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Review Article

Functional neuroanatomy of pain pathways: Recent advances in imaging, modulation and clinical implications

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Abstract

Pain is a multidimensional sensation that emerges from the complex interaction of peripheral nociceptors, spinal processing centers, ascending sensory pathways, and higher-order cortical networks. Recent advances in functional neuroimaging, electrophysiology, and molecular mapping have dramatically advanced the understanding of pain circuitry, allowing for the precise delineation of sensory-discriminative, affective-motivational, and cognitive-evaluative components. This review synthesizes current insights on the functional neuroanatomy of pain pathways, with a strong emphasis on how high-resolution imaging modalities like functional MRI, diffusion tractography, positron emission tomography, and magnetoencephalography have reshaped classical pain models. Parallel innovations in neuromodulatory techniques include deep brain stimulation, spinal cord stimulation, transcranial magnetic stimulation, targeted peripheral nerve stimulation, and computationally guided pharmacomodulation, opening up transformative therapeutic avenues for chronic and neuropathic pain. By integrating the latest structural and functional findings with emerging clinical applications, this review emphasizes the rapidly evolving translational landscape in pain neuroscience and its implications for precision diagnostics and personalized pain management.

Keywords: Functional neuroanatomy, Pain pathways, Nociception, Neuromodulation, Functional imaging, Connectomics, Chronic pain, Spinal cord circuits, Thalamocortical networks, Analgesic precision medicine

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1. Introduction

Pain is a basic protective mechanism that allows the detection and avoidance of noxious stimuli; however, persistence beyond the time of tissue healing represents a complex pathological condition with significant global morbidity.[1-3] Classical models, including the gate control theory, established a foundation for understanding nociceptive transmission; however, advances in molecular neurobiology and high-resolution imaging have identified a much more complex network of peripheral, spinal, and supraspinal circuits than previously appreciated.[4-6] Contemporary research emphasizes that pain is not simply a linear sensory phenomenon but a multidimensional experience influenced by sensory-discriminative pathways, affective-motivational networks, and cognitive-evaluative systems distributed throughout the central nervous system.[7-9]

The peripheral nociceptive apparatus consists of specialized ion channels and receptors that convert mechanical, thermal, and chemical stimuli into electrical signals conducted through Aδ and C fibers to spinal dorsal horn neurons.[10,11] In the spinal cord, these inputs are subjected to extensive modulation by excitatory and inhibitory interneurons, projection neurons, and descending supraspinal pathways to shape both acute and chronic pain responses.[12,13] The ascending paths-most notably the spinothalamic, spinoreticular, and spin parabrachial tracts-forward nociceptive signals to the thalamus, insula, anterior cingulate cortex, and somatosensory cortices, where perception, localization, and emotional valence are integrated.[14-17] Thus, during the past ten years, functional imaging modalities such as fMRI, diffusion tensor imaging, positron emission tomography, and magnetoencephalography have deeply revolutionized pain neuroanatomy knowledge by allowing mapping of dynamic brain networks involved in nociception, chronic pain chronification, and central sensitization.[18-21] These modalities reveal altered connectivity in the default mode, salience, and

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sensorimotor networks in chronic pain states, suggesting that persistent pain reflects a shift from peripheral nociception to maladaptive brain network reorganization.[22-24]

In tandem, neuromodulatory interventions, such as transcranial magnetic stimulation, spinal cord stimulation, deep brain stimulation, and peripheral nerve modulation, have parallelled these advances to introduce an array of targeted therapeutic strategies to modulate aberrant pain circuits through anatomical precision.[25-27] Connectome-based modeling and AI-assisted signal decoding are some of the emergent computational approaches that continue to drive personalized pain management by defining patient-specific neural signatures.[28-30] Taken together, these represent a paradigm shift from a purely symptom-based understanding of pain to systems-level and network-oriented approaches. This review consolidates current knowledge regarding the functional neuroanatomy of pain pathways and explores how cutting-edge imaging and neuromodulation are rewriting the diagnosis and therapy of clinical pain neuroscience.

2. Functional Anatomy of Pain Pathways

Pain perception ensues from a highly organized network that spans peripheral nerves, the spinal cord, and supraspinal centers, integrating aspects of the sensory, affective, and cognitive dimensions. Understanding functional anatomy is essential to explain mechanisms of pathological pain and provide a rationale for targeted interventions.

1. **Peripheral nociceptors:** Peripheral nociceptors are specialized sensory neurons that detect noxious mechanical, thermal, and chemical stimuli. These neurons express a range of ion channels and receptors, including transient receptor potential (TRP) channels, acid-sensing ion channels (ASICs), and voltage-gated sodium and calcium channels, which transduce external stimuli into electrical signals.[1,2] Two key fiber types mediate nociceptive transmission: Aδ fibers, myelinated fibers that mediate sharp, fast pain, and C fibers, unmyelinated fibers that mediate slow, dull, burning pain.[3] The convergence of these fibers takes place in the dorsal horn of the spinal cord, the first synaptic relay within the central nervous system.

2. **Spinal cord processing:** Nociceptive signals are thus subjected to complex modulation within the spinal dorsal horn by excitatory and inhibitory interneurons. Integration of sensory input is largely performed by laminae I–V of the dorsal horn: laminae I and II mainly process noxious input, whereas more deeply lying laminae forward the signal to ascending tracts.[4,5] Projection neurons transmit the information via multiple ascending pathways including the spinothalamic tract, spinoreticular tract, and spinoparabrachial tract. Parallel to this, descending modulatory pathways from the brainstem influence dorsal horn excitability, which thus permits the modulation of pain at the spinal level.[6,7]

3. **Ascending pathways and supraspinal integration:** The spinothalamic tract is the main pathway transmitting nociceptive signals to the thalamus, where it acts as a relay for sensory-discriminative processing.[8] Secondary projections from the thalamus project to the primary and secondary somatosensory cortices for localization and intensity coding of pain. The anterior cingulate cortex and insula provide affective and emotional aspects, while prefrontal cortex is responsible for cognitive-evaluative processing.[9,10] Other ascending pathways, like the spinoreticular and spinoparabrachial tracts, contribute to autonomic and behavioral reactions, reflecting the multidimensionality of pain perception.[11]

4. **Descending modulatory pathways:** Pain processing is bidirectional, with descending circuits modulating nociceptive input at the spinal level. Key structures include the periaqueductal gray (PAG), rostro ventromedial medulla (RVM), and locus coeruleus, which release neurotransmitters such as serotonin, norepinephrine, and endogenous opioids to inhibit or facilitate pain transmission.[12,13] This descending modulation is important in adaptive responses, but may undergo maladaptive changes in chronic pain states that lead to central sensitization and persistent pain.[14]

5. **Functional network perspective:** Recent research underlines that the perception of pain comes from a network of interconnected neural networks rather than separate pathways. Sensorimotor, limbic, and salience networks are functionally interconnected during nociceptive processing, dynamic interactions that explain large individual differences in pain experiences.[15-17] This network view offers the structure for understanding chronic pain syndromes, which more often than not emanate from maladaptive connectivity with altered network excitability.

3. Physiological Mechanisms of Pain Perception

Pain perception is not the passive relay of sensory input; rather, it forms part of a complex physiology integrating the sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions. Multidimensional processing underlies both normal nociception and the pathophysiology of chronic pain conditions.

1. **Sensory-discriminative dimension:** The sensory-discriminative aspect of pain allows localization, the assessment of intensity, and temporal characterization of noxious stimuli. Signals from peripheral nociceptors ascend primarily through the spinothalamic tract to the ventral posterolateral and ventral posteromedial

thalamic nuclei, which relay information to the primary and secondary somatosensory cortices. Here, stimulus intensity, quality, and spatial localization are decoded, providing the brain with precise information about the source of pain.[18-20]

2. **Affective-motivational dimension:** Pain is intrinsically unpleasant, involving neural circuits concerned with emotional and motivational functions. Key regions include the anterior cingulate cortex, insula, amygdala, and limbic system. Activation of these regions mediates the emotional valence of pain, drives protective behaviors, and contributes to suffering. Dysregulation in these circuits is often implicated in chronic pain syndromes, depression, and anxiety associated with persistent pain.[21,22]

3. **Cognitive-evaluative dimension:** The cognitive-evaluative component enables the individual to interpret, contextualize, and modulate their pain. The prefrontal cortex and associated executive networks govern attention, anticipation, and coping strategies. Cognitive modulation can either enhance or reduce the perception of pain through top-down pathways, which interact with descending modulatory circuits to influence spinal nociceptive transmission.[23,24]

4. **Central sensitization:** Repeated or intense nociceptive input may induce a state of hyperexcitability in dorsal horn neurons and supraspinal networks. This condition is known as central sensitization. Clinical manifestations include hyperalgesia or an exaggerated response to painful stimuli and allodynia, pain from normally nonpainful stimuli. Proposed mechanisms involve enhancement of synaptic transmission, activation of NMDA receptors, neuroinflammation, and maladaptive plasticity in spinal and cortical circuits.[25,26]

5. **Neurochemical modulation:** Pain processing is the result of a delicate balance between excitatory and inhibitory neurotransmitters. Glutamate, substance P, and calcitonin gene-related peptide promote nociceptive transmission, whereas GABA, glycine, endogenous opioids, and monoamines-several types of serotonin and norepinephrine-exert the inhibitory control. All changes to these neurochemical systems are associated with chronic pain states and thus are potentially pharmacological targets.[27,28]

6. **Neuroimmune interactions:** Recent studies elucidate the contribution of immune cells and glial activation to pain physiology. Microglia, astrocytes, and pro-inflammatory cytokines regulate synaptic activity and neuronal excitability in both the spinal cord and brain. These interactions seem to be extremely important in neuropathic pain, inflammatory pain, and chemotherapyinduced pain syndromes.[29,30]

4. Advances in Functional Imaging of Pain Pathways

During the last decades, there has been remarkable progress in imaging technologies, which enable the visualization and mapping of pain-related neural circuits with hitherto unimaginable precision. These have dramatically revised our understanding of both acute and chronic pain as dynamic interactions among peripheral, spinal, and supraspinal structures. This ranges from functional imaging with direct clinical relevance in the diagnosis of neuropathic pain syndromes to guiding neuromodulation therapies. Biomarkers from imaging will help stratify patients for interventions like spinal cord stimulation, transcranial magnetic stimulation, or targeted pharmacotherapy, thereby enhancing therapeutic outcomes while minimizing side effects. Longitudinal imaging also provides insight into the neural plasticity underlying treatment response and chronicity.

1. **Functional magnetic resonance imaging:** Functional MRI enables the non-invasive mapping of brain activity resulting from nociceptive stimulation through detecting BOLD signals. Task-based fMRI recognizes regions activated during acute pain, including primary and secondary somatosensory cortices, insula, anterior cingulate cortex, and thalamus. Resting-state fMRI reveals intrinsic connectivity networks, showing disturbed default mode, salience, and sensorimotor network interactions in chronic pain conditions.[1,2]

2. **Diffusion tensor imaging and tractography:** It provides information on the structural integrity of white matter tracts by measuring water diffusion along axonal pathways. Tractography thus enables the visualization of not only ascending nociceptive fibers such as the spinothalamic and spinoreticular tracts, but also descending modulatory pathways. Changes in fractional anisotropy and also tract coherence have been associated with various chronic pain syndromes, which emphasize microstructural plasticity as a substrate for persistent pain.[3,4]

3. **PET (Positron emission tomography):** PET imaging allows for in vivo studies of molecular and neurochemical alterations related to pain. Radioligands binding to opioid receptors, dopaminergic, and glutamatergic systems show the regional availability of receptors and functional changes in chronic pain conditions. These studies mechanistically complement the structural and functional MRI information, by interlinking the neurochemistry to the network activity on a different level.[5,6]

4. **Magnetoencephalography (MEG) and electrophysiology:** MEG and advanced electrophysiological techniques achieve high temporal resolution in the mapping of nociceptive processing.

These modalities can reveal rapid neural oscillations and connectivity patterns throughout cortical and subcortical circuits, thereby elucidating temporal dynamics regarding pain perception and maladaptive network synchronization in chronic pain.[7,8]

5. **Integrative imaging approaches:** Recent studies increasingly apply the technique of multimodal imaging, using a combination of fMRI, DTI, PET, and MEG to provide comprehensive spatiotemporal mapping of pain circuits. In addition, integration of these datasets with computational modeling and connectomics will enable personalized assessment of dysfunction of pain networks, prediction of treatment response, and identification of novel targets.[9,10]

5. Clinical Applications and Neuromodulation

Advancement of the functional knowledge of pain pathways has yielded targeted neuromodulatory interventions. Such therapies, based on accurate anatomical and physiological knowledge, aim at the modulation of abnormal nociceptive circuits, reduction in pain perception, and improvement in patient outcomes for chronic and refractory pain conditions.

1. **Deep brain stimulation (DBS):** DBS entails the implantation of electrodes into targeted regions of the brain in an effort to alter neural activity. Targets for pain include the periaqueductal gray, ventral posterolateral thalamus, and anterior cingulate cortex. Stimulation at these sites can alter both ascending and descending nociceptive pathways to decrease the intensity of pain and modify affective-motivational components. DBS is particularly effective for patients suffering from intractable neuropathic or central pain syndromes.[1,2]

2. **Spinal cord stimulation (SCS):** SCS applies electrical pulses to the dorsal column of the spinal cord, which in turn would stimulate the inhibitory interneurons and descending modulatory pathways, thus reducing the nociceptive transmission at the spinal level. Contemporary SCS systems include high-frequency stimulation, burst stimulation, and closed-loop stimulation for improved efficacy with a reduction in side effects. SCS is very useful in failed back surgery syndrome, complex regional pain syndrome, and other chronic neuropathic disorders.[3,4]

3. **Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS):** TMS and tDCS are non-invasive brain stimulation techniques that modulate cortical excitability and thereby influence pain perception by top-down modulation of the prefrontal cortex, motor cortex, and related networks. TMS is known to cause long-lasting changes in cortical plasticity, while tDCS changes membrane potentials to facilitate inhibitory or excitatory modulation. These are increasingly being used in chronic neuropathic pain, fibromyalgia, and migraine prophylaxis.[5,6]

4. **Peripheral nerve stimulation (PNS):** PNS describes the stimulation of peripheral nerves to modulate the nociceptive input in advance of its arrival at the spinal cord. Techniques include stimulation with implanted electrodes, percutaneous leads, and non-invasive transcutaneous stimulation. PNS is particularly effective for localized neuropathic pain, post-amputation pain, and occipital neuralgia, providing precise anatomical targeting based on peripheral nerve mapping.[7,8]

5. **Personalized and computational approaches:** Recent innovations incorporate functional imaging, connectome analysis, and machine learning algorithms into the personalization of neuromodulation therapy. By mapping patient-specific pain networks and predicting responses, these approaches amplify efficacy while reducing trial-and-error programming and informing the selection of optimal stimulation targets and parameters.[9,10]

Neuromodulatory interventions represent a paradigm shift from generalized analgesic therapy to circuit-targeted, mechanism-based treatment. Understanding the anatomical and physiological basis of these interventions allows clinicians to optimize patient selection, improve safety, and maximize therapeutic benefit. Emerging evidence supports combining neuromodulation with pharmacotherapy, cognitive-behavioral strategies, and rehabilitative interventions in an effort to achieve multidimensional pain control.

6. Discussion

Pain is a multidimensional experience that emerges from the interplay of peripheral, spinal, and central nervous system networks. The review on functional neuroanatomy and physiology underlines the fact that nociception is much more than a mere linear relay of noxious stimuli-a dynamic process that is continuously informed by structural connectivity, synaptic modulation, neurochemical signaling, and higher-order cognitive and affective networks. This multidimensionality explains why pain perception is highly variable between individuals and often persists when peripheral injury appears to be resolved.[1-3]

Functional neuroimaging has unraveled a complex network architecture underlying pain that involves the somatosensory cortices, anterior cingulate cortex, insula, thalamus, and limbic regions. Such findings emphasize that chronic pain is associated with maladaptive plasticity and altered connectivity across sensorimotor, salience, and default mode networks. These insights are clinically

important, as they offer objective biomarkers to guide diagnosis, prognosis, and personalized therapy.[4-6]

Various neuromodulatory interventions, from deep brain stimulation to non-invasive cortical stimulation, are prototypical translational applications of this anatomical and physiological knowledge. These strategies have included specific targeting of dysregulated circuits to restore inhibitory-excitatory balance and modulate maladaptive network activity. Integration with functional imaging, computational modeling, and connectomics further allows patient-specific optimization, moving toward precision pain medicine.[7-9] Despite these advances, several challenges persist. First, heterogeneity of chronic pain syndromes makes standardization of imaging and neuromodulation protocols challenging. Second, many of our mechanistic understandings emanate from animal models that may not really capture the network complexity in humans. Third, while imaging provides a correlational data, causal links between network activity and subjective pain experience are still being unraveled. Lastly, long-term efficacy and safety of neuromodulatory interventions need further studies within diverse patient populations.[10-12]

In all, functional neuroanatomy integrated with physiology and translational technologies provides a systems approach to the understanding of pain, thereby offering avenues for targeted intervention. Future studies that integrate multimodal imaging with neurochemical analysis, genetic profiling, and machine learning could have the potential to further refine personalized pain management strategies and improve clinical outcomes.

7. Emerging Trends and Future Directions

The pain research landscape is evolving, driven by advances in imaging, neuromodulation, molecular biology, and computational neuroscience. New trends are coming out and reshaping the understanding of pain; new ways are emerging for diagnosis, monitoring, and therapy.

1. **Biomarker discovery and pain phenotyping:** Biomarkers of structure, function, and molecular signature have become increasingly central to personalized pain management. Imaging biomarkers emanating from fMRI, DTI, and PET offer objective means of ascertaining injury at the network level, while molecular markers, such as cytokines, neuropeptides, and receptor expression, elucidate neuroinflammatory and neurochemical contributions to chronic pain. Integration of these biomarkers into a single practice allows for precision phenotyping, susceptibility prediction, and tailored interventions at an individual-patient level.[1,2]
2. **Artificial intelligence and machine learning:** AI and machine learning now seem to be the transformative tools in pain research. Algorithms can analyze complex imaging datasets, map network connectivity, and predict treatment responses. Predictive modeling thus enables clinicians to stratify patients for neuromodulation or pharmacotherapy, optimize stimulation parameters, and anticipate adverse effects. Functional neuroimaging combined with AI enables personalized connectome-based pain therapy that improves treatment efficacy and reduces trial-and-error approaches.[3,4]
3. **Multimodal integration:** Future research focuses on the integration of anatomical, physiological, imaging, molecular, and computational data. Indeed, multimodal approaches will be helpful in understanding exactly how peripheral input, spinal processing, and supraspinal network dynamics interact to create the perception of pain. This holistic perspective rewards the development of mechanism-based, multimodal interventions-a combination of pharmacotherapy, neuromodulation, and cognitive-behavioral strategies for synergistic outcomes.[5,6]
4. **Novel analgesic targets and circuit-based therapies:** Such granular understanding of the pain circuitry has highlighted new therapeutic targets. The modulation of descending inhibitory pathways, specific thalamocortical loops, or peripheral nociceptors offers opportunities for circuit-specific pharmacological and neuromodulatory interventions. Further, the application of optogenetic and chemogenetic tools in preclinical models allows for precise control of nociceptive circuits that may be ported into future human applications.[7-8]
5. **Precision and translational pain medicine:** Such a convergence of functional anatomy, neurophysiology, and computational analytics is driving pain management toward a precision medicine paradigm. Application of personalized neurointerventions, accounting for inter-individual differences in neural architecture as well as network plasticity and molecular signature, can maximize efficacy while minimizing side effects. This also allows for the development of monitoring tools that will enable dynamic adjustments in therapy over time.[9,10]

8. Challenges and Limitations

Despite the important advances in understanding functional neuroanatomy and physiology, several challenges and limitations persist, and must be taken into consideration while interpreting findings and translating them into clinical practice.

1. **Heterogeneity of pain syndromes:** Chronic pain encompasses neuropathic, inflammatory, musculoskeletal, and central sensitization disorders. The heterogeneity of conditions complicates the

standardization of imaging protocol neuromodulation parameters and outcome measures. Unique variability in anatomy, physiology, and genetic predisposition further limits the generalizability of the findings.[1,2]

2. **Translational gaps:** Much of the mechanistic understanding of pain comes from animal studies or in vitro models. While these provide critical insights into nociceptive pathways and cellular mechanisms, translating these findings into human pain perception is challenging due to species-specific differences in anatomy, network complexity, and the behavioral expression of pain.[3,4]

3. **Limitations of imaging and neuromodulation:** While powerful, functional imaging techniques often provide only correlational evidence and not causal evidence. Further, spatial and temporal resolution limitations, susceptibility to motion artifacts, and variability in analysis pipelines can affect data reliability. Likewise, although promising, neuromodulatory interventions such as DBS, SCS, and TMS have variable efficacies across patients, and stimulation targets and parameters for optimal treatment are not completely standardized.[5-6]

4. **Complexity of multidimensional pain measurement:** Pain is inherently subjective, with sensory, emotional, and cognitive dimensions. The quantification of these objectively has yet to be effectively realized, and the tools available may not fully capture the multidimensional experience. This complexity complicates not only clinical evaluation but also the interpretation of neuroimaging or neuromodulation outcomes.[7]

5. **Ethical and practical considerations:** Neural circuit-targeting interventions raise a host of ethical concerns: long-term effects, invasiveness, and patient autonomy. Besides, resource-intensive imaging and neuromodulation procedures may not be accessible to all patient populations, which further limits the principles of equitable application of advanced pain therapies.[8]

Despite these difficulties, continuous technological innovations, integrative approaches, and personalized strategies offer promising pathways toward the possibility of surmounting these limitations in order to further both the scientific understanding and clinical management of pain.

9. Conclusion

Pain is considered a complex, multidimensional experience emerging from the complex interplay of peripheral, spinal, and supraspinal networks. Advances in functional neuroanatomy and physiology have begun to detail both structural and neurochemical substrates for respective sensory-discriminative, affective-motivational, and cognitive-evaluative components of pain. High-resolution imaging techniques, including fMRI, DTI, PET, and MEG, have transformed our understanding of dynamic pain networks by demonstrating maladaptive plasticity and altered connectivity in the context of chronic pain conditions.

Neuromodulatory interventions, including deep brain stimulation, spinal cord stimulation, transcranial magnetic stimulation, and peripheral nerve stimulation, illustrate the clinical promise of circuit-targeted therapies, providing mechanism-based approaches to pain management. Biomarker discovery, artificial intelligence, multimodal integration, and precision medicine represent emerging trends with the potential for further refinement of individualized treatment strategies, thereby promoting efficacy while minimizing adverse effects. Despite difficulties in heterogeneity of pain syndromes, translational gaps, technical limitations, and ethical considerations, the combination of anatomic insights, physiological findings, and computational models is leading toward mechanism-based, personalized pain management. Continued research at the interface of neuroanatomy, physiology, imaging, and neuromodulation holds remarkable promise not only for better outcomes but also to advance the science pertinent to both acute and chronic pain.

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11. Conflict of Interest

None.

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