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Review article

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Bioelectronics for targeted pain management

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Abstract

Pain management in humans is an unresolved problem with substantial medical, societal and economic implications. Traditional strategies such as opioid-based medications are highly effective but pose many long-term risks, including addiction and overdose. In this Review, we discuss these persistent challenges in medical care along with advances in bioelectronics that enable safer and more effective alternative treatments. Emerging approaches leverage wireless embedded networks and machine learning to accurately detect and quantify the symptoms of pain, establishing a foundation for targeted, on-demand treatment. These platforms offer a powerful complement to wearable and implantable neural interfaces that can control these symptoms with unprecedented spatiotemporal and functional selectivity. Now, emotional and cognitive aspects of pain can be addressed through immersive multisensory engagement with systems for augmented and virtual reality. Trends in diagnostic and interventional technologies show how their integration is well suited to addressing some of the most intractable problems in pain management.

Sections

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Key points

- Pain management is a complex and unresolved issue, with solutions that are often insufficient. The use of opioids presents additional risks, including addiction and overdose.
- Non-addictive alternatives to opioid interventions are generally understudied and variably effective at managing the symptoms of pain.
- Wearable bioelectronics and machine-learning approaches present solutions for measuring the effects of pain.
- Advanced wearable and implantable neural interfaces deliver precise, on-demand relief with high spatial and functional accuracy.
- Targeting the emotional and cognitive dimensions of pain can be achieved using immersive technologies such as augmented and virtual reality.
- The integration of monitoring and treatment into closed-loop systems is a consistent and successful trend among emerging approaches.

Introduction

Pain is a marked health issue that affects a large portion of the global population, with profound consequences for individuals and society. According to the US Centers for Disease Control and Prevention (CDC), approximately 51.6 million US adults (20.9%) experienced chronic pain between 2019 and 2021 (ref. 1). Furthermore, 17.1 million individuals (6.9%) endured high-impact chronic pain, which severely limits daily activities and quality of life[1]. The Institute of Medicine estimated that the annual cost of pain in the USA in 2010 ranged from US$560 to US$635 billion, factoring in both healthcare expenses and lost productivity[2].

One of the long-standing challenges in treating pain is that a huge variation exists in its origins, mechanisms and specific symptoms[3,4] (Fig. 1). Specific conditions present unique challenges and require careful monitoring of symptoms. Traditional pain assessment methods, which rely heavily on patient self-reporting and clinical observations, are subjective and can often be inaccurate because of bias or cognitive limitations[5].

As of 2025, healthcare providers wield a broad range of both pharmacological and non-pharmacological approaches for managing pain. Medications, including opioids and non-opioids, are a cornerstone of medical treatments. However, the opioid epidemic in the USA casts a spotlight on risks associated with opioid use, including addiction and overdose[6]. The emergence of high rates of substance abuse disorders motivates healthcare providers to transition towards non-opioid pharmacological treatments[7], such as non-steroidal anti-inflammatory drugs and antidepressants. Meanwhile, non-addictive alternatives to opioid interventions are generally understudied and variably effective at managing the symptoms of pain[8,9].

Here, we discuss technology-driven strategies and treatments that address the persistent nature of these threats. Bioelectronic wearables[10,11] and ingestibles[12,13] leverage advanced sensors and intelligent systems, offering an objective means of tracking pain-related physiological changes and enabling individualized treatment strategies. For treating pain, neuromodulation modalities, such as transcranial magnetic stimulation (TMS) and spinal cord stimulation (SCS), are increasingly being used[14,15]. High-profile clinical trials have paved the way for clinical translation of invasive[16–18] and non-invasive[19,20] neural interfaces for pain management. In addition, localized drug delivery devices offer new opportunities that leverage both the functionality of medications and the spatial selectivity of neuromodulation[21]. In 2024, preclinical demonstrations of a drug delivering implant raise new prospects for addressing the competing challenge of opioid medication overdose[22]. Emerging augmented reality and virtual reality (AR/VR) technologies present capabilities for creating engaging sensory experiences[23] and can be used to target the cognitive and emotional aspects of pain.

In this Review, we first introduce the broader context of pain medicine, clinical challenges and patient needs. We then discuss advances in comprehensive pain management with networks of multimodal sensors for monitoring pain; neural and AR/VR interfaces for targeted intervention; and intelligent systems for controlling these modalities. Enhancing selectivity — the ability to safely and effectively target symptoms without eliciting side effects — is a longstanding goal of bioelectronic medicine. Towards this goal, a consistent trend among emerging approaches is the integration of monitoring and treatment into closed-loop systems.

Intelligent systems for monitoring pain

One of the cornerstones of effective pain management is the accurate classification of pain, which also informs the development and deployment of targeted assessment and treatment tools. Pain can be broadly categorized into acute and chronic conditions. Acute pain is sudden, arising from specific injury, such as a broken bone. Chronic pain is defined as pain lasting for more than 3 months, continuing even in the absence of clear tissue damage or an identifiable physiological cause[24]. Pain can be further classified into four primary categories[24] (Table 1).

Traditional pain assessment methods, which rely heavily on patient self-reporting and clinical observations, are subjective. To address biases and cognitive limitations inherent in this approach[5], objective measures of pain based on wearable sensors and machine-learning techniques are being explored[25] (Fig. 2). These technologies raise the prospect of precise, individualized treatment strategies.

Physiological sensors for pain

Physiological sensing modalities are being investigated as objective methods to measure pain[26]. Most approaches focus on cardiovascular and respiratory parameters, premising that pain induces a characteristic pattern of autonomic activity[27,28]. Heart rate[29,30], blood pressure[31], respiration rate[32], skin sweating[33] and pupil size variations[34] establish the basis for accurate classification of pain compared with self-report ratings. Electrical activity in muscles, measured using electromyography (EMG), provides a general indicator of psychophysical stimulation[35]. Best results of classification accuracy from these studies range from 68.1% ($n = 40$)[31] to 90.9% ($n = 90$)[35]. Continuous monitoring of multiple physiological signatures at once is used to mitigate confounding factors, such as motion artefacts and environmental noise, affecting individual sensor readings[36,37]. Further development of multimodal approaches will help clinicians detect pain episodes earlier, assess the severity of pain more accurately and evaluate the effectiveness of treatment interventions in real time[25].

One of the challenges in implementing a real-time multimodal system is that physiological measurements are typically performed in clinical and point-of-care settings with bulky instrumentation.

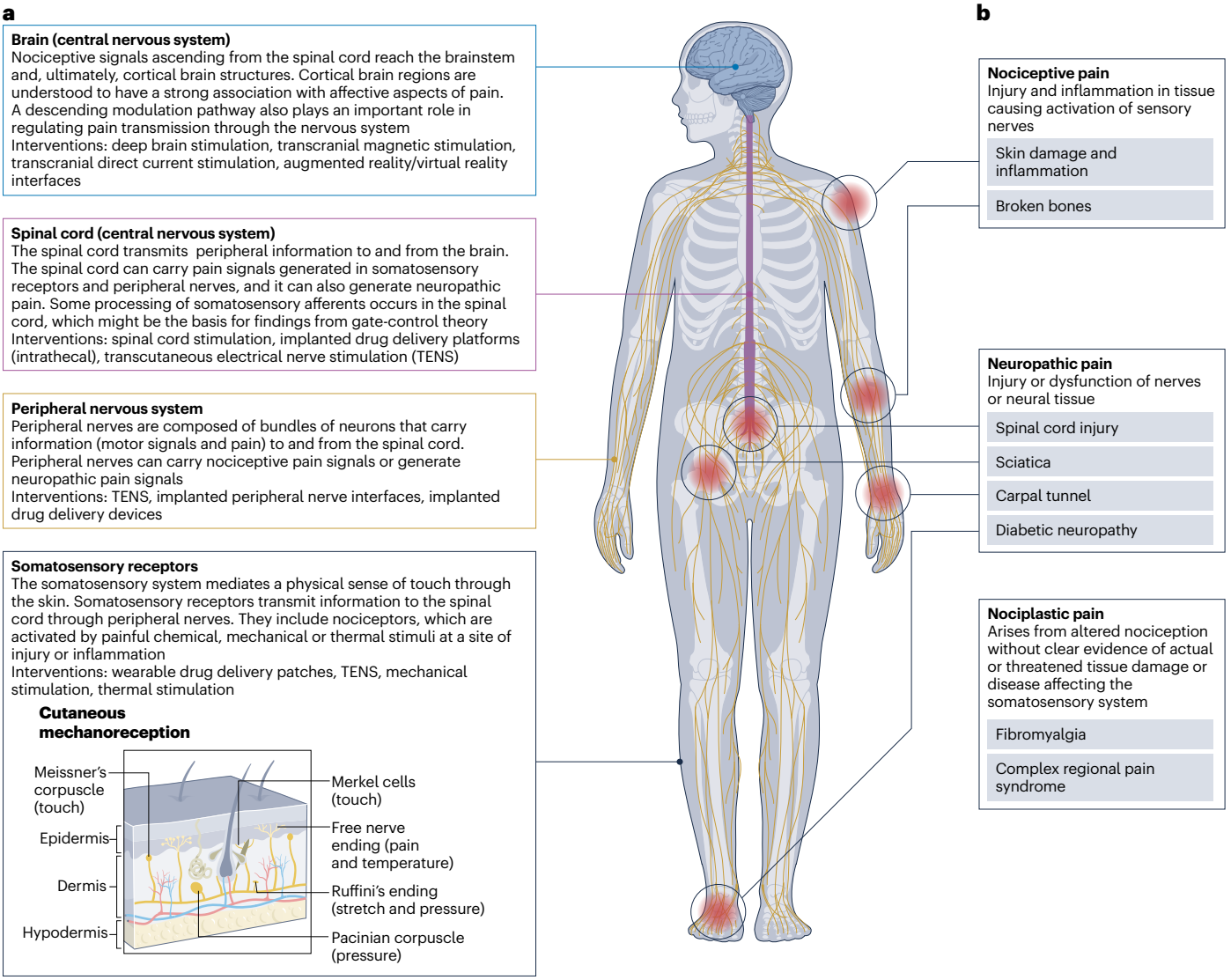

Fig. 1 | Overview of pain types and the organ systems it affects. a, Components of the nervous system that carry and generate pain signals and potential interventions. **b**, Common classifications and characteristic examples of pain types.

Traditionally, measuring electrical activity in the body requires adhesion of multiple hard-wired, rigid leads, which severely limits the applications these can be used for[38]. Enabled by advances in flexible electronics, a wide range of sensing modalities can now be incorporated into soft, skin-conformable devices that can be worn during regular activities of the user. In 2020, for example, a wireless system of electrocardiography (ECG) and pulse oximetry sensors that could even be worn safely by neonatal infants with fragile skin was demonstrated[39]. Electrocardiography measures electrical activity in the heart from skin-mounted electrodes (Fig. 2a), and pulse oximetry measures blood oxygenation from relative absorption of visible and infrared light[11,40,41]. Along with electrical and optical modalities, flexible sensors can monitor cardiovascular and respiratory events through acoustic and vibration measurements[10,42,43]. Wearable sensors can also measure detailed physical and biochemical properties of sweat[44–46].

Advanced capabilities for monitoring activity of the autonomic nervous system raise the prospects of monitoring pain objectively outside the clinic. Comfort and convenience are fundamental to the goals of wearable devices, motivating patient adherence. The use of soft, silicone-based encapsulation creates a comfortable interface that can be worn over long periods of time[47–49]. Furthermore, technologies that integrate electronics into textiles and clothing are being developed, offering a breathable interface[50–52]. Advances in self-powering also promise to limit reliance on manual user charging[53–55]. By making devices as wearable as clothing, the field can expand access to physiological pain monitoring techniques.

Tracking patterns of behaviour

Not only are the symptoms of pain reflected in physiological activity but also in the behaviours of the patient. Vocalization[56], facial expression[57]

Table 1 | Pain types and their characteristics

Pain type	Definition and source	Common conditions	Symptoms	Common treatments
Nociceptive pain[291]	Activation of nociceptors in response to damaging or potentially damaging stimuli, generally associated with tissue injury or inflammation	Post-surgery pain, arthritis inflammation, cuts, broken bones	Sharp, throbbing or aching sensation; visceral pain may be deep and pressure-like	Conventional analgesics, including NSAIDs and opioids
Neuropathic pain[292]	Caused by injury or dysfunction to nerves and neural tissue, usually chronic in nature	Diabetic neuropathy, post-herpetic neuralgia, spinal cord injury	Burning, shooting or stabbing pain, with heightened sensitivity to touch or temperature	Opioids, anticonvulsants, antidepressants, neuromodulation, surgical nerve block
Nociplastic pain[293]	Arises from altered nociception without clear evidence of actual or threatened tissue damage or disease affecting the somatosensory system	Fibromyalgia, tension-type headaches, complex regional pain syndrome	Widespread pain, often with fatigue, cognitive disturbances and sleep disruptions	Anticonvulsants, antidepressants, physical therapy, psychological interventions, neuromodulation
Mixed pain[294]	Combination of nociceptive and neuropathic pain mechanisms	Lower back pain, cancer pain	Include both nociceptive and neuropathic pain symptoms	Opioids, NSAIDs, anticonvulsants, antidepressants, neuromodulation, surgical nerve block

Pain can be classified into four primary categories: nociceptive, neuropathic, nociplastic and mixed pain[24]. Each category reflects different underlying mechanisms that not only drive clinical presentation but also determine the suitability of specific therapeutic and technological approaches. NSAID, non-steroidal anti-inflammatory drug.

and body movement[58] provide quantifiable measures that clinicians use to evaluate pain. Wearable devices with embedded inertial measurement units[59–61], strain sensors[62–64] and radio angle-of-arrival[65] are used to quantify and track body movements. Machine learning offers an array of tools for analysing body movements and facial expressions from stereo vision[66], light detection and ranging[67,68] and conventional camera imaging[69,70]. With the introduction of AR/VR systems, such as Vision Pro from Apple and Meta smart glasses, motion tracking has become accessible to many users. These technologies raise the prospects for evaluating behavioural features and objectively monitoring pain during daily activities.

Evaluating emotional state with affective computing

Psychological and neurobiological models of pain consider two dimensions: the intensity of sensation and the unpleasantness associated with it. Affective disorders such as depression and anxiety frequently accompany pain[71]. Pain that occurs in a threatening context, such as disease or injury, carries an additional emotional weight[72]. By contrast, the perceived control over pain can carry a more benign emotional context[73]. Human emotional state also has an enormous influence on pain; a negative emotional state increases pain, whereas a positive state lowers pain. Thus, the emotional affective dimension of pain can perpetuate a cycle of pain and negative emotions[74].

The growing fields of affective computing and sentiment analysis offer an array of tools for evaluating the emotional affective state of users. These systems analyse behavioural indicators, including facial expressions and vocal patterns, to detect specific emotions — such as happiness, sadness, fear, anger, disgust and surprise — or overall polarity, such as positive and negative feelings[75]. The affective state of the patient, especially negative feelings they associate with the pain itself, ultimately influences the dosage required for effective management of pain symptoms[76]. The application of affective computing to pain monitoring might enable intervention strategies to be calibrated more effectively.

Brain activity can be measured with electroencephalography (EEG) sensors (Fig. 2a) to evaluate emotional affective states[77] and accurately detect symptoms of pain, validated against the standard visual analogue scale[78–80]. Best results of classification accuracy range from 65% ($n = 51$)[78] to 94.8% ($n = 30$)[79]. Wireless, wearable EEG devices[81,82] further enhance possibilities for monitoring pain during daily activities.

Affective computing and sentiment analysis build off ongoing advances in machine learning, including in the areas of natural language processing[83] and computer vision[84]. Supervised learning techniques for classifying linguistic and visual inputs, such as deep learning[85] and long short-term memory networks[86], enable specific emotions to be identified. Tensor fusion networks have demonstrated to outperform benchmark algorithms, such as support vector machines and convolutional neural networks, for the detection of positive and negative feelings from gestures and voice (77.1% accuracy on CMU-MOSI data set)[87]. Multimodal sensor data combined with these sophisticated classification algorithms will help illuminate the emotional affective dimension of pain and guide targeted interventions.

Wireless, cloud-based networks

The emergence of increasingly powerful wearable technologies has been driven by the concepts of internet-of-things and wireless sensor networks[88]. Although embedded systems are traditionally characterized by constrained resources, such as memory and computational speed, new system-on-chip integrated circuits greatly expand these functionalities (Fig. 2b). Along with controlling the sensing and input to these systems, these computational resources enable complex communication strategies. Wearable devices can leverage protocols such as Bluetooth Low Energy[11,39,46] and near-field communication[40,50]. Wireless operation is critical for pain monitoring devices to be used during normal activities.

Connecting medical devices to the internet enables data transmission in real time, taking advantage of cloud computing infrastructure for storage, processing and analysis[89]. Data generated from users can be sent to secure servers where they can be persistently stored, empowering both patients and healthcare providers with access to critical information that will enable targeted solutions for pain management. Furthermore, computational resources hosted in the cloud enhance capabilities for analysing this data. Machine-learning approaches offer powerful solutions for processing, organizing, interpreting and visualizing the large volume of data generated through the wearable systems[90,91].

Automated and augmented decision-making

Wearable devices embedded with EMG, EEG and pulse oximetry sensors collect real-time physiological data. These signals are processed through supervised and unsupervised machine-learning algorithms to classify pain into nociceptive, neuropathic or nociplastic categories[92–94]. This approach helps reduce diagnostic errors and might ultimately help minimize opioid use[95].

Machine learning not only enables the symptoms of pain to be monitored in real time but also to predict them in advance. For example, analysis of trunk movement can be used to forecast lower back pain in postpartum women (>94% accuracy for trunk biomechanics, $n = 100$)[96], and processing of MRI data can anticipate surgical pain management outcomes for individuals with trigeminal neuralgia (96.7% accuracy relative to numerical rating scale, $n = 35$)[97]. Another machine-learning approach, using a support vector machine, predicts how patients respond to opioid analgesia with an accuracy of 65% (relative to numerical rating scale, $n = 51$)[78]. This binary classifier was trained using features derived from resting EEG and EEG during cold pain stimuli. The algorithm optimizes the decision threshold between two groups without a priori assumptions, ensuring robust predictions even with limited sample sizes[78]. By facilitating proactive decision-making, these supervised machine-learning algorithms shift the paradigm from reactive to anticipatory pain management strategies.

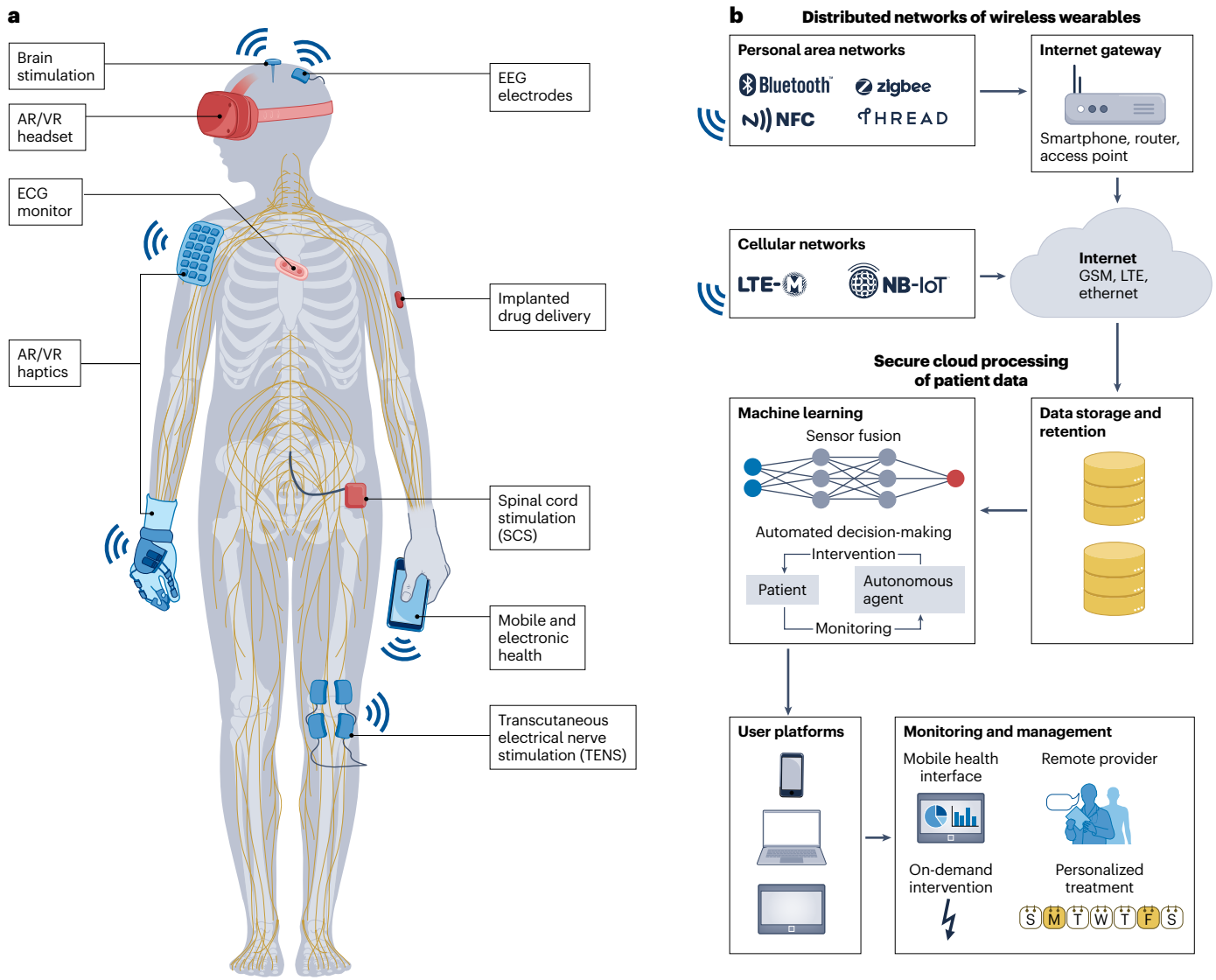

Fig. 2 | A vision for a wirelessly networked, closed-loop pain management system. a, A closed-loop system for monitoring pain with physiological sensors (including electrocardiography (ECG) and electroencephalography (EEG)) and treating pain with augmented reality and virtual reality (AR/VR) interfaces (for example, AR/VR headsets and AR/VR haptics), neuromodulation (for example, brain, spinal cord and TENS) and drug delivery. **b**, Wireless protocols capable of networking large numbers of wearable devices; cloud infrastructure capable of ingesting and processing multimodal, high-volume data; and interfaces for augmenting decision-making for patients and their healthcare providers. GSM, global systems for mobile communications; IoT, internet-of-things; LTE, long-term evolution; NFC, near-field communications.

Ultimately, machine-learning algorithms can prescribe specific treatment strategies for personalized intervention[98]. A study of 278 individuals with chronic back pain showed that an interactive voice response system can direct psychotherapy sessions to deliver substantial pain relief. Despite requiring substantially less therapist time, a higher proportion (37% versus 19%, respectively) of participants receiving artificial intelligence (AI)-guided therapy experienced improvements in self-report ratings than those receiving conventional therapist-guide treatment[99]. Machine learning can be also used to improve self-report ratings of pain by selecting which individuals will respond to localized surgical treatment (90.1% accuracy, $n = 36$)[100]. Delivering precise, data-driven recommendations, these systems represent a notable step towards standardized, patient-centred care that addresses physiological, behavioural and emotional dimensions of pain.

Although machine learning and AI introduce impressive capabilities for monitoring patients and guiding treatment, they also bring new challenges. Compromises in security, opacity and quality risk undermining trust and slowing adoption of pain management strategies. Given the wide diversity in origins and mechanisms of pain, algorithmic bias is a particular concern. Designers need to carefully consider whether the population of intended users is represented appropriately in the underlying data set. Ultimately, the process for establishing appropriate parameters for data collection and analysis needs to involve all stakeholders, including patients and healthcare providers[101].

On-demand intervention with wearable and implantable neuromodulation

Along with monitoring pain symptoms, bioelectronics presents powerful solutions for intervention[102–104]. Electrical nerve stimulation modalities (Fig. 3a) are widely recognized in clinical pain management for on-demand treatment to targeted areas of tissue[14,15]. Driving electrical impulses to key points along pain transmission pathways (Fig. 1a), this approach aims to modulate the activity of nerves and central pain processing centres[105]. Regularly applied for chronic pain, electrical stimulation has also gained attention for its role in acute pain management amid the opioid crisis[106,107]. However, this modality has tradeoffs in terms of selectivity and invasiveness, and highly selective interfaces are being fine-tuned to improve long-term stability[108]. The temporal characteristics of pain indicate the appropriate use of wearable and implantable systems. Acute and chronic pain might motivate non-invasive and invasive approaches, respectively (Tables 2 and 3).

Non-invasive stimulation

Neural tissue in both the central and peripheral nervous systems can be targeted non-invasively through wearable, skin-mounted electrodes. At the skin–electrode interface, electronic current converts to ionic current, driving localized neural activity[109]. Because these interfaces are relatively easy to wear and remove, they are well suited for both chronic and acute applications. The use of materials such as gold, platinum and carbon nanomaterials reduces the risks of harmful thermal and chemical effects during operation[109,110]. By making these electrodes as soft as the underlying skin, mechanical irritation and discomfort are minimized[111]. Composite electrodes based on silicone elastomers and hydrogels offer improved mechanical compatibility and skin contact[112–114]. Comfort can be further improved by using porous, breathable interfaces[115–117]. As demonstrated for wearable sensors[50–52], the use of textile encapsulations could greatly improve the overall gas permeability and long-term stability of non-invasive stimulation.

Non-invasive modalities such as transcutaneous electrical nerve stimulation (TENS), transcranial direct current stimulation (tDCS) and TMS leverage these principles for clinical pain management.

Transcutaneous electrical nerve stimulation. Many anatomical targets are currently being explored for non-invasive electrical stimulation in the peripheral nervous systems. TENS, for example, targets sensory neurons with electrical current delivered near the source of pain (Figs. 2a and 3a) and is being explored for a wide range of conditions, including neuropathic, osteoarthritis, fibromyalgia and postoperative pain[107,118,119]. According to a randomized clinical trial evaluating postoperative individuals after caesarean delivery, integrating a TENS device into a multimodal analgesic protocol can reduce inpatient opioid use by ~47% while maintaining similar pain scores[19] (Table 3). Non-invasive stimulation through skin-mounted electrodes was also demonstrated to reduce pain in tetraplegic individuals[20]. Although impressive pain reduction outcomes have been demonstrated since 2015, some studies have yielded conflicting judgements in terms of efficacy, partially because of the variations in electrode locations and frequency parameters[120,121]. The use of closed-loop systems with feedback from impedance[122], EMG[123] and EEG[124,125] might help deliver more consistent outcomes in these approaches.

Transcranial direct current stimulation. Along with targets in the peripheral nervous system and spinal cord, non-invasive stimulation of the brain can provide pain relief. In tDCS, electrodes mounted on the surface of the head deliver low levels of current, typically 2 mA, to regions of interest in the brain[126] (Fig. 3b). Positive analgesic effects of tDCS can be seen in conditions such as fibromyalgia[127], multiple sclerosis[128] and spinal cord injury[129] (Table 3). Similar to TENS, tDCS is characterized by inconsistent outcomes in clinical studies, likely influenced by a lack of standardized treatment protocols[130,131]. Additionally, inconsistency is caused by current spread, that is, the effect for which stimulation through conventional tDCS electrodes tends to leak non-specifically into adjacent regions in the brain where unintended effects might arise[132]. Approaches such as high definition tDCS, which delivers precise spatiotemporal patterns of current, might overcome these existing challenges[133,134]. Advances in mechanically compliant electrode arrays will enable greater accuracy and resolution[111], opening up new possibilities for non-invasive brain stimulation.

Transcranial magnetic stimulation. Similar to tDCS, TMS is a promising modality for pain management that non-invasively targets the brain[135]. This modality drives repeated pulses of ~1.5 T magnetic fields through coils directed at the skull (Fig. 3b). These fields elicit electrical current in the neural tissue, inducing persistent changes in brain function. For example, repetitive TMS applied to the motor cortex was found to reduce self-report ratings of pain intensity for 49 individuals with neuropathic pain compared with a sham group of 48 control individuals[136] (Table 3). Systematic reviews also demonstrate that TMS therapy has a superior effect on quality of life of individuals with fibromyalgia after a month of treatment compared with a sham group[137]. To target brain regions more effectively, it is possible to use EEG to guide a robotic arm towards therapeutic targets[138]. Compared with other non-invasive electrical stimulation techniques, TMS requires large currents that currently restrict it to point-of-care settings. Twice-daily treatments have been shown to improve outcomes compared with once-daily treatments[139,140], suggesting that there might be advantages to pursuing wearable, chronic implementations of TMS.

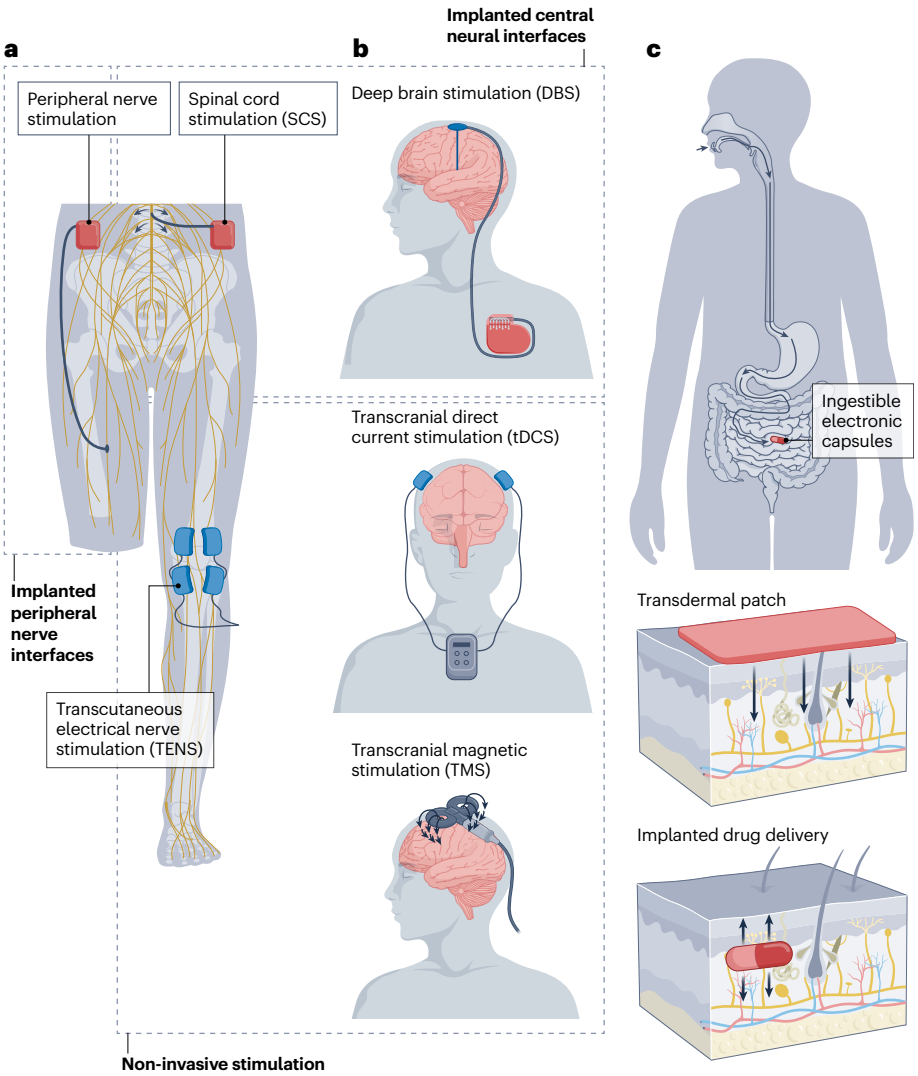

Fig. 3 | Wearable and implantable neural interfaces for electrical nerve stimulation. a, Electrical nerve stimulation modalities in the somatosensory system (transcutaneous electrical nerve stimulation, TENS), spinal cord stimulation (SCS) and peripheral nerve stimulation. **b**, Electrical and magnetic brain stimulation modalities: deep brain stimulation (DBS), transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). **c**, Ingestible, wearable and implanted drug delivery devices for precision pain management.

Implanted peripheral neural stimulation

Even if non-invasive, non-surgical approaches, such as skin-mounted electrodes, are appealing for many patients, they generally offer poorer control over deeper targets than invasive approaches[108]. Additional modes of operation are possible with implanted electrodes that deliver electrical current directly to peripheral nerves[108] (Fig. 3a). Stimulation of peripheral nerves with short pulses of current elicits activity that travels distally to muscles and proximally to the brain[141]. Meanwhile, signals travelling across peripheral nerves can be blocked from reaching their destinations by delivering direct current or kilohertz-frequency alternating current[142–144]. Clinical studies demonstrate that electrical nerve blocks can intercept pain signals before they reach the central nervous system[145], inhibiting the perception of postamputation pain[17] and lower back pain[16] (Table 3). Implanted peripheral neural interfaces empower patients with targeted, on-demand control over their symptoms.

Although implanted devices generally offer greater selectivity and access to neural targets compared with non-invasive approaches, the safety and stability of these neural interfaces remain a long-standing challenge[108]. Electrical current can be delivered through cuff electrodes that wrap around the nerve[146–148] or from intrafascicular electrodes that pierce through it[149–151]. The presence of these electrodes can provoke a foreign body response, and mechanical mismatch with the surrounding tissue can cause reoccurring damage[152–154]. Advances in materials science and flexible electronics have improved the stability of these interfaces: soft, conformable materials minimize mechanical insult[155–157], and biocompatible coatings inhibit reactions from the immune system[158]. Peripheral neural interfaces have successfully operated beyond 3 years from initial implantation[159], showing feasibility for long-term operation[160,161].

Systems currently deployed in clinical trials require implantation not only of electrodes but also the bulky electronics that powers them. Explantation of neural interfaces from the spinal cord and peripheral nerves is sometimes needed following premature battery depletion and lead-wire fractures[162]. These risks can be greatly reduced by using wireless power transfer[163–166]. Wirelessly powered neural interfaces are small enough to be fully implanted in freely moving rats without external wires[165]. Clinical evidence supports the potential of these systems, with a randomized trial showing greater pain reduction in patients

receiving active stimulation ($n = 45$) compared with controls ($n = 45$)[167]. Treated patients reported improved quality of life and satisfaction, with no serious device-related adverse events arising over 1 year. Minimizing the footprint of the implanted system using this approach will greatly enhance prospects for long-term stability.

Long-term operation might not be desirable for the treatment of acute conditions, such as pain arising after surgical operations. Bioresorbable conductors, dielectrics, semiconductors and encapsulating materials[168] enable peripheral nerve interfaces that dissolve into the body after therapeutic use[165,169,170]. The implantation of these temporary devices could help manage the acute symptoms of postoperative pain before they have a chance of evolving into a chronic condition[171].

Implanted electronics in the brain and spinal cord

Regardless of the origins of pain, its perception is ultimately mediated by the central nervous system. Deep structures in the spinal cord and brain have become accessible to electrical stimulation modalities, driven by developments in microelectronics over the last century. Despite risks associated with surgical intervention in these vulnerable areas, patients have turned to SCS and deep brain stimulation (DBS) for cases that remain intractable to less-invasive approaches.

Spinal cord stimulation. The spinal cord has emerged as a compelling target for pain relief. In SCS, electrodes are inserted through the skin or fully implanted, along with powering electronics (Figs. 2a and 3a). Despite its surgical nature, SCS has demonstrated favourable outcomes with minimal side effects[172]. SCS is approved by the FDA agency for neuropathic pain conditions such as failed back surgery syndrome[173], complex regional pain syndrome[174] and diabetic neuropathy[18] (Table 3). Innovations, such as the use of closed-loop systems[175,176] and high-frequency blocking currents[18,177,178], improve outcomes even further. Non-invasive approaches with surface-mounted electrodes are also being explored, making this approach attractive to a broader community of patients[20]. SCS continues to be a cost-effective[179] and safe therapeutic option for chronic pain management.

Brain stimulation. DBS is an established treatment for a wide range of movement disorders, with more than 160,000 patients undergoing implantation worldwide. A lead wire with electrodes arrayed longitudinally and radially at the end delivers electrical current directly to midbrain structures[180] (Figs. 2a and 3b). Along with the midbrain, the motor cortex is currently being studied as a target for pain relief[181]. Connected by an extension running through the neck, the leads are powered by a rechargeable battery located in the torso. DBS has been explored for treating chronic pain since the 1970s, but this indication remains unapproved by the FDA agency[182]. Studies are limited by small sample sizes and lack of randomization. Despite inconsistent outcomes in clinical studies[183], systematic reviews report a marked positive effect for DBS in reducing chronic neuropathic pain[184,185] (Table 3). Alternative approaches, leveraging embedded sensors for measuring brain activity, might open new opportunities for closed-loop systems that selectively adapt to pain-specific biomarkers[186]. Furthermore, low-power operation and energy-harvesting[187] will markedly increase the safety and long-term stability of brain stimulators.

Thermal, mechanical and emerging stimulation strategies

Along with electrical current, neural tissue is sensitive to thermal and mechanical stimulation. The effect of temperature on neural activity, mediated in part through the activation of thermally sensitive ion channels[188], was revealed in foundational neurophysiological investigations[189]. Fast, transient heat stimulates neural activity whereas prolonged heat blocks neural activity[190]. Direct heating with infrared light has previously been demonstrated in vitro to block nerves[190]. Furthermore, infrared stimulation of human spinal nerve roots has been demonstrated[191]. In 2022, a multimodal peripheral nerve cuff was shown to block nerves by delivering focal cooling in vivo[169]. Thermal energy can also be generated from magnetic nanoparticles upon exposure to a rapidly alternating magnetic field, eliciting similar effects to DBS in preclinical studies[192]. Overall, thermal modulation might offer a highly selective and minimally invasive approach for stimulating neural tissue.

Neurons are also sensitive to direct mechanical stimuli, through specific interactions with mechanosensitive ion channels[193]. Low-intensity pulsed ultrasound, understood to operate through both thermal and mechanical effects[194], has demonstrated a marked positive effect on pain reduction for patients with knee osteoarthritis[195]. Direct mechanical stimulation might also be possible using magnetic nanomaterials[196]. Both ultrasound and nanomaterial-mediated approaches offer far less-invasive methods of neuromodulation than implanted electrical modalities. Furthermore, ultrasound can stimulate deeper structures than infrared light or skin-mounted electrodes[197].

Table 2 | Temporal characteristics of pain and on-demand intervention

Pain type	Description	Interventions
Acute pain	Acute pain serves as an immediate response to injury or disease, acting as a biologically useful signal that prompts individuals to take action to alleviate the cause of pain. This type of pain is usually associated with a specific event or injury, such as surgery, trauma or infection, and is characterized by its direct correlation to tissue damage[24]	Expecting the pain to ultimately resolve, a non-invasive approach with wearable devices, such as TENS, offers an effective strategy
Chronic pain	Chronic pain persists beyond the expected period of tissue healing, lasting for months or even years. It may continue even in the absence of clear tissue damage or identifiable physiological causes. Unlike acute pain, chronic pain does not serve a protective function and is often resistant to conventional analgesics[24]	For treating chronic pain, more invasive approaches can be considered, such as SCS and peripheral neural stimulation, in which the devices are left implanted over long periods of time
Acute postoperative pain	Post-surgical pain typically peaks in the immediate postoperative period and subsides as the tissue heals. This acute pain may evolve into chronic pain if it is not managed effectively from the beginning[171]	For acute postoperative pain, bioresorbable neurostimulators can be utilized that resorb into the body after a deterministic period of time[165]

Pain can be broadly categorized into acute and chronic conditions. Acute pain is sudden, arising from specific injury, such as a broken bone. Chronic pain is defined as pain lasting for more than 3 months, continuing even in the absence of clear tissue damage or an identifiable physiological cause[24]. Acute and chronic pain might motivate non-invasive and invasive approaches, respectively. SCS, spinal cord stimulation; TENS, transcutaneous electrical nerve stimulation.

Table 3 | Example performance of pain interventional modalities

Modality	Regulatory status for pain indications	Example	Study design	Pain aetiology	Sample volume	Reported outcome
Non-invasive stimulation						
tDCS	CE Mark (including migraine headaches and fibromyalgia)	127	Double-blind, sham-controlled, randomized	Fibromyalgia	36	46.3% mean improvement in visual analogue scale after 1 month
TENS	FDA (including post-surgical pain, post-traumatic pain, chronic pain)	19	Triple-blind, sham-controlled, randomized	Post-caesarean pain	134	47% less inpatient postoperative opioid use on average
TMS	FDA (migraine headaches)	136	Double-blind, sham-controlled, randomized	Neuropathic pain	152	21.4% mean improvement in brief pain inventory after 25 weeks
Implanted peripheral neural stimulation						
Repetitive pulse stimulation	FDA (peripheral neuropathy)	StimRouter[167]	Double-blind, sham-controlled, randomized	Peripheral neuropathic pain	94	27.2% mean improvement in numerical rating scale after 3 months
High-frequency alternating current	FDA (post-amputation pain)	Altius[17]	Double-blind, sham-controlled, randomized	Post-amputation pain	170	24.7% of participants experienced ≥50% reduction in numerical rating scale after 30 min
Implanted central neural stimulation						
DBS	FDA (off-label for pain)	Medtronic 3387 (ref. 185)	Prospective, open label	Neuropathic pain	15	52.8% median improvement in visual analogue scale after 36 months
Spinal cord stimulation	FDA (including diabetic neuropathy, lower-back pain)	Senza[18]	Open-label, controlled, randomized	Diabetic neuropathy	216	77.6% mean improvement in visual analogue scale after 6 months
Localized drug delivery						
Wearable drug-eluting patch	FDA (including moderate-to-severe pain)	Transdermal buprenorphine[222]	Single-blinded, controlled	Cancer pain	42	62.5% mean improvement in numerical rating scale after 90 days
Implanted pump	FDA (including chronic intractable pain)	SynchroMed II[246]	Open-label, randomized, controlled	Cancer pain	1,403	20.3% mean improvement in numerical rating scale after 12 months
Augmented and virtual reality						
Audiovisual	FDA (including chronic lower-back pain)	263	Open-label, randomized, controlled	Burn pain	90	47.1% mean improvement in visual analogue scale from standard-of-care
Haptic and cutaneous	FDA (including needle procedures, pain relief from minor injuries)	Buzzy[199]	Open-label, randomized, controlled	Intravenous insertion pain	47	47.3% mean improvement in Wong–Baker FACES pain rating scale from control

Each section given subsequently, non-invasive stimulation, implanted peripheral neural stimulation, implanted central neural stimulation, localized drug delivery and augmented and virtual reality, corresponds to the categories of interventional approaches discussed in this Review. Regulatory status and clinical trial results are reported for notable examples from each category. CE, Conformité Européenne; DBS, deep brain stimulation; tDCS, transcranial direct current stimulation; TENS, transcutaneous electrical nerve stimulation; TMS, transcranial magnetic stimulation.

Thermal and mechanical stimuli can also reduce pain by taking advantage of how the spinal cord integrates sensory information passed to it through peripheral nerves. In human skin, the nervous system uses specialized receptors, mechanoreceptors and thermoreceptors, as the basis for our physical sense of touch and temperature. According to gate-control theory, the activation of nerve fibres that transmit thermal and mechanical stimuli can interfere with signals transmitted by pain fibres[198]. Commercial devices, such as Buzzy from Pain Care Labs, seek to leverage these principles, delivering vibration and cooling to the skin in response to a painful experience or procedure. Clinical studies demonstrate that this approach substantially reduces the perception of pain in patients when intravenous injections[199–202] or dental procedures[203,204] are performed. These stimuli also reduce musculoskeletal pain[205].

Localized drug delivery

Medications, including opioids and non-opioids, are one of the simplest and oldest methods of modulating the nervous system[206]. However, repeated, long-term, systemic administration of opioid painkillers poses many long-term risks for the patients, including

addiction and de-sensitization[207]. The addictive and dangerous qualities of medication-based interventions are not unavoidable. Off-target effects can, in fact, be avoided by enhancing functional selectivity[208,209]. Furthermore, intelligent control over the release of these medications could help ensure patient adherence to treatment regimens.

Microfluidic and micro-electromechanical systems enable wearable, ingestible and implantable devices that target pain with spatial and temporal precision[21,210] (Fig. 3c). Both passive and actively powered platforms deliver useful agents such as local anaesthesia, opioid medications, non-steroidal anti-inflammatory drugs and inhibitory neurotransmitters. This approach combines the functional selectivity of medication-based interventions with the direct spatial selectivity of neuromodulation.

Ingestible electronics for programmable release of medications

Oral administration of medications can result in highly inconsistent release profiles, with blood concentrations varying between each regular dose[211]. Extended-release formulations based on polymeric carriers limit the dangerous side effects that come with undulating bioavailability[212], but exact temporal profiles can be hard to predict. Advances in bioelectronics yield miniaturized devices that can be swallowed, digested and, ultimately, excreted by a patient[213] (Fig. 3c). While travelling through the gastrointestinal system, these devices release medications at specific, programmed time intervals. Ingestible electronics demonstrates features for adaptively responding to individual metabolisms and sensor-based cues.

Gastrointestinal drug delivery platforms leverage microprocessor-based computational and communications elements that fit into ingestible capsules. Devices can be tracked on their trajectory through the stomach and intestines[214], all while delivering precise doses of a pharmacological agent. IntelliCap from Medimetrics, which was given the CE Mark, uses a mechanical plunger to deliver a drug payload of 300 µl over intervals ranging between 10 min and 48 h (refs. 215,216). This approach is especially well suited for proteins, such as insulin, which become degraded by gastric acid during normal systemic administration[217]. Currently limited by risks of retention in the gastrointestinal tract[218], further miniaturization will allow even more sophisticated systems to be ingested.

The maximum release interval of these platforms is limited by battery lifetime (for example, IntelliCap can release medication over 48 h on a single charge[217]). Using energy-harvesting electronics[219], devices could operate over arbitrarily long periods of time in the chemical environment of the gastrointestinal tract. Furthermore, using stimuli-responsive materials, the retention of devices could be externally controlled[220], ultimately enabling intelligent devices to deliver pain medications over the timescale of months.

Along with actuators for delivering medication, ingestible electronics integrate sensors for tracking drug metabolism and other critical biomarkers. Radiofrequency identification capsules verify patient adherence to medication programmes[12], and physiological sensors monitor respiration, heart rate and blood oxygenation[13]. Closed-loop systems leveraging these technologies could detect signs of an overdose, halting release or delivering opioid antagonists, such as Naloxone, accordingly[22]. Thus, ingestible electronics will present healthcare providers with potent new tools for combatting overdose and addiction.

Wearable drug delivery patches

Oral administration of medications results in metabolic processing by the liver, which can reduce the effectiveness of intended treatment and can even harm organ systems. Hypodermic injections solve this problem, but they require administration by healthcare providers. For lipophilic drugs, such as fentanyl, transdermal delivery through skin-adhered patches offers an effective means of controlling pain symptoms[221,222] (Fig. 3c). In addition, by avoiding the liver, this route of administration enables new medications, such as buprenorphine, which treats both pain and substance abuse disorder[221,222] (Table 3). New principles of operation enable patients to administer their own treatment in a consistent, on-demand manner.

The first key element of a drug delivery system is a reservoir that stores a pharmacological agent. In transdermal delivery, a wearable, externally mounted reservoir releases the agent directly to the skin[223]. Local anaesthetics[224], local analgesics[225] and non-steroidal anti-inflammatory drugs[226] delivered using this method primarily act on the underlying volume of tissue. This simple but powerful approach also enables drugs with central mechanisms of action, such as opioids, to absorb systemically into blood circulation. Drug-eluting polymers have been approved by the FDA agency for the delivery of opioid-based medications[221].

Transport across the barrier of the skin can be facilitated through transcutaneous microneedles[227,228], thermal ablation[229], lipophilic carriers[230] and electroporation[231], enabling rapid delivery of a wider range of medications compared with oral administration. In addition, approaches based on iontophoresis[232–234], optical irradiation[235] and ultrasound[236,237] enable the pharmacological agent to be released on-demand. Thus, along with covering new pain medications, transdermal delivery can increase the temporal precision of treatment over conventional approaches.

Implanted devices for delivery to deep tissue and organs

As in neurostimulation modalities, the use of implanted devices for drug delivery offers greater precision and access to deep organs, such as peripheral nerves. Compared with wearable patches, implanted devices are not constrained by the lipophilic barrier of the skin; a wider range of pharmacological agents are compatible with this approach, including inhibitory neurotransmitters[238], opening new opportunities for treating pain.

Similar to drug delivery patches, the simplest format for an implantable system is a polymeric reservoir that passively releases a pharmacological agent over time (Fig. 3c). For example, Probuphine, an FDA-approved implant, releases buprenorphine subcutaneously over the course of 6 months (Table 3). For individuals with opioid abuse disorder, this format ensures adherence to a prescribed pain treatment regimen[239]. Although Probuphine needs to be surgically removed after the conclusion of treatment, approaches that leverage biodegradable materials could soon enable implants like this to harmlessly dissolve[240,241]. These materials can even be designed to respond to external stimuli, triggering release upon optical irradiation[242], joule heating[243] and electrochemical corrosion[244].

Implanted drug delivery systems present a compelling use case for interventions that require rapid response. During fentanyl overdose, for example, maximum respiratory depression occurs within minutes of injection[245]. In 2024, a preclinical study demonstrates a closed-loop system that monitors for signs of overdose and releases naloxone, an opioid antagonist, in response[22]. In this system, an implanted microfluidic pump delivered life-saving medication at therapeutic levels within 2 min. A pump-based mechanism is also used in the SynchroMed II Infusion System (Medtronic), an FDA-approved implant that delivers pain medications, including morphine and ziconotide[246] (Table 3).

However, this system is bulky and suffers pump-motor failures[247]. Long-term stability and effectiveness of mechanical pump-based delivery approaches could be improved introducing small-scale electromechanical systems based on electrolysis[163] and hydrogel electro-swelling[248].

Many pharmacological agents have charge groups, enabling delivery under the driving force of an electric field. Electrophoretic drug delivery is highly efficient and, consequently, easier to miniaturize than mechanical delivery[249–252]. The use of electrochemical diodes[253] permits precise spatiotemporal control over the release of pharmacological agents, including inhibitory neurotransmitters. As demonstrated in 2025 in preclinical studies, these miniaturized iontronic systems open up opportunities for pain management[238].

One of the fundamental challenges for implanted systems is that they rely on a finite stock of a pharmacological agent. When the agent runs out, the device needs to be physically accessed for the reservoir to be refilled or replaced. For specific ions present in normal matrices, ion concentration polarization with ion-selective membranes offers the prospect of remotely refilling the internal reservoir[254–256]. The development of this system beyond preclinical studies has the potential to further expand the long-term stability of implantable drug delivery systems for pain management.

Augmented and virtual reality for cognitive and affective intervention

When individuals focus on pain, cortical activity in regions associated with pain processing intensifies, whereas distraction from pain reduces such activity[257]. Pain also presents emotional affective dimensions that can exacerbate its perception[71]. However, until recently, the role of cognitive and emotional processes has remained underexplored for pain management[74]. The introduction of AR/VR systems and sophisticated wearable technologies, capable of eliciting emotional and engaging interactions on-demand[258,259], has raised new prospects for attention-modifying and emotion-modifying approaches for pain interventions. Similar to direct electrical stimulation and implanted drug delivery, wearable AR/VR systems offer a targeted, tunable alternative to pain medication (Fig. 4).

Audiovisual AR/VR with headsets

Following the commercial success of VR headsets, such as Quest from Meta, a range of configurations across the AR/VR continuum have been explored for pain management. VR headsets offer immersive, interactive experiences that effectively focus the attention of the user away from noxious stimuli. Clinical studies have shown impactful outcomes for acute pain arising from dental care[260,261], burn treatment[262–264]

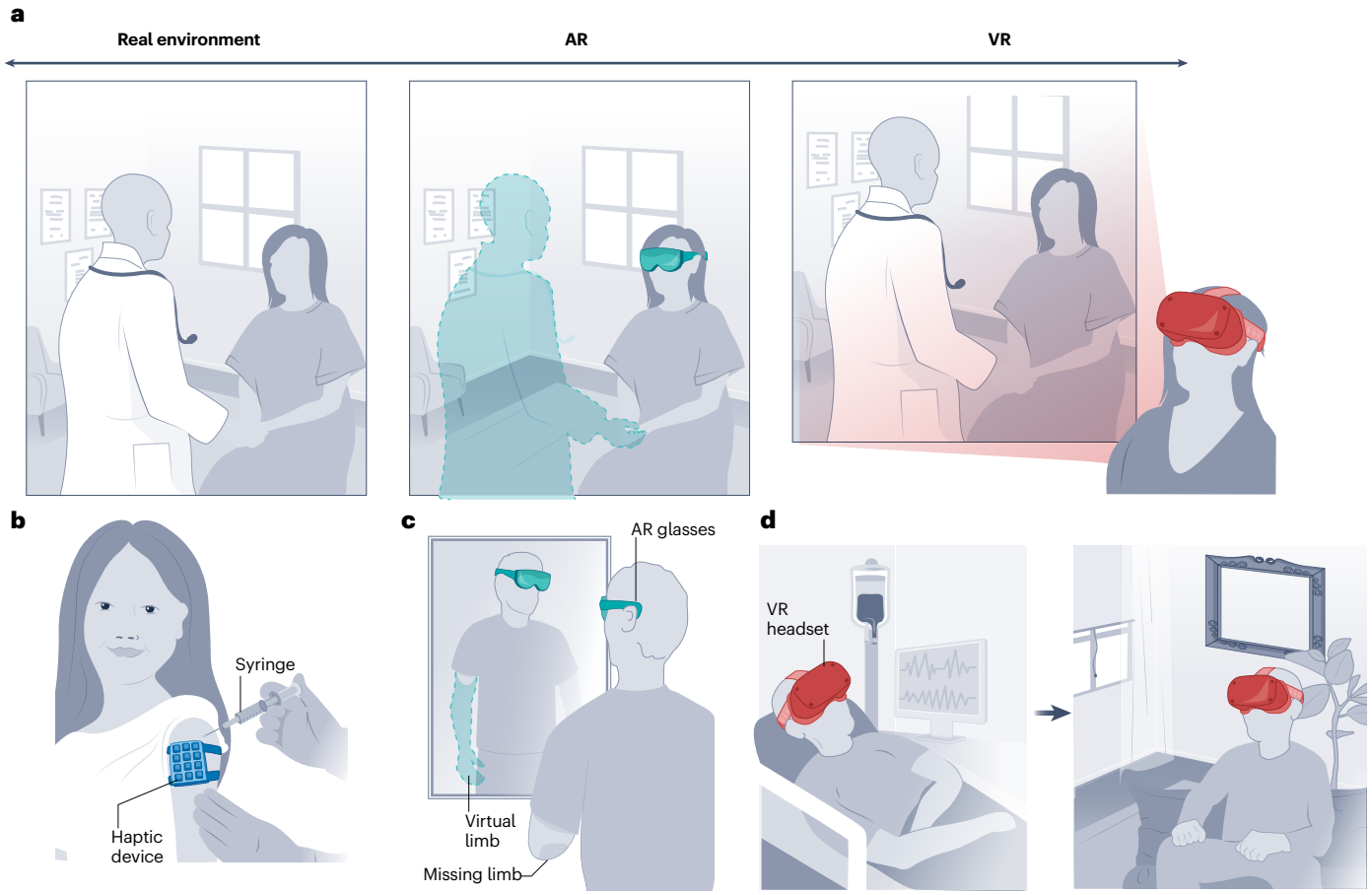

Fig. 4 | Use cases for augmented and virtual reality in pain management. **a**, Diagram of the physical–virtual reality (VR) continuum, including augmented reality (AR), which incorporates both real and virtual environments. **b**, Haptic vibration for distraction during injection; for example, during dental procedures and intravenous syringe injections. **c**, Embodiment of amputated limbs using AR/VR systems to treat phantom limb pain. **d**, VR for distraction during clinical procedures, such as chemotherapy, and a proposed transition for extending this pain management approach outside the clinic.

Glossary

Analgesia
The partial or complete abolition of pain via medication or other means.

Anticonvulsants
Anticonvulsants, also referred to as anti-epileptic drugs, suppress the rapid firing of neurons. Medications such as gabapentin and pregabalin are commonly prescribed in neuropathic pain conditions.

Antidepressants
Antidepressant medications are primarily indicated for treating clinical depression and anxiety. Tricyclic antidepressant and selective serotonin reuptake inhibitor classes also demonstrate favourable outcomes in treating neuropathic pain and fibromyalgia.

Deep brain stimulation
(DBS). Invasive stimulation of the midbrain through a surgically mounted probe (~2 cm deep) that delivers electrical current.

Electrocardiography
(ECG). The measurement of temporally resolved electrical potentials, generated from heart electrical activity, across electrodes mounted on the torso.

Electroencephalography
(EEG). The measurement of temporally resolved electrical potentials, generated from brain electrical activity, across electrodes mounted on the head.

Electromyography
(EMG). The measurement of temporally resolved electrical potentials, generated from muscle electrical activity, across electrodes mounted on the skin over the targeted muscle.

Local anaesthesia
The partial or complete abolition of all senses, including mechanical touch and temperature, through a topically administered medication such as lidocaine or bupivacaine.

Neuromodulation
A general term for electrical stimulation modalities, including both non-invasive and invasive neural interfaces in the peripheral and central nervous system.

Non-steroidal anti-inflammatory drugs
Non-steroidal anti-inflammatory drugs, primarily acting outside the central nervous system, reduce inflammation throughout the body and produce an analgesic effect. Common non-steroidal anti-inflammatory drugs include ibuprofen, acetaminophen, aspirin and naproxen.

Opioids
Opioids are medications derived from opium that bind opioid receptors in the brain, eliciting a powerful analgesic effect. Common opioid pain medications include morphine, fentanyl, buprenorphine, hydrocodone, methadone and codeine.

Pulse oximetry
The measurement of oxygen carried in blood cells, commonly performed by directing light through the finger and detecting absorption (photoplethysmography).

Spinal cord stimulation
(SCS). Stimulation of the spinal cord with electrical current. SCS can be non-invasive, using skin-mounted electrodes. SCS can also be invasive, using percutaneous or fully implanted electrodes.

Transcranial direct current stimulation
(tDCS). Non-invasive stimulation of the brain through electrodes mounted on the head that deliver small electrical currents (~2 mA).

Transcranial magnetic stimulation
(TMS). Non-invasive stimulation of the brain through electromagnetic coils that deliver repetitive magnetic pulses.

Transcutaneous electrical nerve stimulation
(TENS). Non-invasive stimulation of sensory nerves through skin-mounted electrodes that deliver electrical currents.

and syringe injections[265–267] (Table 3). For patients undergoing burn wound care, interaction with snow and other cold imagery in a virtual environment had a marked positive effect on visual analogue scale ratings[263]. Improved outcomes have also been demonstrated for treating chronic cancer[268] and neck pain[269]. Although most current VR-based interventions for pain management centre around clinical point-of-care procedures, the rising accessibility and lowering costs (~US$300–1,000 for commercial VR headsets in 2025) of AR/VR technologies and immersive visual media open opportunities for consumers to direct their own treatment.

Along with cognitive effects, AR/VR systems offer a powerful tool for addressing emotional affective dimensions of pain[270]. Emotions are deeply attached to our sensory experiences, and AR/VR modalities, including audiovisual headsets and wearable haptic devices, are capable of reproducing these experiences in an immersive way[258]. Affective disorders, including anxiety and depression, accompany the experience of pain, exacerbating it. AR/VR-enhanced psychotherapies demonstrate marked positive improvements in the symptoms of these conditions[271]. Thus, this interventional approach presents a powerful complement to the affective monitoring strategies.

AR/VR therapy has primarily been studied as a supplemental form of pain relief. For example, during studies of burn dressing pain relief, it is common to compare the effectiveness of medication with medication plus VR[264]. Although comparative analysis relative to other approaches is limited, VR use can reduce the overall amount of opioid medication needed[272]. These promising results show potential merits for further investigation into AR/VR as a standalone form of treatment.

The emerging frontier of haptic AR/VR

Although users commonly associate AR/VR with audiovisual headsets, our hearing and vision are only a subset of our important senses. Our physical sense of touch is similarly capable of embodying immersive, affective experiences[273]. As recognized by the 2021 Nobel Prize in Physiology or Medicine awarded to David Julius and Ardem Patapoutian, a rich composition of afferent mechanoreceptors that exist in the skin acts collectively to define our physical perception of the world[274]. The introduction of wearable haptic devices, leveraging electrotactile[122,275], electrostatic[276,277], pneumatic[278,279] and electromagnetic[280–282] mechanisms, offers new opportunities for interfacing with these receptors. For example, an untethered, multimodal mechanical system, developed in 2024, stores energy in skin to deliver pressing, stretching and vibration[23]. Along with mechanical touch, thermal AR/VR systems reproduce patterns of temperature across the body[283,284]. These advances introduce impressive affordances for delivering realistic, intuitive sensations.

Haptic stimulation on its own is an effective method of altering attention and reducing perceived pain[285,286]. Along with attention-modifying effects, immersive virtual experiences with haptic feedback offer a powerful tool for influencing user emotions and reducing pain[259,287]. Physical sensations enhance the embodiment of virtual experiences, for example, improving self-report ratings for phantom limb pain treatment[288–290]. Furthermore, gate-control theory suggests that mechanical and thermal stimuli might elicit direct analgesic effects at the neurobiological level as the basis for improved pain ratings for dental procedures[203,204], syringe injections[199–202] and musculoskeletal pain[205] (Table 3). In 2021, a study involving 142 participants found that cutaneous stimuli, vibration and cooling resulted in lower mean self-report ratings of pain compared with audiovisual VR (57.7% versus 48.1%, respectively, relative to current standard of care)[265]. Leveraging cognitive, emotional and neurological mechanisms, wearable haptic interfaces present intriguing possibilities for pain management.

Outlook

Pain is a profound and unresolved health challenge. This problem has been greatly exacerbated by the competing challenges of the opioid overdose epidemic[6]. Many of the limitations in pain management arise from a lack of selectivity and precision. For example, limitations in pain evaluation can lead to poorly matched intervention strategies and dosages. In addition, the addictive and dangerous qualities of opioid medications are mediated by their off-target interactions across the central and peripheral nervous system. Advances in the areas of wearable bioelectronics, machine learning, neural interfaces and AR/VR offer prospects for solving these long-standing challenges.

One of the cornerstones of effective pain management is the accurate classification of pain, as it might arise from different underlying mechanisms and respond to distinct therapeutic interventions. Traditional approaches for evaluating pain in the clinic rely on subjective evaluations, which can lead to delays in calibrating safe and effective intervention strategies and dosages. This limitation has motivated the implementation of objective measures based on autonomic activity, physical behaviour and emotional effects. However, the validation of these approaches has been challenging, as the gold standard, patient self-reported ratings, is considered unreliable. With the introduction of sophisticated bioelectronic wearables that track body motion, monitor sweat and sense cardiovascular activity, capabilities now exist for constructing rich training data for pain symptoms. Component analysis of this high-volume, multimodal data set might yield reliable metrics for healthcare providers to apply in place of subjective assessments.

The ability to collect large amounts of data requires suitable analysis methods for drawing meaningful observations and predictions. New strategies in machine learning and AI not only enable effective analysis of high-volume data generated from wearable sensors but also augment and automate the abilities of healthcare providers to make decisions based on incoming information. An intelligent, wearable system of wireless sensors and stimulation modalities that adaptively detect and treat pain, respectively, is needed.

The interventional arm of the intelligent system includes neural interfaces, which induce targeted functional activity in peripheral nerves, the spinal cord and the brain (Fig. 2a). Modalities such as TMS and SCS have broad regulatory approval for treating pain, in contrast to others, such as DBS and tDCS (Table 3). Inconsistent results in clinical trials have been attributed to a lack of standardized operating procedures with respect to electrode locations and stimulus parameters[121,183]. Ongoing efforts focus on the development of closed-loop systems, which might increase the consistency and effectiveness of each modality. Future progress in pain care would also greatly benefit from cost analyses that compare all the given modalities with a common frame of reference.

Similar to electrical neural interfaces, localized chemical delivery platforms aim to avoid pernicious effects such as overdose and addiction that arise frequently from opioid-based pain medications. Ingestible, wearable and implanted electronics delivers powerful medications to precise targets along the paths of pain transmission. Multiple drug delivery platforms have regulatory approval for treating pain, each characterized by distinct tradeoffs in terms of selectivity, invasiveness and compatibility with medications. Ongoing research aims to make these approaches more accessible to patients through miniaturization and novel delivery strategies.

A high-level concept for closed-loop pain management includes a machine-learning agent that adapts targeted treatment modalities based on the detection of specific symptoms (Fig. 2b). One example of a closed-loop system within this framework might be a wearable seismocardiography sensor wirelessly linked to an ingestible electronic pill that monitors heart rate variability for signs of pain and releases analgesic medications in response. Another example would be an AR headset that monitors facial expressions for signs of anxiety and, on an as-needed basis, delivers calming virtual stimuli to treat the affective dimension of pain. AR functionality can fit into standard glasses frames (for example, Meta or XREAL), and these treatments could even be delivered during normal daily activities.

The emotional affective dimension of pain can perpetuate a cycle of pain and negative emotions. However, the role of cognitive and emotional processes has remained underexplored for pain management. Powerful advances in affective computing and AR/VR systems enable the affective states of patients to be monitored and influenced, respectively. Although users commonly associate AR/VR with audiovisual headsets, our physical sense of touch, mediated by the sensory receptors in our skin, is similarly capable of embodying immersive, affective experiences. Haptics might also expand the accessibility of virtual experiences to individuals with visual or hearing impairments. Haptic AR/VR technologies will soon become accessible to consumers, enabling deeper examination of pain relief mechanisms: (1) cognitive distraction, (2) emotional affective augmentation, and (3) spinal gating of somatosensory signals. The development of systems that can elicit physical sensory experiences across the skin, an exciting direction in bioelectronics[23], will present new opportunities for leveraging these mechanisms.

An intelligent system emerges for monitoring pain, making decisions about treatment and performing rapid, targeted intervention. This vision is comprehensive, in that it aims to monitor and treat the physiological, behavioural and emotional symptoms of pain. The realization of this vision will have profound implications for the quality of life of patients, addressing the far-reaching social and economic costs of pain.

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M.T.F., J.A.F., M.A.P., A.H.A. and L.F. researched data for the article. M.T.F., J.A.F., M.A.P., A.H.A., L.F., J.A.R. and S.J.L. substantially contributed to the discussion of the content. M.T.F., J.A.F., M.A.P., A.H.A. and L.F. wrote the manuscript. M.T.F., J.A.F., M.A.P., A.H.A., L.F., D.G., H.M. and S.J.L. reviewed and edited the manuscript before submission.

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