychiatric factors. Obes Surg 2021;31:2669–2681
50. Putnam NM, Reynolds EL, Banerjee M, et al. Neuropsychological outcomes in individuals with type 1 and type 2 diabetes. Front Endocrinol (Lausanne) 2022;13:834978
51. Reynolds EL, Votruba K, Jack CR, et al. Association between brain health outcomes and metabolic risk factors in persons with diabetes. Ann Clin Transl Neurol 2023;10:1891–1898
52. Reynolds EL, Votruba KL, Watanabe M, et al. The effect of surgical weight loss on cognition in individuals with class II/III obesity. J Nutr Health Aging 2023;27:1153–1161
53. Callaghan BC, Reynolds E, Banerjee M, Chant E, Villegas-Umana E, Feldman EL. Central obesity is associated with neuropathy in the severely obese. Mayo Clin Proc 2020;95:1342–1353
54. Blaszkiewicz M, Willows JW, Dubois AL, et al. Neuropathy and neural plasticity in the subcutaneous white adipose depot. PLoS One 2019;14:e0221766
55. Wang P, Loh KH, Wu M, et al. A leptin-BDNF pathway regulating sympathetic innervation of adipose tissue. Nature 2020;583:839–844
56. Brito DVC, Esteves F, Rajado AT, et al.; ALFA Score Consortium. Assessing cognitive decline in the aging brain: lessons from rodent and human studies. NPJ Aging 2023;9:23
57. Brisset M, Nicolas G. Peripheral neuropathies and aging. Geriatr Psychol Neuropsychiatr Vieil 2018;16:409–413
58. Novak A, Vizjak K, Rakusa M. Cognitive impairment in people with epilepsy. J Clin Med 2022;11:267
59. Swift TR, Gross JA, Ward LC, Crout BO. Peripheral neuropathy in epileptic patients. Neurology 1981;31:826–831
60. Kays JL, Hurley RA, Taber KH. The dynamic brain: neuroplasticity and mental health. J Neuropsychiatry Clin Neurosci 2012;24:118–124
61. Damci A, Schruers KRJ, Leue C, Faber CG, Hoeijmakers JGJ. Anxiety and depression in small fiber neuropathy. J Peripher Nerv Syst 2022;27:291–301
62. Torta R, Ieraci V, Zizzi F. A review of the emotional aspects of neuropathic pain: from comorbidity to co-pathogenesis. Pain Ther 2017;6(Suppl. 1):11–17
63. Stogios N, Gdanski A, Gerretsen P, et al. Autonomic nervous system dysfunction in schizophrenia: impact on cognitive and metabolic health. NPJ Schizophr 2021;7:22
64. Roos RAC. Huntington's disease: a clinical review. Orphanet J Rare Dis 2010;5:40
65. Li J, Wang Y, Yang R, et al. Pain in Huntington's disease and its potential mechanisms. Front Aging Neurosci 2023;15:1190563
66. Alcántar-Garibay OV, Incontri-Abraham D, Ibarra A. Spinal cord injury-induced cognitive impairment: a narrative review. Neural Regen Res 2022;17:2649–2654

67. Evans TM, Jaramillo CA, Sataranatarajan K, et al. The effect of mild traumatic brain injury on peripheral nervous system pathology in wild-type mice and the G93A mutant mouse model of motor neuron disease. Neuroscience 2015;298:410–423
68. McDonald SJ, Sharkey JM, Sun M, et al. Beyond the brain: peripheral interactions after traumatic brain injury. J Neurotrauma 2020;37:770–781
69. Redondo-Castro E, Navarro X. Peripheral nerve alterations after spinal cord injury in the adult rat. Spinal Cord 2013;51:630–633
70. Wulf MJ, Tom VJ. Consequences of spinal cord injury on the sympathetic nervous system. Front Cell Neurosci 2023;17:999253
71. van der Burgh HK, Westeneng H-J, Walhout R, et al. Multimodal longitudinal study of structural brain involvement in amyotrophic lateral sclerosis. Neurology 2020;94:e2592–e2604
72. Gentile F, Scarlino S, Falzone YM, et al. The peripheral nervous system in amyotrophic lateral sclerosis: opportunities for translational research. Front Neurosci 2019;13:601
73. Passarelli JP, Nimjee SM, Townsend KL. Stroke and neurogenesis: bridging clinical observations to new mechanistic insights from animal models. Transl Stroke Res 2024;15:53–68
74. Morkavuk G, Işõk K, Odabaşõ Z. Ischemic stroke cases presenting with hand weakness mimicking peripheral neuropathy. Turk J Phys Med Rehabil 2022;68:543–546
75. Song CK, Schwartz GJ, Bartness TJ. Anterograde transneuronal viral tract tracing reveals central sensory circuits from white adipose tissue. Am J Physiol Regul Integr Comp Physiol 2009;296:R501–R511
76. Wang Y, Leung VH, Zhang Y, et al. The role of somatosensory innervation of adipose tissues. Nature 2022;609:569–574
77. Huesing C, Qualls-Creekmore E, Lee N, et al. Sympathetic innervation of inguinal white adipose tissue in the mouse. J Comp Neurol 2021;529:1465–1485
78. Sharma S, Littman R, Tompkins JD, et al. Tiered sympathetic control of cardiac function revealed by viral tracing and single cell transcriptome profiling. Elife 2023;12:e86295
79. Coote JH. Myths and realities of the cardiac vagus. J Physiol 2013;591:4073–4085
80. Hsieh S-T, Lin W-M, Chiang H-Y, et al. Skin innervation and its effects on the epidermis. J Biomed Sci 1997;4:264–268
81. Vulchanova L, Riedl MS, Shuster SJ, et al. P2X3 is expressed by DRG neurons that terminate in inner lamina II. Eur J Neurosci 1998;10:3470–3478
82. Efes ED. The mechanism of the effect of the sympathetic nervous system on skin receptors. Neirofiziologiia 1992;24:552–558; discussion 633-635 [in Russian]
83. Hsieh Y-L, Lin C-L, Chiang H, et al. Role of peptidergic nerve terminals in the skin: reversal of thermal sensation by calcitonin gene-related peptide in TRPV1-depleted neuropathy. PLoS One 2012;7:e50805
84. Wang Z-M, Messi ML, Grinevich V, Budygin E, Delbono O. Postganglionic sympathetic neurons, but not locus coeruleus optostimulation, activates neuromuscular transmission in the adult mouse in vivo. Mol Cell Neurosci 2020;109:103563
85. Chiocchetti R, Grandis A, Bombardi C, et al. Extrinsic and intrinsic sources of calcitonin gene-related peptide immunoreactivity in the lamb ileum: a morphometric and neurochemical investigation. Cell Tissue Res 2006;323:183–196
86. Lee J, Yamamoto T, Hayashi S, et al. Enhancement of CGRP sensory afferent innervation in the gut during the development of food allergy in an experimental murine model. Biochem Biophys Res Commun 2013;430:895–900
87. Yang D, Jacobson A, Meerschaert KA, et al. Nociceptor neurons direct goblet cells via a CGRP-RAMP1 axis to drive mucus production and gut barrier protection. Cell 2022;185:4190–4205.e25
88. Sharkey KA, Williams RG, Dockray GJ. Sensory substance P innervation of the stomach and pancreas. Demonstration of capsaicin-sensitive sensory neurons in the rat by combined immunohistochemistry and retrograde tracing. Gastroenterology 1984;87:914–921
89. Mittal R, Debs LH, Patel AP, et al. Neurotransmitters: the critical modulators regulating gut-brain axis. J Cell Physiol 2017;232:2359–2372
90. Han Y, Wang B, Gao H, et al. Vagus nerve and underlying impact on the gut microbiota-brain axis in behavior and neurodegenerative diseases. J Inflamm Res 2022;15:6213–6230
91. Makhmutova M, Caicedo A. Optical imaging of pancreatic innervation. Front Endocrinol (Lausanne) 2021;12:663022
92. Hampton RF, Jimenez-Gonzalez M, Stanley SA. Unravelling innervation of pancreatic islets. Diabetologia 2022;65:1069–1084
93. Alvarsson A, Jimenez-Gonzalez M, Li R, et al. A 3D atlas of the dynamic and regional variation of pancreatic innervation in diabetes. Sci Adv 2020;6:eaaz9124
94. Berthoud H-R. Anatomy and function of sensory hepatic nerves. Anat Rec A Discov Mol Cell Evol Biol 2004;280:827–835
95. Chida Y, Sudo N, Takaki A, Kubo C. The hepatic sympathetic nerve plays a critical role in preventing Fas induced liver injury in mice. Gut 2005;54:994–1002
96. Goehler LE, Sternini C. Neuropeptide Y immunoreactivity in the mammalian liver: pattern of innervation and coexistence with tyrosine hydroxylase immunoreactivity. Cell Tissue Res 1991;265:287–295
97. Ueno T, Bioulac-Sage P, Balabaud C, Rosenbaum J. Innervation of the sinusoidal wall: regulation of the sinusoidal diameter. Anat Rec A Discov Mol Cell Evol Biol 2004;280:868–873
98. Kroeger I, Erhardt A, Abt D, et al. The neuropeptide calcitonin gene-related peptide (CGRP) prevents inflammatory liver injury in mice. J Hepatol 2009;51:342–353
99. Laschinger M, Wang Y, Holzmann G, et al. The CGRP receptor component RAMP1 links sensory innervation with YAP activity in the regenerating liver. FASEB J 2020;34:8125–8138
100. Cobo R, García-Piqueras J, Cobo J, Vega JA. The human cutaneous sensory corpuscles: an update. J Clin Med 2021;10:227
101. Rodríguez Cruz PM, Cossins J, Beeson D, Vincent A. The neuromuscular junction in health and disease: molecular mechanisms governing synaptic formation and homeostasis. Front Mol Neurosci 2020;13:610964
102. Agashe S, Petak S. Cardiac autonomic neuropathy in diabetes mellitus. Methodist Debakey Cardiovasc J 2018;14:251–256
103. Dogiparthi SN, Muralidhar K, Seshadri KG, Rangarajan S. Cutaneous manifestations of diabetic peripheral neuropathy. Dermatoendocrinol 2017;9:e1395537
104. Parasoglou P, Rao S, Slade JM. Declining skeletal muscle function in diabetic peripheral neuropathy. Clin Ther 2017;39:1085–1103
105. Kuźnik E, Dudkowiak R, Adamiec R, Poniewierka E. Diabetic autonomic neuropathy of the gastrointestinal tract. Prz Gastroenterol 2020;15:89–93
106. Zheng Z, Shimamura K, Anthony TL, Travagli RA, Kreulen DL. Nitric oxide is a sensory nerve neurotransmitter in the mesenteric artery of guinea pig. J Auton Nerv Syst 1997;67:137–144
107. Dong F, Yang X-J, Jiang T-B, Chen Y. Ischemia triggered ATP release through Pannexin-1 channel by myocardial cells activates sympathetic fibers. Microvasc Res 2016;104:32–37
108. Shome S, Rana T, Ganguly S, et al. Dopamine regulates angiogenesis in normal dermal wound tissues. PLoS One 2011;6:e25215
109. Page AJ, O'Donnell TA, Cooper NJ, Young RL, Blackshaw LA. Nitric oxide as an endogenous peripheral modulator of visceral sensory neuronal function. J Neurosci 2009;29:7246–7255
110. Miller KE, Hoffman EM, Sutharshan M, Schechter R. Glutamate pharmacology and metabolism in peripheral primary afferents: physiological and pathophysiological mechanisms. Pharmacol Ther 2011;130:283–309
111. Li J, King NC, Sinoway LI. Interstitial ATP and norepinephrine concentrations in active muscle. Circulation 2005;111:2748–2751
112. Häbler HJ, Wasner G, Jänig W. Attenuation of neurogenic vasoconstriction by nitric oxide in hindlimb microvascular beds of the rat in vivo. Hypertension 1997;30:957–961
113. Than K, Kim E, Navarro C, et al. Vesicle-released glutamate is necessary to maintain muscle spindle afferent excitability but not dynamic sensitivity in adult mice. J Physiol 2021;599:2953–2967

114. Kennedy C. ATP as a cotransmitter in sympathetic and parasympathetic nerves - another Burnstock legacy. Auton Neurosci 2021;235:102860
115. Li ZS, Pham TD, Tamir H, Chen JJ, Gershon MD. Enteric dopaminergic neurons: definition, developmental lineage, and effects of extrinsic denervation. J Neurosci 2004;24:1330–1339
116. Terry N, Margolis KG. Serotonergic mechanisms regulating the GI tract: experimental evidence and therapeutic relevance. Handb Exp Pharmacol 2017; 239:319–342
117. Bertrand G, Chapal J, Loubatieres-Mariani MM. Potentiating synergism between adenosine diphosphate or triphosphate and acetylcholine on insulin secretion. Am J Physiol 1986;251:E416–E421
118. Bodin P, Burnstock G. Purinergic signalling: ATP release. Neurochem Res 2001;26:959–969
119. Love JA, Yi E, Smith TG. Autonomic pathways regulating pancreatic exocrine secretion. Auton Neurosci 2007;133:19–34
120. Ekblad E, Alm P, Sundler F. Distribution, origin and projections of nitric oxide synthase-containing neurons in gut and pancreas. Neuroscience 1994;63:233–248
121. Yamauchi T, Iwai M, Kobayashi N, Shimazu T. Noradrenaline and ATP decrease the secretion of triglyceride and apoprotein B from perfused rat liver. Pflugers Arch 1998;435:368–374
122. el-Salhy M, Stenling R, Grimelius L. Peptidergic innervation and endocrine cells in the human liver. Scand J Gastroenterol 1993;28:809–815
123. Saijyo T, Nomura M, Nakaya Y, Saito K, Ito S. Autonomic nervous system activity during infusion of L-arginine in patients with liver cirrhosis. Liver 1998;18:27–31
124. Malliani A, Lombardi F, Pagani M. Sensory innervation of the heart. Prog Brain Res 1986;67:39–48
125. Gulbenkian S, Saetrum Opgaard O, Ekman R, et al. Peptidergic innervation of human epicardial coronary arteries. Circ Res 1993;73:579–588
126. Hasan W. Autonomic cardiac innervation: development and adult plasticity. Organogenesis 2013;9:176–193
127. Roosterman D, Goerge T, Schneider SW, Bunnett NW, Steinhoff M. Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. Physiol Rev 2006;86:1309–1379
128. Gordon T, Niven-Jenkins N, Vrbová G. Observations on neuromuscular connection between the vagus nerve and skeletal muscle. Neuroscience 1980;5:597–610
129. Dunning BE, Taborsky GJ Jr. Galanin—sympathetic neurotransmitter in endocrine pancreas? Diabetes 1988;37:1157–1162
130. Jensen KJ, Alpini G, Glaser S. Hepatic nervous system and neurobiology of the liver. Compr Physiol 2013;3:655–665
131. Liu K, Yang L, Wang G, et al. Metabolic stress drives sympathetic neuropathy within the liver. Cell Metab 2021;33:666–675.e4
132. Adori C, Daraio T, Kuiper R, et al. Disorganization and degeneration of liver sympathetic innervations in nonalcoholic fatty liver disease revealed by 3D imaging. Sci Adv 2021;7:eabg5733