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# Pain-related changes in the brain: diagnostic and therapeutic potentials

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Emerging evidence suggests that chronic pain is a disease that can alter brain function. Imaging studies have demonstrated structural remapping and functional reorganization of brain circuits under various pain conditions. In parallel, preclinical models have demonstrated that chronic pain causes long-term neuroplasticity. For example, thalamo–cortical oscillations are dysregulated and neurons in the sensory thalamus undergo ectopic firing linked to misexpression of membrane ion channels. In theory, physiological changes at the single-unit, multi-unit, and circuitry levels can be used as predictors of pain, and possibly to guide targeted neuromodulation of specific brain regions for therapeutic purposes. Therefore, multidisciplinary research into the mechanisms of pain-related phenomena in the brain may offer insights into novel approaches for the diagnosis, monitoring, and management of persistent pain.

## Persistent pain disrupts normal brain function

Although the brain lacks nociceptors, chronic pain can significantly alter brain function. In its mild form, pain has inconsequential clinical outcomes. However, long-lasting pain is considered pathological when it becomes clinically intractable and described by the patient in vague or unusual terms such as electric-like, especially in the absence of overt tissue damage [1]. Pathological pain is correlated with co-morbid cognitive and mood disorders [2] and can be actively modulated by cognitive processes. For example, individuals asked to look at their hand while it is being subjected to an infrared laser stimulus report less intense pain compared to when they are looking away at another object, suggesting that active recruitment of visual brain circuits can reduce the experience of acute pain [3].

This review presents evidence of pain-related changes in the brain, such as overactivation of neuronal assemblies, network malfunction, and variations in gray matter density. Electrophysiological and cellular mechanisms thought to mediate aberrant neuronal activity at the single-unit level are also discussed. It is argued that continued research into pain-associated phenomena in the brain, whether considered as epiphenomena or causative agents of pain, is a win–win strategy warranted by diagnostic and therapeutic potentials.

## Altered neuronal code: single-unit sensitization and bursting

A close look at the single-cell level in the brain reveals a particular case of neuroplasticity (see Glossary) secondary to neuropathic injury. This is manifest in a decreased firing threshold, as well as increased spontaneous firing and enhanced firing evoked by repetitive stimulation, a phenomenon known as sensitization [4]. Pain-related central sensitization has been documented in the spinal cord dorsal horn [5], brain stem rostral ventromedial medulla (RVM) [6–8], ventral posterolateral (VPL) nucleus of the thalamus [9–12], amygdala [13,14], anterior cingulate cortex (ACC) [15] and primary somatosensory (S1) cortex [16]. For example, in vivo extracellular single-unit activity (SUA) recorded from VPL neurons shows increased rates of spontaneous firing. Increased evoked firing in these neurons is also observed in response to noxious and non-noxious stimuli applied to the hyperalgesic hindpaw (Figure 1a,b) [17]; similar results have been reported for models of sciatic injury [17], spinal cord injury [18,19], and diabetic neuropathy [20]. It is also worth noting that thalamic lesions resulting from stroke have long been known to cause central pain syndrome in humans [21] and neuropathic behavior in rats [22]. Thus, alterations in thalamic processing of the ascending nociceptive input, caused by either thalamic sensitization or loss of neurons, may directly contribute to pathological pain states. In the ACC, basal neuronal firing and responses to colorectal distension are increased in a rat model of visceral hypersensitivity, whereas neuronal activity evoked by noxious

## Glossary

**Functional connectivity**: coordination of activity between different neuronal assemblies, such as during the execution of a complex cognitive task or perceptual process.
**Local field potential (LFP)**: low-frequency ($<0.2$ kHz) content of the electrophysiological signal generated by membrane currents of neurons in a local neighborhood of the recording electrode. The high frequency ($>1$ kHz) content represents predominantly neuronal action potential spiking. Thus, the coordinated activity of cell populations is reflected by regular oscillations in LFPs, which could be used to study network functions related to sensory and motor phenomena.
**Neuroplasticity**: structural or functional change in the response of a neuron to the same stimulus, which may manifest as synaptic reorganization, sprouting, or modulated excitability.
**Rhythmic oscillation**: brain rhythms, for example due to neuronal interactions in corticothalamic systems, coalesce in the form of major oscillations that characterize different brain states, such as spontaneous low-frequency sleep oscillations, as well as beta and gamma activities.
**Sensitization**: increased synaptic efficacy and/or neuronal excitability following an intense peripheral noxious stimulus, tissue injury, or nerve damage [5] (sensitization is also a form of neuroplasticity).

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cutaneous stimuli is not affected [23]. In the amygdala, neurons in the central nucleus develop increased background and evoked activity following arthritis induction in the knee [24]. In the RVM, neurons mediating descending modulation of spinal nociceptive circuitry (classified as on-cells or off-cells) exhibit enhanced responses to noxious mechanical stimulation applied to the hypersensitive hind-paw within 7–14 days after sciatic nerve injury [25]. Interestingly, on-cells are thought to promote nociception, whereas off-cells exert opposite effects [25,26]. Neurons recorded from S1 cortex of neuropathic rats following spinal cord contusion manifest higher spontaneous firing rates, and greater responses evoked by innocuous and noxious mechanical stimulation of the hindpaw, compared to control rats [16].

In addition to the tonic firing rate, burst firing is an important feature of the neuronal code and can effectively impact postsynaptic neurons [27]. Burst duration [28] and the relative timing of burst spikes [27] can encode specific stimulus features [29]. Accordingly, tonic and burst firing modes of thalamocortical neurons is thought to gate sensory signal transmission from the thalamus to the cortex [30]. Interestingly, ∼30% of VPL thalamic neurons manifest abnormal burst patterns in rats with pain-like behavior [17], whereby spontaneously occurring bursts tend to be of the short bursting mode (∼2–3 spike/s and 0.5–1 burst/s). In the intralaminar thalamic nuclei of patients with chronic deafferentation pain, single units discharge action potentials spontaneously at a high rate, often rhythmically [31], as well as in bursts described as short (2–6 spikes/burst at a frequency of 1–4 burst/s) or long (30–80 spikes/burst at a similar frequency) [31,32]. Burst firing has been documented in the ventral thalamus in a patient with root injury and occurs during episodes of self-reported touch-evoked allodynia [33]. Interestingly, thalamic bursting can lead to synaptic potentiation in the ACC, with important consequences regarding cortical integration of the nociceptive input and memory formation related to painful events [34]. It is worth noting that abnormal changes in the patterns of burst firing are a more reliable marker for pain-related plasticity rather than the occurrence of burst firing *per se*, because burst firing can occur in deafferented subjects without pain [35].

### Thalamic channelopathy?
Relative to the wealth of data describing pain-related imaging and electrophysiological aberrations in the brain, few studies have addressed the underlying cellular basis of such phenomena. Misexpression of membrane ion channels and modulation of receptors have been proposed as contributing factors to neuroplasticity, particularly in the thalamus [36]. In VPL neurons, sensitization and abnormal bursting activity are linked to the voltage-gated sodium channel Nav1.3. Nav1.3 produces a rapidly repriming tetrodotoxin (TTX)-sensitive current that permits neuronal firing at higher-than-normal frequencies [37]. This channel is normally absent in VPL neurons at an adult stage but becomes aberrantly expressed following peripheral or central neuropathic injury [11,18,19,38]. Down-regulation of Nav1.3 expression in the VPL is sufficient to reverse neuronal sensitization, abnormal bursting, and

neuropathic behavior in rodent models [36]. Such findings suggest that Nav1.3 channelopathy in the thalamus contributes to pain-related phenomena.

With regard to medial and reticular thalamic projection neurons, abnormal bursting has been reported in patients with neurogenic pain [39]. This has been proposed as the common pathophysiology for sensory, motor, and limbic positive symptoms [40]. Presumably different from Nav1.3-associated bursting of VPL neurons, these low-threshold spike bursts are generated by $Ca^{2+}$ influx through T-type $Ca^{2+}$ channels [41]. Such firing perturbs ongoing oscillatory activity in the thalamocortical circuitry and leads to increased power in the cortical theta rhythm [42]. Although inactive under normal physiological conditions, these channels are de-inactivated on hyperpolarization [41], which could hypothetically be triggered by deafferentation of an injured peripheral nerve. Indeed, it has been shown that bimodal (tonic and burst) firing of thalamocortical neurons is modulated by T- and L-type $Ca^{2+}$ currents with behavioral consequences in a rodent visceral pain model [30]. Knockout of T-type Cav3.2 channels in mice decreases burst incidence in reticular thalamic neurons, concomitant with higher burst ratio and spikes/burst in VPL neurons [43]. Thus, it has been hypothesized that T-type $Ca^{2+}$ channels contribute to thalamocortical dysrhythmia, which has been proposed as a possible generalized mechanism underlying several cognitive disorders [41].

### Receptor modulation in the thalamus, ACC, and periaqueductal gray
It is thought that ryanodine receptors (intracellular calcium-release channels) contribute to nociception-induced changes in the electrophysiological properties of ventrobasal thalamic neurons. Activation of these receptors decreases neuronal firing and nociceptive behavior, whereas blocking them induces the opposite effects in a rat model of inflammatory pain [44]. It has also been speculated that strychnine-sensitive glycine A receptors contribute to the analgesic action of glycinergic analogs according to *in vitro* data using thalamic slice preparations [45]. Moreover, independent studies demonstrated that nicotinic acetylcholine receptors and cannabinoid CB2 receptors enhance the responses of VPL neurons in neuropathic pain models [46,47] (although it is unclear whether CB2 receptor expression is localized to neurons and/or glial cells).

In the ACC, mRNA and protein expression levels of muscarinic-1 and -2 receptors are modulated following peripheral nerve injury [48], whereas in the ventrolateral periaqueductal gray, a key component of the descending pain modulatory system, local inhibition of the nociceptin/orphanin (NOP) receptor system by microinfusion of a selective NOP receptor antagonist reverses mechanical allodynia secondary to peripheral neuropathic or inflammatory pain [49].

### Overactivated circuits
Preliminary evidence of pain-related functional changes in the brain was initially revealed by functional magnetic resonance imaging (fMRI) [50,51]. Although activation patterns may vary, the regions most consistently reported to have increased blood-oxygen-level-dependent (BOLD)
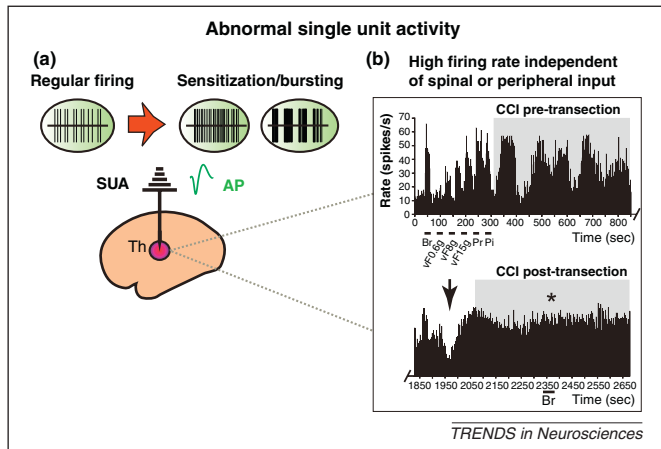
**Figure 1**. Abnormal single unit activity. **(a)** Pathological pain is associated with irregular firing modes at the single-unit activity (SUA) level, notably in thalamic neurons, manifesting as an increased rate of action potential (AP) discharge and abnormal bursting [17]. **(b)** Upper panel: representative example showing a high rate of evoked SUA in response to natural stimuli (Abbreviations: Br, brush; vF, vFrei filaments; Pr, pressure; Pi, pinch) and rhythmic oscillation (shaded areas) recorded extracellularly from the VPL nucleus of the thalamus in a rat with chronic constriction injury (CCI) of the sciatic nerve [17]. Lower panel: oscillatory activity was abolished after complete spinal transection (indicated with an arrow), but not the high rate of spontaneous firing. The asterisk indicates the absence of a response to a brush stimulus after transection. Adapted, with permission, from [17].

signals associated with experimentally induced pain include the thalamus, S1 cortex, ACC, prefrontal cortex (PFC), insula, and (for less-understood reasons) the cerebellum [52], forming a so-called pain matrix (Figure 2a,b) [53–56]. In general, pain-related imaging data have been replicated in anesthetized animals [57], in particular nociception-induced cerebellar activation [58,59].

Improved experimental designs for imaging techniques (e.g., near-threshold pain–non-pain paradigm) have been successful in eliminating nonspecific comorbid factors associated with pain [60]. Moreover, machine learning algorithms have become increasingly popular for fMRI signal decoding because of their ability to predict a sensory experience on the basis of spatially correlated fMRI voxels [61–63]. For example, combining fMRI with support vector machine learning allows prediction of thermal pain experiences in human subjects with more than 80% accuracy [64]. Further analytical improvements in imaging paradigms are likely to lead to greater reliability in visualizing the exact brain regions associated with persistent pain.

In addition to activation of localized brain regions as shown by fMRI, emerging data demonstrate variations in brain volume and gray matter density in patients with chronic pain. The volume of the human hippocampus is reduced in patients with chronic back pain, complex regional pain syndrome, and osteoarthritis [65]. In parallel, extracellular signal-regulated kinase (ERK) expression and phosphorylation, as well as neurogenesis, are reduced in the hippocampus of mice with sciatic neuropathic pain [65]. Voxel-based morphometry of T1-weighted images show no gray matter volume change in patients with temporomandibular disorders [66]. However, gray matter volume in patients with trigeminal neuropathic pain is reduced in S1 cortex, anterior insula, putamen, nucleus accumbens, and thalamus, but increased volume was noted in the posterior insula [66], suggesting that different brain mechanisms may underlie the pathogenesis of neuropathic

versus non-neuropathic pain. By contrast, decreased [67,68] (as well as increased [69]) gray matter density has been observed in the thalamus of patients with osteoarthritis or temporomandibular pain. Interestingly, some of these changes are reversible after effective pain relief [67].

**Dysfunctional networks**
Communicating brain regions form functional neuronal networks. Signal decoding methods in imaging studies, such as multivariate voxel analysis, suggest a strong link between chronic pain and dysfunctional connectivity across brain networks. Variable methods of experimentally induced acute and moderate pain have shown that functional connectivity is strengthened between the anterior insula and the orbitofrontal cortex [61–63]. If combined, these brain regions of interest can significantly enhance prediction accuracy, with ensuing diagnostic potential (Box 1). However, fMRI has demonstrated that increased connectivity between the secondary somatosensory cortex, anterior and posterior insula, and ACC reduces the experience of pain [3], resulting in analgesic effects produced in the visual context of seeing a body part during moderate and acute noxious stimulation, also referred to as visually induced analgesia.

As an alternative to imaging techniques, electrophysiological signals from functional brain networks can be recorded in the form of local field potentials (LFPs). Intraoperative recordings of cortical LFPs have been used in humans subjected to cutaneous application of a moderately noxious laser stimulus. Although invasive, this technique was useful for analyzing the directional and temporal dynamics within and between cortical structures in awake subjects combined with Granger causality analysis [70]. The results suggest that S1 cortex may be the primary driver for activity in other parts of the pain matrix.

In comparison to intracranial recording there is preference for the use of noninvasive techniques as biomarkers for pain, such as electroencephalography (EEG) [71] and magnetoencephalography (MEG) for the analysis of oscillatory (i.e., rhythmic) LFPs. Comparison of resting EEG between healthy subjects and patients with neurogenic pain reveals a significantly higher spectral power in patients over the frequency range 2–25 Hz, with a leftward shift of the dominant median peak [72]. Therapeutic lesion in the thalamus (central lateral nucleus) of these patients significantly reduces pain within 12 months after surgery and decreases the average EEG power in the theta band to nearly normal values. This suggests that both EEG signals and pain are determined by tightly coupled brain mechanisms, presumably mediated by thalamocortical loops. In a similar study, enhanced EEG power was observed in the high theta (6–9 Hz) and low beta frequency ranges (12–16 Hz) localized to pain-associated cortical areas including the insula, cingulate cortex, PFC, and S1 [73]. In parallel, MEG revealed a leftward shift of 2–3 Hz from the normal range of 8–10 Hz in the median dominant spectral power of patients with complex regional pain syndrome (Figure 3a,b) [74]. It has long been postulated that MEG, in general, reveals abnormal theta-range spectral power in patients with different cognitive disorders, such as schizophrenia and obsessive–compulsive disorders [74–76].
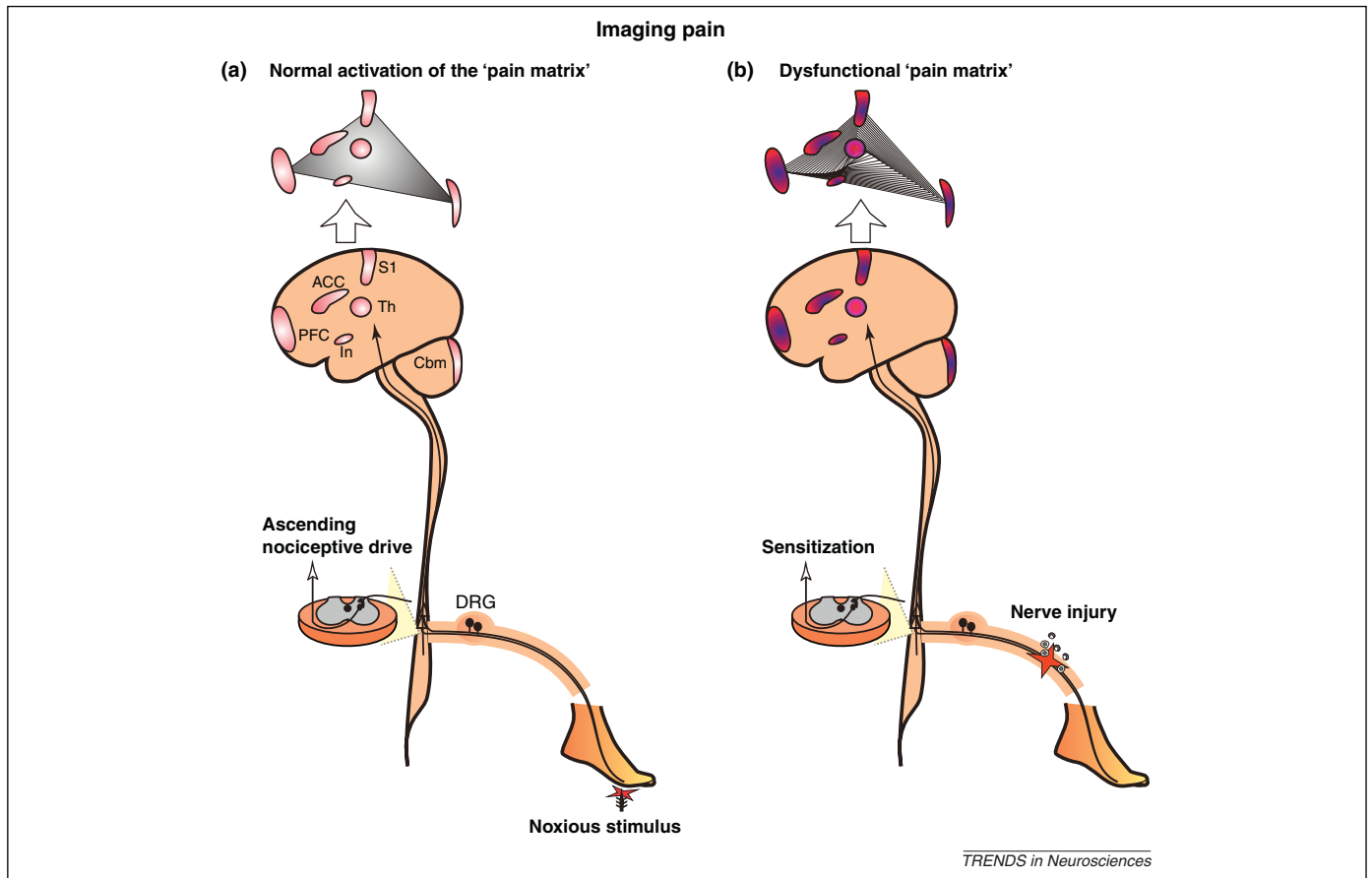
**Figure 2**. Imaging pain. **(a)** An acute, transient, and moderately noxious stimulus in a human subject consistently evokes blood-oxygen-level-dependent (BOLD) responses in brain regions including the thalamus (Th), primary somatosensory (S1) cortex, anterior cingulate cortex (ACC), prefrontal cortex (PFC), insula (In), and cerebellum (Cbm), forming parts of a so-called pain matrix [55]. **(b)** Pathological pain conditions lead to sensitization along the nociceptive circuitry and dysfunctional connectivity in the pain matrix.

### Disruption of a delicate inhibitory–excitatory balance in large-scale loops

Regarding dysfunctional brain networks, possible involvement of oscillatory activities in large-scale loops generated by the hippocampus and PFC has not been ruled out. Studies related to these loops, which play critical roles in cognitive and mood disorders, have emphasized the importance of an inhibitory–excitatory balance in predicting aberrant mental states in general [77]. In the hippocampus, oscillation in the gamma frequency is instantaneously modulated depending on this balance, and thus influences information flow across several cortical areas [78]. It is likely that this balance is shifted under chronic pain conditions because of a loss of input following deafferentation, or perhaps as a result of enhanced input due to nerve irritation, although this assumption has not been empirically tested.

### Pain-associated neuroinflammatory responses in the brain

Microglial activation has been demonstrated in the VPL contralateral to the injured sciatic nerve, concomitant with upregulation of phosphorylated p38 mitogen-activated protein kinase (MAPK), in a model of neuropathic pain [79]. Local infusion of a microglial inhibitor within the VPL attenuates p38 MAPK levels and reverses thermal hyperalgesia in the affected limb. A causal relation between microglia in the VPL and neuropathic behavior was also demonstrated in an animal model of spinal cord lesion through a mechanism involving cysteine–cysteine chemokine ligand 21 (CCL21) signaling to the VPL from a below-lesion level [80]. In humans, positron emission tomography (PET) using [11C]-(R)-PK11195, a marker of activated microglia and brain macrophages, clearly showed that
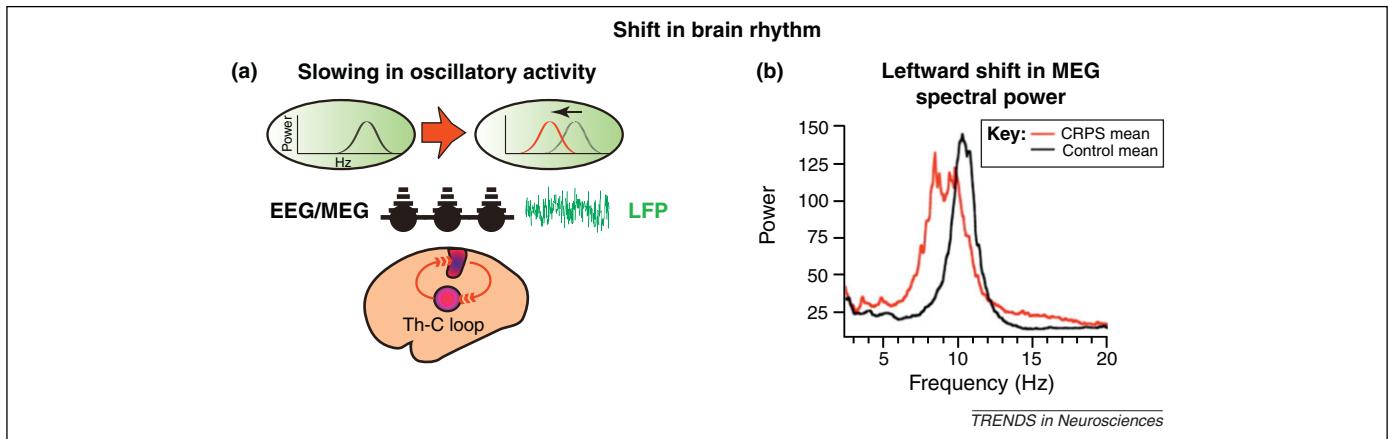
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**Box 1. Imaging: diagnostic value for pain?**

Imaging methods played a key role in visualizing brain regions that mediate sensory experiences, suggesting diagnostic potential. Standard MRI produces detailed anatomical images of the brain, for example, showing changes in brain volume under chronic pain conditions [101]. fMRI characterizes temporal differences in brain activity in response to stimulation, for example, demonstrating an altered functional state in the brain of patients with chronic back pain [102]. Pitfalls include the following:

(i) fMRI data are often inconsistent across time and between subjects, which undermines potential diagnostic values. For example, there is an obvious distinction in brain activation patterns between auditory and visual stimulations, but blurred distinction between noxious and non-noxious somatosensory stimulations [55] (although fMRI data suggest parallel processing of nociceptive and non-nociceptive afferents in S1 and S2 [103]). Furthermore, somatic pain, hypnotic influence, and imagery of pain all result in overlapping brain activation patterns [104].

(ii) BOLD signals are an indirect measure of overall neuronal and/or glial metabolic activity, but are so far incapable of detecting single-cell fast synaptic activity [105], a key component of the neuronal code.

**Figure 3**. Shift in brain rhythm. **(a)** Recording local field potential (LFP) with electroencephalography (EEG) or magnetoencephalography (MEG) shows slowing of rhythmic activity, mostly in the frequency range 8–12 Hz, when plotting power versus frequency of the LFP signal using fast Fourier transfer data analysis [73]. These power shifts are thought to reflect an underlying disturbance in thalamocortical (Th-C) loops (also known as thalamocortical dysrhythmia). **(b)** Spectral analysis of spontaneous activity measured via MEG from patients with complex regional pain syndrome (CRPS, red) type l and control subjects (black) as a function of frequency, showing a leftward shift to lower frequencies in patients compared to controls [74]. Adapted, with permission, from [74].

microglial activation may occur trans-synaptically in the thalamus in individuals with chronic pain and phantom sensations following limb amputation [81]. It is possible that remote microglial activation in the brain may account for pain-related fluctuations in gray matter density (described above) owing to their migratory and proliferative abilities in a state of activation, although other changes such as in the number (or volume) of neuronal cell bodies and dendritic fields could also play a role. In the RVM, a major component of brainstem descending pain-modulatory circuitry, microglial activation markers (CD11b and Iba1) are upregulated within 1–3 days after sciatic injury in rats, along with prolonged elevation of the cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-1β [82]. Neutralization of endogenous TNFα and IL-1β in the RVM reverses behavioral hypersensitivity in these rats. Thus, microglia may mediate neuronal sensitization and disruption of normal network activity in the brain under pain conditions [10,83]. However, one study reported no change in supraspinal microglial cell number or morphology following sciatic injury [84].

**Evidence-based pharmacotherapy**
Direct approaches for localized brain intervention have been attempted, such as specific pharmacological approaches in rodent models. In a notable study, rational drug design was recently used to block pain-induced neuroplasticity in a brain nociceptive network [85]. It was initially reported that the presynaptic release probability of glutamate and post-synaptic AMPA receptor-mediated responses in the ACC were enhanced in neuropathic mice after sciatic injury, in addition to increased phosphorylation of the GluA1 subunit of the AMPA receptor. Presynaptic changes in excitatory transmission could arguably support plastic changes in the thalamus. By contrast, synaptic changes were absent in mice genetically lacking calcium-stimulated adenylyl cyclase 1 (AC1) [86]. Subsequently, a chemically screened inhibitor of AC1 produced significant analgesia in rodent neuropathic pain models when administered intraperitoneally, orally, or locally within the ACC, with no measurable side effects (Figure 4a,b) [15,85].

In separate studies, pharmacological inhibition of synaptic transmission in S1 attenuated neuronal hyperexcitability in the ACC of mice, concomitant with reversal of neuropathic behavior [87,88]. *In vivo* two-photon calcium imaging was also used to demonstrate pain-related neuronal sensitization within intermediate layers II and III in S1 of these mice [87], in support of parallel findings using c-Fos as a marker of increased neuronal activity [89].

**Individualized neuromodulation**
Other therapeutic approaches aimed at reversing pain-related changes in the brain include neuromodulation of specific networks by electric stimulation. In a clinical setting, LFP recordings have been used to guide and optimize the effectiveness of neuromodulation in the brain for pain therapy, with the aim of restoring normal connectivity among specific structures within the pain matrix [70,90]. In animal models, two studies have recently tested the effects of deep brain stimulation (DBS) on sensitization of single units in the brain, as well as on pain behavior [17,91]. Although the mechanisms of DBS remain speculative [92], studies related to DBS for motor disorders suggest that high-frequency stimulation (HFS, >100 Hz) can mimic the functional effects of ablation [93], also referred to as jamming of the neuronal circuitry [92]. Therefore, in an attempt to reverse sensitization of VPL neurons, HFS (100–150 Hz) within the VPL effectively decreased neuronal hyperexcitability and thermal hyperalgesia in a model of peripheral neuropathic pain, whereas stimulation at a low frequency (LFS, 20–40 Hz) had no effect on SUA of VPL neurons [17]. Interestingly, LFS (50 Hz) in the VPL produces little or no analgesia in rats [94]. In a rodent model of central pain, LFS (50 Hz) within the motor cortex reduced mechanical allodynia and thermal hyperalgesia [91]. The study demonstrated that these effects were mimicked by DBS in the zona incerta of the subthalamus and blocked by reversible inactivation of this region. This suggests that the potential analgesic effects of motor cortex stimulation may be due to disinhibition of the zona incerta, thus causing analgesia by restoring inhibition in the thalamus [91].
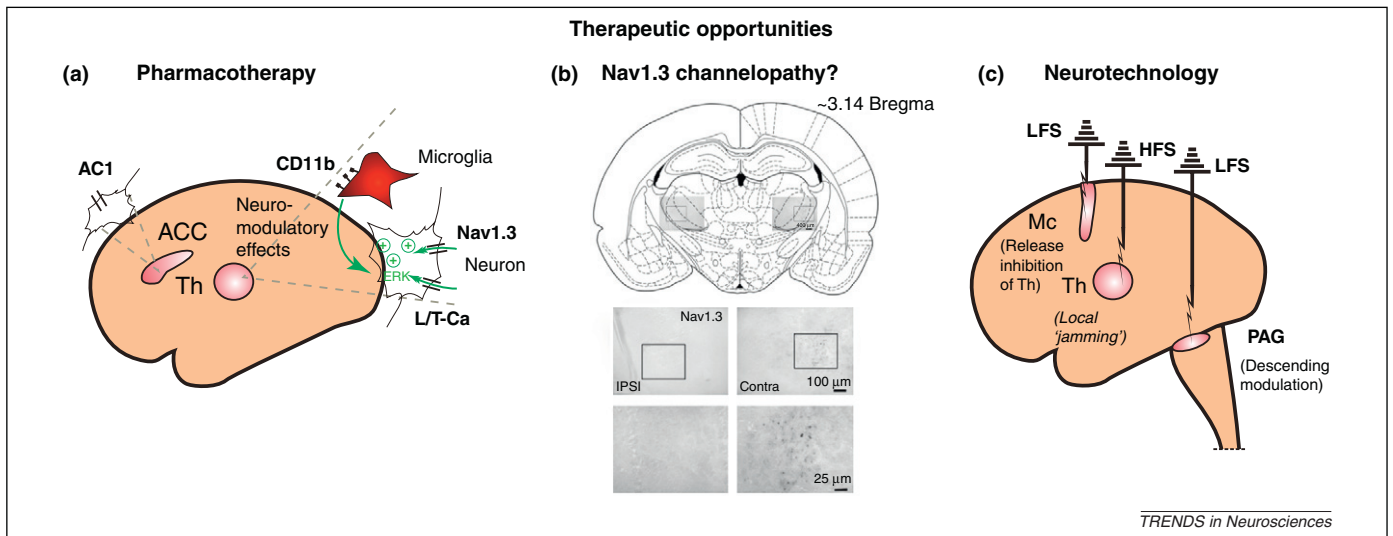
**Figure 4**. Therapeutic interventions in the brain for pain management. Schematic representation of two potential approaches for localized intervention in identified brain regions using pharmacotherapy or neurotechnology. **(a)** Upregulation of Nav1.3 in VPL neurons within the thalamus is causally related to neuronal sensitization and neuropathic behavior, phenomena that are reversed by knockdown of Nav1.3 (see panel b) [18]. Other candidate therapeutic targets include L- and T-type calcium channels (L/T-Ca) in the thalamus, which activate the pronociceptive ERK signaling pathway, thus increasing the concentration of cations (+) intracellularly and contributing to neuronal membrane depolarization [30,43]. In addition, calcium-stimulated adenylyl cyclase 1 (AC1) in the ACC is a valid therapeutic target for inducing analgesia in rodent neuropathic pain models [85], whereas microglial cells upregulate CD11b and p38 MAPK, contributing to neuronal sensitization in the VPL and neuropathic behavior [79]. **(b)** Schematic representation of a coronal rat brain section corresponding to bregma –3.14 mm showing the image locations in the VPL. Representative images from *in situ* hybridization for detection of Nav1.3 mRNA are shown for the ipsilateral (IPSI) and contralateral (CONTRA) sides in the brains of adult rats 10 days after chronic constriction injury (CCI) of the sciatic nerve [38]. On the ipsilateral side, only a very faint Nav1.3 signal was detectable. On the contralateral side, a punctate Nav1.3 signal was aberrantly present in CCI animals. Higher magnification insets are shown for the IPSI and CONTRA sides (bottom panels). Adapted, with permission, from [38]. **(c)** Neurotechnological approaches for managing severe and intractable pain conditions are based mainly on neuromodulation using DBS (high-frequency or low-frequency stimulation of an alternating current; HFS or LFS), transcranial direct current, or magnetic stimulation. Although the classical DBS approach is to target brain regions involved in descending modulatory systems (e.g., in the periaqueductal gray, PAG) or spinal cord pathways (dorsal column), experimental evidence suggests that the nociceptive circuitry can be directly targeted within the brain to inhibit neuronal firing, such as HFS in the rat VPL [17]. Other options include motor cortex modulation with LFS, which is thought to release inhibition onto thalamic neurons [91]. Abbreviations: ACC, anterior cingulate cortex; DBS, deep brain stimulation; ERK, extracellular signal-regulated kinase; Nav1.3, voltage-gated sodium channel; MAPK, mitogen-activated protein kinase; Th, thalamus; VPL, ventral posterolateral.

Accordingly, it is envisioned that neuromodulation of brain activity can be optimized when guided by empirical evidence from imaging and/or electrophysiological techniques discussed above (Figure 4c). Neuromodulation for direct inhibition of neuronal activity in hyperactive brain regions is proposed as an alternative to traditional approaches involving stimulation of descending analgesic systems or the ascending spinal cord dorsal column system, which are thought to produce analgesic effects indirectly. Importantly, in reference to the possible role of brain glia in pain-induced neuroplasticity, effects of the various neuromodulation techniques on glial cells need to be addressed in more detail. For example, it has been demonstrated that astrocytic calcium signaling in the hippocampus is critical for cholinergic-induced synaptic plasticity and long-term potentiation [95] and thus is likely to be important in neuronal plasticity related to long-term nociception. However, the impact of DBS on glial cells is unknown.

## Pain-related changes in the brain: epiphenomena or pain generators?

The list of pain-related changes in the brain is extensive [96]; Box 2 describes pain-related biochemical changes in the brain. The dependence of pain-induced changes in the brain on peripheral and/or spinal cord input is an important question that remains only partly answered. In neuropathic pain models following sciatic or spinal cord injury, for example, extracellular SUA data suggest that the high rate of spontaneous firing is independent of ongoing ascending spinal cord drive, because enhanced firing persists even after interruption of ascending spinal barrage by spinal cord transection at a thoracic level (Figure 1b) [17,19]. However, similar inferences with regard to evoked neuronal responses would not be feasible using a similar experimental strategy.

The concept of central pain generators (originally proposed with regard to centrally mediated phantom pain [97]), as well as post-stroke thalamic pain syndrome (discussed above), strongly argues in favor of a critical contribution of the central nervous system in the

### Box 2. Pain-related biochemical changes in the brain

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that can be used to detect and measure the concentration of metabolites and neurotransmitters in the brain. MRS can be used to monitor biochemical changes in specific brain regions associated with disease processes. Combined with a pattern recognition method called statistical classification strategy, MRS can be used to discriminate low-back-pain patients from control subjects with an accuracy ranging between 97% and 100% when derived from spectral analysis of brain regions including the PFC, ACC, and thalamus [106]. In another study, wavelet-based feature extraction and classification algorithms were applied to MRS data to discriminate between patients with spinal cord injury and pain and those without pain [107]. This study revealed that thalamic changes were more strongly linked to spinal cord injury *per se*, whereas spectral features in the PFC and ACC more accurately predicted neuropathic pain [107], suggesting that biochemical changes in these brain regions may be used as biochemical fingerprints of different pain states.

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**Box 3. Outstanding questions**

- To what extent is cortical plasticity dependent on peripheral drive, particularly in the case of peripheral neuropathic pain?
- What is the critical time point at which therapeutic intervention should be planned to prevent pain-related changes in the brain from becoming intractable?
- For electrical brain stimulation, questions that arise are when, where, and how to stimulate. Individualized stimulation paradigms that tease apart the effects of stimulation frequency and amplitude and the possibility of current steering are factors that might help to increase the clinical efficacy of electrical stimulation of the nervous system.
- A recent study showed that noxious heat intensity was correlated with activation in S1 and S2 cortices, motor cortex, and superior temporal lobe, areas that are significantly more related to heat ratings than pain in human subjects [108]. Moreover, bilateral lesions of the hindlimb area of S1 attenuates inflammatory pain behavior in rats, but do not reduce escape or avoidance behavior [109]. This raises the question as to whether somatosensory cortices encode stimulus intensity rather than pain evaluation.
- There is growing evidence from imaging studies that chronic pain and acute pain may not recruit the same brain circuits. PET studies demonstrated that spontaneous neuropathic pain is associated with changes in thalamic activity and other brain structures preferentially involved in the emotional dimension of pain [110]. In particular, PET and fMRI yielded variable results with respect to allodynia. Thus, it will be important to more fully address whether acute physiological pain and neuropathic pain have distinct or overlapping brain activation patterns.
- The classical concept of a body-self matrix that generates a body-self neurosignature of pain [56] has gradually been transformed into an empirically driven hypothesis using imaging data. It has been shown that various brain regions form a widely distributed network within this matrix. However, the directional connectivity and synaptic weight between these brain regions remain undetermined.

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generation and maintenance of certain chronic neuropathic pain symptoms. Indeed, effective reversal of pain in humans (and nociceptive behavior in animals) has been achieved with localized intervention in the brain by pharmacological approaches or electrical stimulation, suggesting that the brain is a valid target organ for pain therapy.

## Concluding remarks

In summary, preclinical and clinical evidence suggests that pain is correlated with synaptic plasticity, channelopathy, and receptor modulation in various brain structures. These changes, in addition to a potential neuroinflammatory response induced by microglial activation in the brain, contribute to altered processing of nociceptive information and dysfunctional network connectivity in small- and large-scale loops. Detection of pain-induced changes using noninvasive methods could yield objective diagnostic measures and may guide therapeutic interventions targeting the brain for effective management of chronic pain. An important goal would be to adapt proper investigational tools for efficient screening of pain-related activity in the brain, and to design effective interventional strategies for reversal of brain abnormalities based on a thorough understanding of the basic mechanisms involved (Box 3).

Thanks to recent breakthroughs in computational neuroscience and electrophysiological recording techniques, restoration of nervous system function has become feasible using neuroprostheses and brain–machine interfaces for motor disorders [98] or patient-controlled real-time feedback of brain function [99]. Previously considered science fiction, it is now possible to harness the neuronal code from the brain of an individual with severe motor disability to control the motion of a robotic arm or to communicate the patient's thoughts by commanding a cursor on a computer screen [98]. It is predicted that lessons learned from these neurotechnologies will offer unprecedented opportunities for pain research in the near future. For example, it is envisioned that the development of a sensor for reliable detection of pain-related signals in the brain, coupled with a neuromodulation device for effective reversal of pain biomarkers, could yield a feedback closed-loop system for pain therapy [99,100]. Such a concept has already been validated clinically for the management of refractory epilepsy [100]. Unlike motor or epilepsy disorders, however, a successful neurotechnological approach to the diagnosis and treatment of chronic pain should take into serious consideration the multidimensional aspects of the human pain experience.

## Note added in proof

As this review went to press, Baliki et al. [111] reported that, using longitudinal brain imaging, a set of anatomical and functional changes in the brain reliably distinguished between subjects with subacute back pain that recovered within a year versus those in which pain persisted. These changes include decreased gray matter density, as well as an initial enhanced functional connectivity under chronic pain conditions. Such findings reinforce the idea that studying brain mechanisms under pain conditions carry significant diagnostic potential, which may lead to novel therapies by targeted brain interventions.

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