Radiotracers in the Diagnosis of Pain: A Mini Review

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Abstract

The diagnosis and understanding of pain is challenging in clinical practice. Assessing pain relies heavily on self-reporting by patients, rendering it inherently subjective. Traditional clinical imaging methods such as computed tomography and magnetic resonance imaging can only detect anatomical abnormalities, offering limited sensitivity and specificity in identifying pain-causing conditions. Radiotracers play a vital role in molecular imaging that aims to identify abnormal biological processes at the cellular level, even in apparently normal anatomical structures. Therefore, molecular imaging is an important area of research as a prospective diagnostic modality for pain-causing pathophysiology. We present a mini review of the current knowledge base regarding radiotracers for identification of pain in vivo. We also describe radiocaine, a novel positron emission tomography imaging agent for sodium channels that has shown great potential for identifying/labeling pain-producing nerves and producing an objectively measurable pain intensity signal.

Keywords
- radiotracers
- pain
- positron emission tomography imaging
- single-photon emission computed tomography imaging

Chronic pain affects 50 million people in the United States and is the leading cause of disease burden globally.[1] The diagnosis and understanding of pain is challenging in clinical practice. Assessing pain relies heavily on self-reporting by patients, making it inherently subjective. Pain in humans is typically evaluated with rating scales to determine intensity/severity, such as verbal descriptors or images depicting pain levels, and by using disability indexes and mood screeners.[2] Although self-reported information is important, pain is a highly subjective and deeply personal experience that can be influenced by a host of genetic, biological, environmental, and psychological factors, leaving these measurements extremely difficult to generalize.[2]

Traditional clinical imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) can only detect anatomical abnormalities that often fail to identify the root cause of pain. Depending on age and other factors, up to 80% of asymptomatic patients show abnormalities on MRI spine and knees, and the prevalence of anatomical irregularities is similar between asymptomatic and symptomatic individuals.[3,4] For instance, abnormal processes in the cervical and lumbar spine, such as changes in disk signal, disk displacement, nerve root compression, and facet arthropathy, are observed in 64 to 89% of asymptomatic patients.[3] This lack of specificity directly or indirectly contributes to delayed, ineffective, or unnecessary treatment decisions based on unhelpful imaging results. Consequently, many pain sufferers are never accurately diagnosed, their symptoms are challenging to monitor, and the treatment options are largely based on trial and error. Tools are greatly needed that can both accurately identify the source of pain and objectively measure pain intensity.

Molecular imaging focuses on visualizing and studying the molecular and cellular processes within living organisms.

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It uses specialized imaging techniques and probes that target specific molecules or cellular components, providing detailed insights into normal and pathologic function.[5] The most common molecular imaging modalities are single-photon emission computed tomography (SPECT) and positron emission tomography (PET).[5] SPECT and PET imaging are common techniques used to visualize and evaluate cellular function that can help diagnose and monitor various conditions, such as cancer, cardiovascular diseases, and neurologic disorders such as pain.

In recent years, molecular imaging has emerged as a promising diagnostic modality for identifying pain-causing pathology. This modality may be used to examine and identify abnormal physiologic activity along the nociceptive pathway in both peripheral and central nervous systems, which may in turn help identify pain-producing areas. However, the complex nature of the biochemical pathways involved in chronic pain nociception and central sensitization, such as inflammatory mediators, responsive cells, receptors, and ion channel expression,[6,7] pose challenges to the successful imaging of pain.

For instance, potential toxicity risks with ion channel targeting must be considered. Furthermore, ion channels are expressed ubiquitously and therefore lack the specificity to nervous tissues that may be required for pain imaging. There are also technical limitations on the resolution of these modalities that make it difficult to resolve fine structures such as the dorsal root ganglia or distal peripheral nerves that may be required for pain imaging. However, the development of hybrid hypersensitive nuclear medicine techniques such as PET/MRI has greatly assisted in overcoming some of these challenges.[8] Consequently, a great deal of research efforts currently are focusing on identifying reliable candidate radiotracers for the molecular imaging of pain using PET/MRI. We present a mini review of several radiotracers currently in clinical use or under development.

Review

Single-photon Emission Computed Tomography Imaging

The radiotracers used in SPECT imaging bind to a specific target and emit gamma photons detected by cameras that when integrated with CT imaging create detailed images of tissues/organisms.[9,10] Radiotracers are chosen based on the target protein or tissue of interest and administered intravenously. Computer algorithms use the acquired data to construct cross-sectional images or three-dimensional (3D) representations of the distribution of injected radiotracer molecules, and the resulting SPECT image provides information on the function (metabolism) of the tissue under investigation. Currently SPECT scans are primarily used to diagnose and monitor disease progression in conditions such as heart disease; bone disorders, to identify sources of internal bleeding; and neurologic disorders such as Parkinson's disease and epilepsy.[11–13]

A variety of SPECT radiotracers are currently used including technetium-99m (Tc-99m; ►**Fig. 1**), which is the most commonly used medical radioisotope in the world, as well as iodine-123 (I-123), thallium-201 (Tl-201), and gallium-67 (Ga-67), each with its own specific applications and characteristics.[14,15]

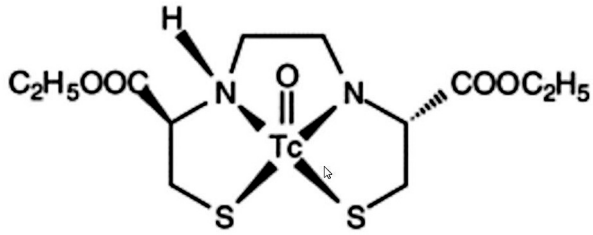

Fig. 1 Technetium 99m.

Technetium 99m-labeled ethyl cysteinate dimer (Tc-99m ECD) is used in brain perfusion studies because it effectively crosses the blood-brain barrier, has a rapid distribution time, and a 1- to 2-hour postinjection tissue retention time that together provide valuable information about regional cerebral blood flow and brain tissue metabolism.[12,13,16] Tc-99m ECD has been studied for the assessment of pain-related conditions by evaluating cerebral blood flow and metabolism in brain areas associated with pain perception and processing. For example, Nakabeppu et al[17] noted decreased bilateral thalamic perfusion in chronic pain sufferers. Nakamura et al reported decreased perfusion in the bilateral prefrontal cortex in patients with chronic low back pain when compared with patients with acute low back pain.[18] Furthermore, a study by Bermo et al showed increased perfusion of the cerebellum in patients undergoing painful burn wound cleaning and debridement.[19] Lastly, Newberg et al also noted asymmetric thalamic perfusion in postoperative dental pain that improved after analgesia was administered.[20]

Aside from brain perfusion measurements, SPECT has been used to help localize pain in the periphery. A recent meta-analysis by Anzola et al concluded that SPECT/CT can be used to accurately identify different sources of knee pain after arthroplasty such as hardware malfunction and patellofemoral syndrome/degeneration and joint instability.[21] Varga et al also recently published a meta-analysis on the role of SPECT imaging in the diagnosis and treatment of chronic neck and back pain caused by spinal degeneration and concluded that using SPECT to diagnose facet arthropathy seems to be associated with a significantly higher rate of facet block success, indicating that SPECT may be useful in identifying pain-producing facet joints.[22] A retrospective analysis of 48 patients, who underwent SPECT/CT to help identify the pain generator in neck and lower back pain and subsequently had cervical or lumbar fusion, noted a significant improvement in self-reported pain scores at 6 months postsurgery, suggesting that SPECT/CT may have some diagnostic advantages over current imaging modalities in correctly identifying pain generators in axial spine disease.[23] A smaller prospective study of back pain in older adult patients ($n = 5$) demonstrated the usefulness of SPECT/CT in correctly identifying the specific cause of pain in patients with lumbar degenerative disease.[24]

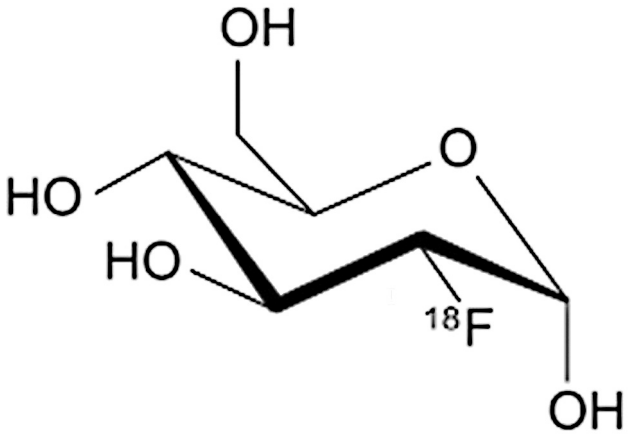

Fig. 2 [18F]-Fluorodeoxyglucose.

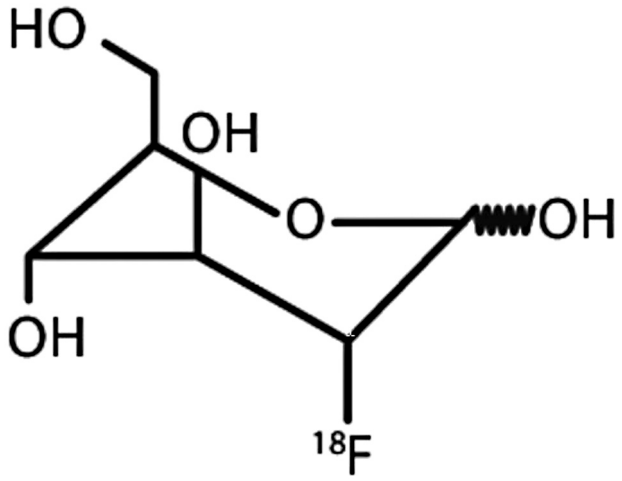

Fig. 3 [18F]-Sodium fluoride.

Positron Emission Tomography Imaging

PET radiotracers emit positrons that collide with electrons, leading to the emission of two gamma rays in opposite directions. The gamma rays are detected by specialized cameras surrounding the patient, enabling the construction of detailed 3D images. The detection of two gamma rays, rather than one (as in SPECT), enables superior spatial resolution for PET.

The following PET radiotracers have been used to assess/study pain in preclinical and/or clinical studies.

[18F]-Fluorodeoxyglucose

The radiotracer [18F]-fluorodeoxyglucose ([18F]-FDG; (►**Fig. 2**) used in PET imaging measures glucose metabolism throughout the body, allowing for the visualization and quantification of changes in metabolic activity associated with pain processing in humans[25] and in animal models.[26]

Several studies have used [18F]-FDG-PET imaging to investigate different aspects of pain. For example, research on neuropathic pain has demonstrated altered glucose metabolism in specific brain regions, such as the thalamus, insula, and anterior cingulate cortex, which are involved in pain perception and modulation.[27] Moreover, [18F]-FDG-PET has shown promise in identifying biomarkers for pain severity and treatment response in chronic pain patients, offering a potential means for personalized pain management.[28]

A study by Biswal and colleagues evaluated [18F]-FDG imaging in six patients with chronic neuropathic pain in their lower extremities (four cases of complex regional pain syndrome, one case of chronic sciatica, and one case of neuropathic pain).[29] They found significantly increased [18F]-FDG uptake in affected nerves and muscles compared with background tissues in five of six patients, demonstrating that [18F]-FDG accurately localizes to sites of increased metabolism or inflammation associated with neuropathic pain and therefore can potentially be used to image pain generators.

[18F]-Sodium-Fluoride

The PET radiotracer [18F]-sodium fluoride ([18F]-NaF; ►**Fig. 3**) is absorbed by osteoblasts into hydroxyapatite within the bone matrix, enabling the noninvasive detection of osteoblastic activity.[30] The use of [18F]-NaF has gained popularity in assessing bone-related conditions, specifically in identifying bone metastases and primary tumors.[30] In the context of pain imaging, [18F]-NaF has shown potential in identifying and characterizing sites of increased bone remodeling associated with painful arthritic conditions.

Jenkins et al studied the association between disability related to low back pain and quantitative measures obtained from [18F]-NaF PET/MRI.[31] Six patients diagnosed with facetogenic low back pain underwent dynamic [18F]-NaF PET/MR imaging that was then compared with subjective clinical measures and MRI evidence of lumbar spondylosis. The study revealed a significant positive correlation between the maximum uptake rate of the facet joint and the degree of clinical disability, suggesting that [18F]-NaF PET may help predict clinical disability associated with facet arthropathy. In a larger study by Spirig et al, 39 patients underwent [18F]-NaF PET/MR for detecting painful facet joints in addition to clinical examination and conventional MRI.[32] The patients were then randomized to receive treatment for facetogenic back pain based on clinical examination and MRI findings or based on [18F]-NaF-positive facet joints. The [18F]-NaF PET/MR did not, however, demonstrate superiority over clinical examination or conventional MRI for the identification of painful facet joints.

The radiotracer [18F]-NaF-PET has also been used to study cancer-related bone pain. For example, a study by Even-Sapir and colleagues demonstrated the clinical utility of [18F]-NaF-PET in distinguishing between benign and malignant bone lesions and assessing response to treatment, thus aiding in the management of cancer-related bone pain.[33]

[18F]-FTC-146

Sigma-1 receptors (S1Rs) [18F]-FTC-146 (►**Fig. 4**) have been under investigation since 2011 and may have implications for pain imaging. S1Rs are a distinct group of chaperone proteins found throughout the central nervous system and peripheral tissues. They play a central role in modulating ion channels and other neurotransmitter systems, contributing

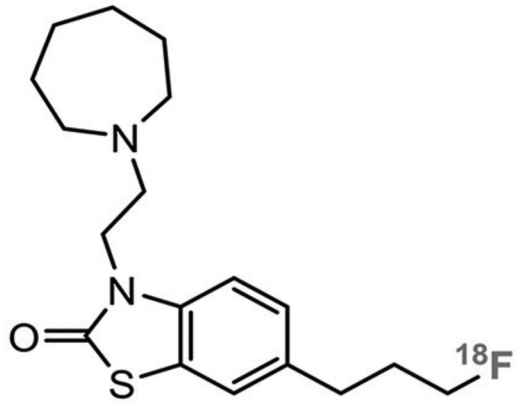

Fig. 4 [18F]-FTC-146.

to various biological processes related to pain, addiction, depression, stroke, and cancer.[34] S1Rs are present in both neurons and glial cells and believed to be essential for preserving and restoring neuronal function. They have been implicated in the pathogenesis of neurodegeneration in diseases such as Alzheimer's and Parkinson's diseases,[35] stroke, and amyotrophic lateral sclerosis.[36,37] S1Rs interact with several ion channels, such as *N*-methyl-*D*-aspartate receptors, and G-protein coupled receptors, such as opioid receptors.[38] Considering the mechanism of action and its interactions with the opioid receptor, it is unsurprising that S1R ligands have been proposed as therapeutic tools for the treatment of chronic pain.[39]

Several candidate radiotracers for S1Rs are under investigation, such as [11C]-SA4503, [18F]-FPS, and [18F]-fluspidine.[40,41] However, each has its own limitations in terms of receptor binding specificity and pharmacokinetics. The radiotracer [18F]-FTC-146 has emerged as a promising radiotracer because unlike previous candidate radiotracers for S1Rs, it has a high binding affinity for S1Rs. It has successfully completed first-in-human studies for pain imaging in complex regional pain syndrome and radiculopathy[42] and is currently being evaluated in phase 2 clinical trials in patients with newly diagnosed osteosarcoma for pre- and posttreatment pain.[43] It may prove useful in the diagnosis of pain and measurement of pain conditions.

[18F]-Saxitoxin

Several small molecule and peptide ligands have been identified as selective binders of sodium channels (NaVs) that are centrally involved in nerve function and therefore have the potential to be used as PET radiotracers to study pain. Saxitoxin (STX; ►**Fig. 5**), for example, binds reversibly and with a low nanomolar affinity to the extracellular pore of tetrodotoxin (TTX)-sensitive NaV isoforms.[44] This feature offers the advantage of a readily accessible target that is expressed on the surface of nerves.

To assess the suitability of [18F]-STX as a PET imaging agent for neuromas, experiments were conducted on rats that underwent a spared-nerve injury (SNI) surgical procedure. SNI is an established rodent model of neuropathic pain, involving transection of the tibial and common peroneal branches of the sciatic nerve while leaving the sural branch

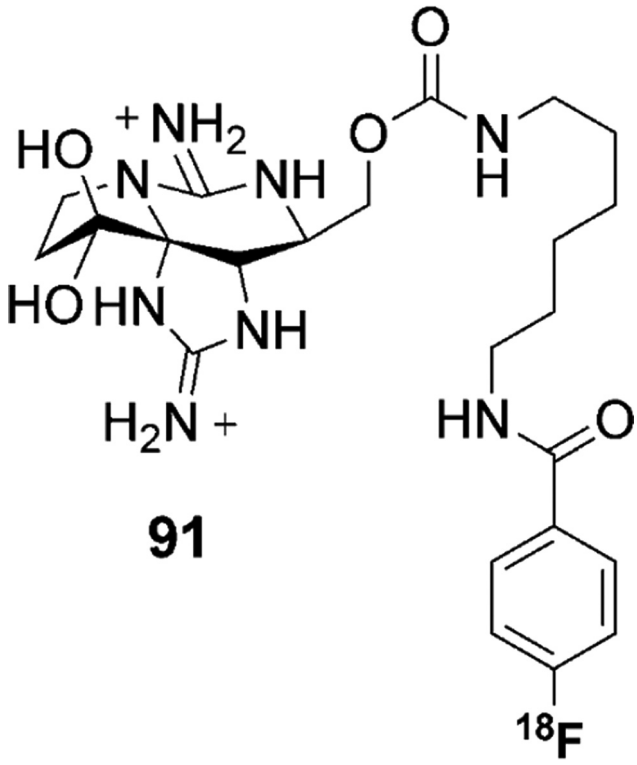

Fig. 5 [18F]-Saxitoxin.

intact. This procedure generates a neuroma at the site of nerve injury, leading to chronic pain lasting several months or longer. In a study by Hoehne and colleagues, the allodynic response in the left hind paws (operated side) of SNI animals was confirmed 4 weeks after surgery using von Frey filaments.[44] Immunohistopathology data of the surgically injured nerve in SNI animals revealed elevated levels of protein expression of NaV1.3 and NaV1.7 compared with control.[44] An elevated uptake of [18F]-STX was already observed in the neuroma at 60 minutes postinjection when compared with adjacent healthy tissue and the healthy uninjured sciatic nerve. Additionally, the retention of [18F]-STX in the neuroma remained elevated over time. Collectively, these findings provide robust evidence supporting the specific uptake of [18F]-STX in the painful neuroma when compared with the surrounding tissue.

Radiocaine

The PET radiotracer [18F]-radiocaine (►**Fig. 6**), based on the local anesthetic lidocaine, a general NaV blocker, was

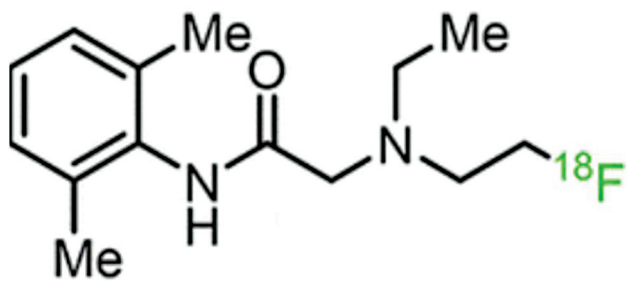

Fig. 6 [18F]-Radiocaine.

recently developed for NaV imaging. NaVs have a crucial role in the electrical signaling of neurons. Specifically, certain NaV isoforms found in peripheral sensory neurons and the dorsal root ganglia of the spinal cord play a crucial role in perceiving and transmitting pain, by generating the action potential (NaV 1.3, 1.7, 1.8, and 1.9).[45] Although aberrant expression and function of these isoforms, particularly NaV 1.7, are implicated in neuropathic pain disorders, there has been limited investigation into the changes in their functional state and expression levels in live organisms. Previously, radiocaine, a F-18 radiotracer based on the local anesthetic lidocaine and a nonselective blocker of NaV channels, was used for imaging NaV 1.5 in the heart.[46] A recent study employed radiocaine to visualize alterations in peripheral neuronal NaV expression in the rodent spinal nerve ligation (SNL) model.[47] The SNL model is a common, well-characterized model of neuropathic pain.[48] Radiocaine PET/MR imaging 3 to 32 days post-SNL revealed a significant increase in radiocaine uptake in the injured sciatic nerve, compared with the uninjured sciatic nerve, at all time points.[47] These promising results indicate that radiocaine PET imaging may be a useful, objective diagnostic tool for neuropathic pain conditions.

Conclusions

This article highlights the tremendous potential of radiotracers to revolutionize the diagnosis, measurement, and treatment of chronic pain. Pain continues to be a massive problem in need of innovative solutions. It is therefore crucial that substantial resources be invested in future research to further develop the capabilities of radiotracers in this field. The Helping to End Addiction Long-Term (HEAL) initiative of the National Institutes of Health is a great example of fostering innovation for pain management.[49]

The pressing need for better tools and technologies to diagnose, measure, and treat pain is clear. By harnessing the power of radiotracers, whose microdosing and selectivity advantages cannot be replicated by other techniques, new approaches can be developed that accurately target the underlying cause(s) of chronic pain. Such innovative approaches would aid in tailoring personalized treatment plans, leading to improved patient outcomes, a higher quality of life, and reduced health-care resource use. Additionally, radiotracers can serve as valuable tools for monitoring symptoms and tracking treatment response, thereby facilitating proactive and optimized pain management strategies. Moreover, radiotracers offer immense value in research settings. They can provide valuable insights into the mechanisms of chronic pain and potentially serve as objective pain measurement tools, paving the way for the development of novel therapeutic interventions. By deepening our understanding of pain pathways and targets, we can unlock new possibilities for drug development, ultimately offering more effective targeted pain management strategies that are free of drawbacks like addiction and off-target effects. Embracing radiotracers as a powerful ally in the battle against chronic pain would also have significant economic implications. By streamlining the diagnostic process and enabling targeted treatments, unnecessary and costly interventions and surgeries could be minimized. This reduction in health-care costs, coupled with improved patient outcomes, could alleviate the burden on health-care systems and enhance access to pain care for individuals worldwide. In fact, PET scanners are widely available, and their presence continues to expand.

In conclusion, the development and utilization of radiotracers in pain care represents an exciting frontier in medical science. By investing in further research and developing advanced tools and technologies, the full potential of radiotracers will be achieved, thereby transforming the landscape of pain management to alleviate the suffering of millions and pave the way for a future where chronic pain is properly understood, diagnosed, and treated.

Conflict of interest

Dr. Hascalovici is a minority stockholder in Lutroo Imaging LLC.

References

1 Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67(36):1001–1006
2 Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. Pain 2017;158(Suppl 1):S11–S18
3 Brinjikji W, Luetmer PH, Comstock B, et al. Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. AJNR Am J Neuroradiol 2015;36(04):811–816
4 Culvenor AG, Øiestad BE, Hart HF, Stefanik JJ, Guermazi A, Crossley KM. Prevalence of knee osteoarthritis features on magnetic resonance imaging in asymptomatic uninjured adults: a systematic review and meta-analysis. Br J Sports Med 2019;53(20): 1268–1278
5 Pysz MA, Gambhir SS, Willmann JK. Molecular imaging: current status and emerging strategies. Clin Radiol 2010;65(07):500–516
6 Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell 2009;139(02):267–284
7 Min JJ. Molecular pain imaging by nuclear medicine: where does it stand and where is it going? Nucl Med Mol Imaging 2016;50 (04):273–274
8 Musafargani S, Ghosh KK, Mishra S, Mahalakshmi P, Padmanabhan P, Gulyás B. PET/MRI: a frontier in era of complementary hybrid imaging. Eur J Hybrid Imaging 2018;2(01):12
9 Phelps ME. Positron emission tomography provides molecular imaging of biological processes. Proc Natl Acad Sci U S A 2000;97 (16):9226–9233
10 Phelps ME. PET: the merging of biology and imaging into molecular imaging. J Nucl Med 2000;41(04):661–681
11 Amen D. Brain SPECT imaging in clinical practice. Am J Psychiatry 2010;167(09):1125; author reply 1125–1126
12 Catafau AM. Brain SPECT in clinical practice. Part I: perfusion. J Nucl Med 2001;42(02):259–271
13 Camargo EE. Brain SPECT in neurology and psychiatry. J Nucl Med 2001;42(04):611–623
14 Yandrapalli SPY. SPECT Imaging. Treasure Island, FL: StatPearls Publishing October 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK564426/ Accessed August 28, 2023
15 Oohashi M, Toshima H, Hayama K, Ogura I. Gallium-67 SPECT-CT for the evaluation of head and neck: preliminary study on maximum standardised uptake value in lesions, and in the parotid and submandibular glands. Pol J Radiol 2020;85:e224–e229
16 Bermo M, Saqr M, Hoffman H, et al. Utility of SPECT functional neuroimaging of pain. Front Psychiatry 2021;12:705242

17 Nakabeppu Y, Nakajo M, Gushiken T, Tsuchimochi S, Tani A, Kanmura Y. Decreased perfusion of the bilateral thalami in patients with chronic pain detected by Tc-99m-ECD SPECT with statistical parametric mapping. Ann Nucl Med 2001;15(05): 459–463
18 Nakamura Y, Nojiri K, Yoshihara H, et al. Significant differences of brain blood flow in patients with chronic low back pain and acute low back pain detected by brain SPECT. J Orthop Sci 2014;19(03): 384–389
19 Bermo MS, Zacharias C, Patterson D, et al. The role of the cerebellum in pain perception: a brain SPECT perfusion study in patients with burn injuries. J Neuroimaging 2020;30(06): 815–821
20 Newberg AB, Hersh EV, Levin LM, et al. Double-blind, placebo-controlled, randomized pilot study of cerebral blood flow patterns employing SPECT imaging in dental postsurgical pain patients with and without pain relief. Clin Ther 2011;33(12): 1894–1903
21 Anzola LK, Hernandez N, Rodriguez LF, et al. The role of SPECT/CT in painful, noninfected knees after knee arthroplasty: a systematic review and meta-analysis-a diagnostic test accuracy review. J Orthop Surg Res 2023;18(01):223
22 Varga M, Kantorová L, Langaufová A, et al. Role of single-photon emission computed tomography imaging in the diagnosis and treatment of chronic neck or back pain caused by spinal degeneration: a systematic review. World Neurosurg 2023;173:65–78
23 Tender GC, Davidson C, Shields J, et al. Primary pain generator identification by CT-SPECT in patients with degenerative spinal disease. Neurosurg Focus 2019;47(06):E18
24 Kato S, Demura S, Matsubara H, et al. Utility of bone SPECT/CT to identify the primary cause of pain in elderly patients with degenerative lumbar spine disease. J Orthop Surg Res 2019;14 (01):185
25 Torres-Ferrus M, Pareto D, Gallardo VJ, et al. Cortical metabolic and structural differences in patients with chronic migraine. An exploratory ^{18}FDG-PET and MRI study. J Headache Pain 2021;22 (01):75
26 Huo BB, Zheng MX, Hua XY, Shen J, Wu JJ, Xu JG. Metabolic brain network analysis with ^{18}F-FDG PET in a rat model of neuropathic pain. Front Neurol 2021;12:566119
27 Cui Y, Neyama H, Hu D, et al. FDG PET imaging of the pain matrix in neuropathic pain model rats. Biomedicines 2022;11(01):63
28 Yoder JS, Kogan F, Gold GE. Applications of PET-computed tomography-magnetic resonance in the management of benign musculoskeletal disorders. PET Clin 2019;14(01):1–15
29 Biswal S, Behera D, Yoon DH, et al. [18F]FDG PET/MRI of patients with chronic pain alters management: early experience. EJNMMI Phys 2015;2(Suppl 1):A84
30 Park PSU, Raynor WY, Sun Y, Werner TJ, Rajapakse CS, Alavi A. ^{18}F-sodium fluoride PET as a diagnostic modality for metabolic, autoimmune, and osteogenic bone disorders: cellular mechanisms and clinical applications. Int J Mol Sci 2021;22(12):6504
31 Jenkins NW, Talbott JF, Shah V, et al. [^{18}F]-sodium fluoride PET MR-based localization and quantification of bone turnover as a biomarker for facet joint-induced disability. AJNR Am J Neuroradiol 2017;38(10):2028–2031
32 Spirig JM, Hüllner M, Cornaz F, et al. [18F]-sodium fluoride PET/MR for painful lumbar facet joint degeneration—a randomized controlled clinical trial. Spine J 2022;22(05):769–775
33 Even-Sapir E, Metser U, Flusser G, et al. Assessment of malignant skeletal disease: initial experience with 18F-fluoride PET/CT and comparison between 18F-fluoride PET and 18F-fluoride PET/CT. J Nucl Med 2004;45(02):272–278
34 Tsai SY, Hayashi T, Mori T, Su TP. Sigma-1 receptor chaperones and diseases. Cent Nerv Syst Agents Med Chem 2009;9(03):184–189
35 Siddiqui T, Bhatt LK. Targeting sigma-1 receptor: a promising strategy in the treatment of Parkinson's disease. Neurochem Res 2023; May 31 (Epub ahead of print)
36 Mavlyutov TA, Guo LW, Epstein ML, Ruoho AE. Role of the sigma-1 receptor in amyotrophic lateral sclerosis (ALS). J Pharmacol Sci 2015;127(01):10–16
37 Ryskamp DA, Korban S, Zhemkov V, Kraskovskaya N, Bezprozvanny I. Neuronal sigma-1 receptors: signaling functions and protective roles in neurodegenerative diseases. Front Neurosci 2019;13:862
38 Sánchez-Fernández C, Entrena JM, Baeyens JM, Cobos EJ. Sigma-1 receptor antagonists: a new class of neuromodulatory analgesics. Adv Exp Med Biol 2017;964:109–132
39 Merlos M, Romero L, Zamanillo D, Plata-Salamán C, Vela JM. Sigma-1 receptor and pain. Handb Exp Pharmacol 2017; 244:131–161
40 Lee Collier T, O'Brien JC, Waterhouse RN. Synthesis of [18F]-1-(3-Fluoropropyl)-4-(4-cyanophenoxymethyl)-piperidine: a potential sigma-1 receptor radioligand for PET. J Labelled Comp Radiopharm 1996;38(09):785–794
41 Waterhouse R, Nobler M, Zhou Y, et al. First evaluation of the sigma-1 receptor radioligand [18F] 1–3-fluoropropyl-4-((4-cyanophenoxy)-methyl) piperidine ([18F] FPS) in humans. Neuroimage 2004;22:T29–T30
42 Biswal S [18F]FTC-146 PET/MRI in healthy volunteers and in CRPS and sciatica. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT02753101 Accessed August 28, 2023
43 Ganjoo K 18F-FTC-146 PET/CT in newly-diagnosed osteosarcoma. 2023. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04365660 Accessed August 28, 2023
44 Hoehne A, Behera D, Parsons WH, et al. A 18F-labeled saxitoxin derivative for in vivo PET-MR imaging of voltage-gated sodium channel expression following nerve injury. J Am Chem Soc 2013; 135(48):18012–18015
45 Goodwin G, McMahon SB. The physiological function of different voltage-gated sodium channels in pain. Nat Rev Neurosci 2021;22 (05):263–274
46 Hooker JM, Strebl MG, Schroeder FA, et al. Imaging cardiac SCN5A using the novel F-18 radiotracer radiocaine. Sci Rep 2017;7:42136
47 Bartolo ND, Reid SE, Krishnan HS, et al. Radiocaine: an imaging marker of neuropathic injury. ACS Chem Neurosci 2022;13(24): 3661–3667
48 Ho Kim S, Mo Chung J. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain 1992;50(03):355–363
49 National Institutes of Health What is the NIH HEAL initiative? Available at: https://heal.nih.gov/ Accessed August 28, 2023