Mechanisms of Disease: neuropathic pain—a clinical perspective

Ralf Baron

SUMMARY

Neuropathic pain syndromes—pain after a lesion or disease of the peripheral or central nervous system—are clinically characterized by spontaneous and evoked types of pain, which are underpinned by various distinct pathophysiological mechanisms in the peripheral and central nervous systems. In some patients, the nerve lesion triggers molecular changes in nociceptive neurons, which become abnormally sensitive and develop pathological spontaneous activity. Inflammatory reactions of the damaged nerve trunk can induce ectopic nociceptor activity, causing spontaneous pain. The hyperactivity in nociceptors induces secondary changes in processing neurons in the spinal cord and brain, so that input from mechanoreceptive A-fibers is perceived as pain. Neuroplastic changes in the central pain modulatory systems can lead to further hyperexcitability. The treatment of neuropathic pain is still unsatisfactory, and a new hypothetical concept has been proposed, in which pain is analyzed on the basis of underlying mechanisms. The increased knowledge of pain-generating mechanisms and their translation into symptoms and signs might eventually allow a dissection of the mechanisms that operate in each patient. If a precise clinical phenotypic characterization of the neuropathic pain is combined with a selection of drugs that act on those mechanisms, it should ultimately be possible to design optimal treatments for individuals. This review discusses the conceptual framework of the novel mechanism-based classification, encouraging the reader to see neuropathic pain as a clinical entity rather than a compilation of single disease states.

KEYWORDS mechanism-based and symptom-based assessment, neuropathic pain, neuroplastic changes, pathophysiological mechanisms, rational pharmacological treatment

REVIEW CRITERIA

PubMed was searched using Entrez for articles published up to 30 April 2005, including electronic early release publications. Search terms included "neuropathic pain", "postherpetic neuralgia", "diabetic painful neuropathy" or "pathophysiological mechanisms", as well as "quantitative sensory testing". The abstracts of retrieved citations were reviewed and prioritized by relative content. Full articles were obtained and references were checked for additional material when appropriate. Furthermore, literature that the author had on file was used.

R Baron is Head of the Department of Neurological Pain Research and Therapy and Vice Chair of the Department of Neurology, Christian-Albrechts-Universität Kiel, Germany.

Correspondence
Department of Neurological Pain Research and Therapy, Department of Neurology, Christian-Albrechts-Universität Kiel, Schittenhelmstrasse 10, 24105 Kiel, Germany
r.baron@neurologie.uni-kiel.de

Received 9 May 2005 **Accepted** 27 July 2005

www.nature.com/clinicalpractice
doi:10.1038/ncpneuro0113

INTRODUCTION

Traditionally, clinicians have been taught to examine and classify patients on the basis of lesion topography and underlying pathology, an approach that has proved invaluable for understanding the pathophysiology of many diseases, including bacterial meningitis and osteoarthritis. In most of these disorders, pain is a symptom that rapidly disappears after the relevant therapy has been given, but in other conditions, such as diabetes mellitus, the underlying disease cannot be cured, and pain becomes the primary concern rather than a symptom.

In chronic pain conditions—and particularly in the case of neuropathic pain, which arises from damage or disease within the nervous system—a classification based on disease and anatomy is often insufficient. Despite obvious differences in etiology, many of these conditions share common clinical phenomena: for example, touch-evoked pain in postherpetic neuralgia and painful diabetic neuropathy. Conversely, different signs and symptoms can be present in the same disease: for example, pain paroxysms and stimulus-evoked abnormalities in postherpetic neuralgia. Classification on the basis of location also has its shortcomings, as neuroplastic changes following nervous system lesions often give rise to sensory and pain distributions that do not respect nerve, root, segmental or cortical territories.

These observations have raised the question of whether an entirely different strategy, in which pain is analyzed on the basis of underlying mechanisms,[1] could provide an alternative approach for examining and classifying patients, with the ultimate aim of obtaining a better treatment outcome.[2,3] Our increasing understanding of the mechanisms that underlie chronic pain, together with the discovery of new molecular therapy targets, has strengthened the demand for alternative concepts. In this article, I review some important neural mechanisms in neuropathic pain, drawing parallels between clinically testable sensory symptoms and the

GLOSSARY

DYSESTHETIC
A term that refers to an unpleasant abnormal sensation, whether spontaneous or evoked

HYPERALGESIC
An increased response to a stimulus that is normally painful

ALLODYNIC
Pain due to a stimulus that does not normally provoke pain

Box 1 Etiology-based classification of painful peripheral neuropathies.

Focal or multifocal lesions of the peripheral nervous system
Entrapment syndromes
Phantom limb pain, stump pain
Post-traumatic neuralgia
Postherpetic neuralgia
Diabetic mononeuropathy
Ischemic neuropathy
Polyarteritis nodosa

Generalized lesions of the peripheral nervous system (polyneuropathies)
Diabetes mellitus
Alcohol
Amyloid
Plasmocytoma
HIV neuropathy
Hypothyroidism
Hereditary sensory neuropathies
Fabry's disease
Bannwarth's syndrome (neuroborreliosis)
Vitamin B deficiency
Toxic neuropathies (arsenic, thallium, chloramphenicol, metronidazole, nitrofurantoin, isoniazid, vinca alkaloids, taxoids, gold)

Lesions of the CNS
Spinal cord injury
Brain infarction (especially the thalamus and brainstem)
Spinal infarction
Syringomyelia
Multiple sclerosis

Complex neuropathic disorders
Complex regional pain syndromes type I and II (reflex sympathetic dystrophy, causalgia)

pathophysiological mechanisms that might be responsible for these symptoms.

WHAT IS NEUROPATHIC PAIN?

Neuropathic pain syndromes are chronic pain disorders caused as a direct consequence of a lesion or by disease of the parts of the nervous system that normally signal pain.[4] They are heterogeneous conditions that cannot be explained by a single etiology or specific lesion. Chronic neuropathic pain is common in clinical practice, and it greatly impairs the quality of life of patients. Most patients fall into four broad classes (Box 1): peripheral focal and multifocal nerve lesions (traumatic, ischemic or inflammatory), peripheral generalized polyneuropathies (toxic, metabolic, hereditary or inflammatory), CNS lesions (e.g. stroke, multiple sclerosis, spinal cord injury), and complex neuropathic disorders (complex regional pain syndromes [CRPSs]).

CRPSs (formerly called reflex sympathetic dystrophies, Sudeck's atrophy or causalgia) are painful disorders that can develop as a disproportionate consequence of trauma, and they typically affect the limbs.[5] CRPS type I usually develops after extremity trauma without obvious nerve lesion (e.g. bone fracture, surgery). CRPS type II develops after trauma that is associated with a lesion of a large nerve. In contrast to other neuropathic pain syndromes, CRPSs are characterized by additional signs, such as abnormal regulation of blood flow and sweating, and active and passive movement disorders, indicating that CRPSs are systemic CNS diseases. Furthermore, peripheral changes occur, such as edema of skin and subcutaneous tissues, trophic changes, signs of inflammation, and a pain component that is maintained by efferent sympathetic innervation.

SIGNS AND SYMPTOMS IN NEUROPATHIC PAIN

Patients with neuropathic pain demonstrate distinct sensory symptoms that can coexist in various combinations. Bedside sensory examination should include touch, pinprick, pressure, cold, heat, vibration and temporal summation[6,7] (Table 1). Responses can be graded as normal, decreased or increased to determine whether negative or positive sensory phenomena are involved. The stimulus-evoked (positive) pain types are classified as DYSESTHETIC, HYPERALGESIC or ALLODYNIC, and according to the dynamic or static character of the stimulus.[8]

Touch can be assessed by gently applying cotton wool to the skin, pinprick sensation by the response to sharp pinprick stimuli, deep pain by gentle pressure on muscles and joints, and cold and heat sensation by measuring the response to a thermal stimulus, for example, thermorollers kept at 20 °C or 45 °C. Cold sensation can also be assessed by the response to acetone spray. Vibration can be assessed by a tuning fork placed at strategic points (e.g. interphalangeal joints). Abnormal temporal summation is the clinical equivalent of increasing neuronal activity following repetitive C-fiber stimulation at >0.3 Hz. This wind-up-like pain can be produced by mechanical and thermal stimuli.

At present, it is generally agreed that assessment should be carried out in the area of maximal

Table 1 Definition and assessment of negative and positive sensory symptoms or signs in neuropathic pain.

Symptom/sign	Definition	Assessment	Expected pathological response
Negative signs and symptoms			
Hypoesthesia	Reduced sensation to non-painful stimuli	Touch skin with painter's brush, cotton swab or gauze	Reduced perception, numbness
Pallhypoesthesia	Reduced sensation to vibration	Apply tuning fork to bone or joint	Reduced perception threshold
Hypoalgesia	Reduced sensation to painful stimuli	Prick skin with single pin stimulus	Reduced perception, numbness
Thermohypoesthesia	Reduced sensation to cold or warm stimuli	Touch skin with objects of 10 °C (metal roller, glass of water, coolants like acetone) Touch skin with objects of 45 °C (metal roller, glass of water)	Reduced perception
Spontaneous sensations/pain			
Paraesthesia	Non-painful ongoing sensation (ant crawling)	Grade intensity (0–10) Area in cm^2	–
Paroxysmal pain	Shooting electrical attacks for seconds	Number per episode Grade intensity (0–10) Threshold for evocation	–
Superficial pain	Painful ongoing sensation, often of burning quality	Grade intensity (0–10) Area in cm^2	–
Evoked pain			
Mechanical dynamic allodynia	Normally non-painful light-pressure moving stimuli on skin evoke pain	Stroking skin with painter's brush, cotton swab or gauze	Sharp burning superficial pain in the primary affected zone, spreading into unaffected skin areas (secondary zone)
Mechanical static allodynia	Normally non-painful gentle static pressure stimuli on skin evoke pain	Manual gentle mechanical pressure to the skin	Dull pain in the area of affected (damaged or sensitized) primary afferent nerve endings (primary zone)
Mechanical punctate or pinprick hyperalgesia	Normally stinging-but-not-painful stimuli evoke pain	Manual pricking of the skin with a safety pin, sharp stick or stiff von Frey hair	Sharp superficial pain in the primary affected zone, spreading into unaffected skin areas (secondary zone)
Temporal summation	Repetitive application of identical single noxious stimuli is perceived as increasing pain sensation (wind-up-like pain)	Pricking the skin with safety pin at <3 s intervals for 30 s	Sharp superficial pain of increasing intensity
Cold allodynia	Normally non-painful cold stimuli evoke pain	Touch skin with objects of 20 °C (metal roller, glass of water, coolants like acetone) Control: touch skin with objects of skin temperature	Painful, often burning, temperature sensation in the area of affected (damaged or sensitized) primary afferent nerve endings (primary zone)
Heat allodynia	Normally non-painful heat stimuli evoke pain	Touch skin with objects of 40 °C (metal roller, glass of water) Control: touch skin with objects of skin temperature	Painful burning temperature sensation in the area of affected (damaged or sensitized) primary afferent nerve endings (primary zone)
Mechanical deep somatic allodynia	Normally non-painful pressure on deep somatic tissues evokes pain	Manual light pressure at joints or muscle	Deep pain in joints or muscles

pain, using the contralateral area as control. Contralateral segmental changes following a unilateral nerve or root lesion cannot be excluded, however, so an examination at mirror sites might not necessarily represent a true control.

SYMPTOM	NEURONAL PROCESSES, MECHANISMS	TARGETS	OPTIMAL COMPOUNDS	AVAILABLE COMPOUNDS
	Peripheral nociceptor hyperexcitability			
Spontaneous pain (shooting)	Ectopic impulse generation, oscillations in dorsal root ganglion	Sodium channels	Selective sodium-channel blocker	Lidocaine, carbamazepine, oxcarbazepine, lamotrigine, TCA
Spontaneous pain (ongoing)	**Peripheral nociceptor sensitization**			
	Inflammation within nerves Cytokine release	Cytokines	Cytokine antagonists Cyclooxygenase blocker	TNF-α antagonists NSAIDS?
Heat allodynia	*Reduced activation threshold to:* Heat	TRPV1 receptor	TRPV1-receptor antagonists	Capsaicin cream
Cold allodynia	Cold	TRPM8 receptor	TRPM8-receptor antagonists	Menthol?
Static mechanical allodynia	Mechanical stimuli	ASIC receptor?	ASIC-receptor antagonists	?
SMP	Noradrenaline	α receptor	α-receptor antagonists	Phentolamine, sympathetic block, TCA
	Histamine	Histamine H1 receptor	H1-receptor antagonists	TCA
	Central dorsal horn hyperexcitability			
	Central sensitization on spinal level Ongoing C-Input induces increased synaptic transmission	Presynaptic: μ-receptors Calcium channels (α_2-δ)	μ-receptor agonists Calcium-channel blocker, α2-δ ligands	Opioids Gabapentin, pregabalin
	Amplification of C-fiber input			
	Gating of Aβ-fiber input (mechanical dynamic hyperalgesia)	Postsynaptic: NMDA receptors	NMDA-receptor antagonists	Ketamine, dextromethorphan?
Dynamic mechanical allodynia	Gating of Aδ-fiber input (mechanical punctate hyperalgesia)	NK1 receptors Sodium channels Intracellular cascades	NK1-receptor antagonists Selective sodium-channel blocker MAPK mediators	Carbamazepine?
	Intraspinal inhibitory interneurons ↓ (functional, degeneration)			
Punctate mechanical hyperalgesia	GABA-ergic	$GABA_B$ receptors	$GABA_B$ agonists	Baclofen
	Opioidergic	μ-receptors	μ-receptor agonists	Opioids
	Changes in supraspinal descending modulation			
	Inhibitory control (noradrenaline, 5-HT) ↓	α2 receptors 5-HT receptors	α2-receptor agonists NA/5-HT-reuptake-blocker	Clonidine TCA, venlafaxine, duloxetine
	Faciliatory control ↑	?	?	?

Figure 1 Proposed model for the relationship between neuropathic pain mechanisms and clinical symptoms and signs, and possible targets for therapeutic interventions.
5-HT, 5-hydroxytryptamine (serotonin); ASIC, acid-sensing ion channel; GABA, γ-aminobutyric acid; MAPK, mitogen-activated protein kinase; NK1, neurokinin 1; NMDA, N-methyl-D-aspartate; NSAIDS, nonsteroidal anti-inflammatory drugs; SMP, sympathetically maintained pain; TCA, tricyclic antidepressants; TNF-α, tumor-necrosis factor-α.

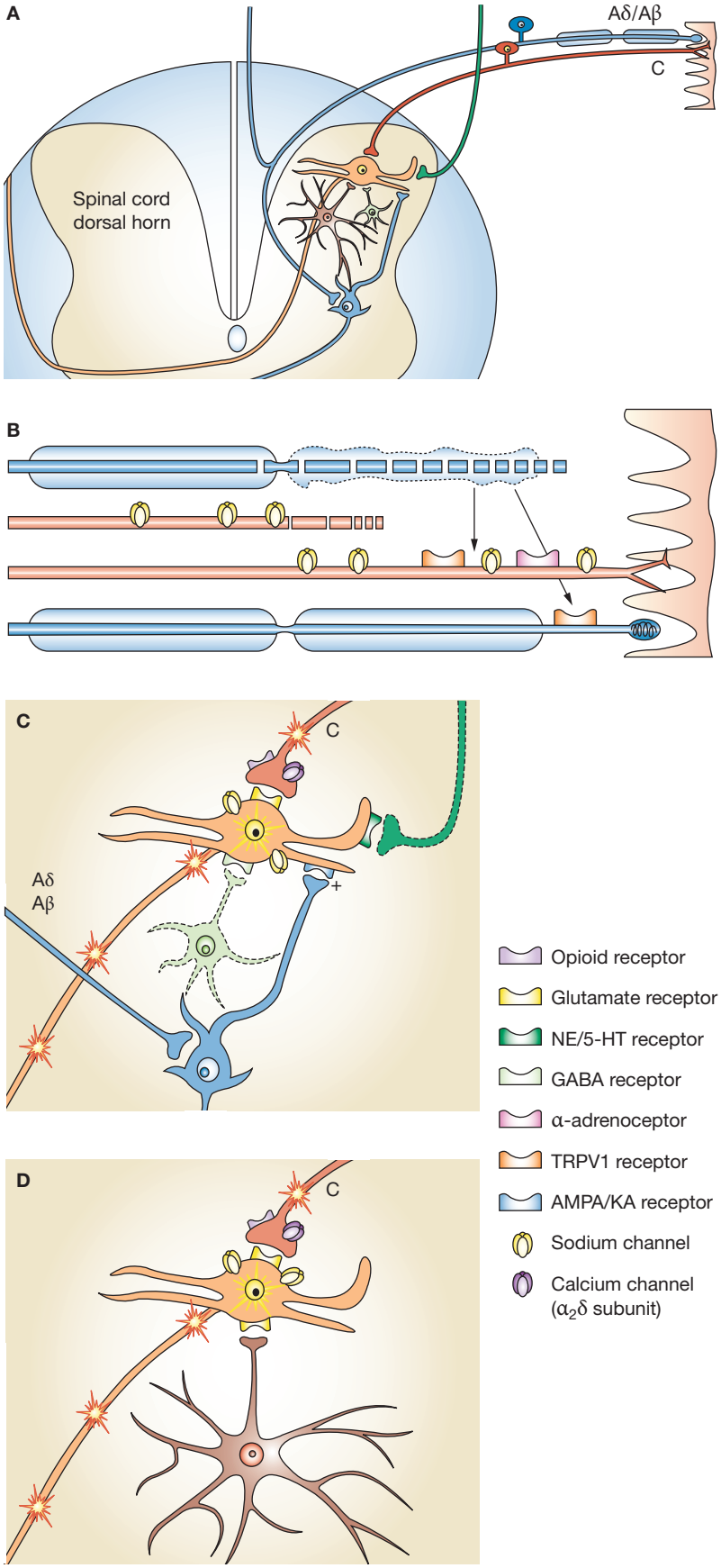

Figure 2 Mechanisms of peripheral and central sensitization in neuropathic pain. (**A**) Primary afferent pathways and their connections in the spinal cord dorsal horn. Nociceptive C-fibers (red) terminate at spinothalamic projection neurons in upper laminae (orange neuron), whereas non-nociceptive myelinated A-fibers (blue) project to deeper laminae. The second-order projection neuron is of the wide dynamic range (WDR) type, that is, it receives direct synaptic input from nociceptive terminals and also multisynaptic input from myelinated A-fibers (non-noxious information, blue neuron system). γ-aminobutyric acid (GABA)-releasing interneurons (green neuron) normally exert inhibitory synaptic input on the WDR neuron. Furthermore, descending modulatory systems synapse at the WDR neuron (the green descending terminal represents an inhibitory projection). Spinal cord glial cells (brown cell) also communicate with the WDR neuron. (**B**) Peripheral changes at primary afferent neurons (nociceptive C-fibers, red; non-nociceptive myelinated A-fibers, blue) after partial nerve lesion, leading to peripheral sensitization. Some axons are damaged and degenerate (upper two axons), whereas others (lower two axons) are still intact and connected with the peripheral end organ (skin). The lesion triggers the expression of sodium channels on damaged C-fibers. Furthermore, products such as nerve growth factor that are associated with Wallerian degeneration are released in the vicinity of spared fibers (arrows), triggering channel and receptor expression (sodium channels, TRPV1 receptors, adrenoceptors) on uninjured fibers. (**C**) Spontaneous activity in C-nociceptors induces secondary changes in central sensory processing, leading to spinal cord hyperexcitability (central sensitization of second-order WDR neurons, indicated by star in orange neuron). This causes input from mechanoreceptive A-fibers (light touch and punctate stimuli; blue neuron system) to be perceived as pain (dynamic and punctate mechanical allodynia; '+' indicates gating at synapse via AMPA/KA [α-amino-3-hydroxy-5-methyl-4-isoxasole propionic acid and kainate] receptors). Several presynaptic (opioid receptors, calcium channels) and postsynaptic molecular structures (glutamate receptors, NE [norepinephrine] receptors, 5-HT [serotonin] receptors, GABA receptors, sodium channels) are involved in central sensitization. Inhibitory interneurons and descending modulatory control systems (green neurons) are dysfunctional after nerve lesions, leading to disinhibition or facilitation of spinal cord dorsal horn neurons and to further central sensitization. (**D**) Peripheral nerve injury activates spinal cord non-neural glial cells (brown cell), which further enhances excitability in WDR neurons by releasing cytokines and increasing glutamate levels. 5-HT, 5-hydroxytryptamine (serotonin); GABA, γ-aminobutyric acid; NE, norepinephrine.

GLOSSARY

TETRODOTOXIN
A neurotoxin derived from the puffer fish that specifically and reversibly blocks voltage-gated sodium channels

NEUROMA
A benign growth of nerve tissue after nerve section

ERYTHROMELALGIA
A rare disorder that is characterized by burning pain, redness and warmth in the extremities

CAPSAICIN
A vanilloid compound that is the 'hot' ingredient in chilli peppers

A more sophisticated neurophysiological technique (quantitative sensory testing [QST]) uses a battery of standardized mechanical and thermal stimuli. When present, allodynia or hyperalgesia can be quantified by measuring intensity, threshold for elicitation, duration and area.

Table 1 defines several sensory signs and symptoms that can be found in painful neuropathies, and summarizes the appropriate tests to assess these symptoms clinically.

PATHOPHYSIOLOGICAL MECHANISMS IN NEUROPATHIC PAIN

Most of the current ideas regarding the pathophysiology of neuropathic pain originated from experimental work in animal models. These studies delineated a series of partially independent pathophysiological mechanisms. In the sections that follow, these mechanisms are presented, followed by a discussion of the possible translation of neuropathic mechanisms into clinical symptoms and signs, and of possible targets for therapeutic interventions (Figure 1).

Peripheral sensitization

Sensitization and ectopic activity in primary afferent nociceptors

Pain sensations are normally elicited by activity in unmyelinated (C-) and thinly myelinated (Aδ-) primary afferent neurons. These nociceptors are usually silent in the absence of stimulation, and respond best to stimuli that are potentially noxious. After a peripheral nerve lesion, however, these neurons become abnormally sensitive and develop pathological spontaneous activity. These pathological changes are underpinned by dramatic molecular and cellular changes at the level of the primary afferent nociceptor that are triggered by the nerve lesion (Figure 2).

Ectopic spontaneous activity following nerve injury is matched by increased expression of messenger RNA for voltage-gated sodium channels in primary afferent neurons. Clustering of sodium channels at sites of ectopic impulse generation might be responsible for the lowering of the action-potential threshold and consequent hyperactivity.[9]

The genes that encode the voltage-gated sodium channels $Na_v1.8$ and $Na_v1.9$ are expressed selectively in nociceptive primary afferent neurons. An embryonic channel, $Na_v1.3$, is upregulated in damaged peripheral nerves, and this is associated with increased electrical excitability. Small primary afferent fibers acquire a unique sodium-channel expression profile after nerve lesion, which makes them an interesting therapeutic target. Future research should be aimed at designing isotype-specific sodium-channel blockers.[10]

After peripheral nerve damage, sodium-channel clusters accumulate not only at the site of the nerve lesion (Figure 2B), but also far proximally within the intact dorsal root ganglion. Here, an alternation between a phasically activating, voltage-dependent, TETRODOTOXIN-sensitive sodium conductance and a passive, voltage-independent potassium leak generates characteristic membrane potential oscillations. Ectopic firing is triggered when the amplitude of oscillation sinusoids reaches threshold.[11] Pathological membrane properties within the dorsal root ganglion (DRG) are of particular therapeutic interest, as the DRG is spared of the blood–brain barrier and might be easily accessible for systemic therapies.[12]

In awake human amputees with phantom limb pain, microneurographic single-fiber recordings from afferent fibers projecting into the NEUROMA have demonstrated spontaneous ectopic activity, as well as barrages of action-potential firing.[13] These patients showed spontaneous burning pain and electric-shock-like sensations, so it is likely that these symptoms are associated with ectopic primary afferent firing. In patients with ERYTHROMELALGIA with burning pain, a mutation was found in the *SCN9A* gene, which encodes the $Na_v1.7$ sodium channel. This led to an altered firing pattern in afferent neurons.[14] Indirect evidence for ectopic afferent activity has been obtained from a subset of neuropathic pain patients in whom lidocaine—a sodium channel blocker—produces pain relief.[15]

Damage to peripheral nerves also induces upregulation of various receptor proteins—some of which are only marginally expressed under physiological conditions—at the membrane of primary afferents. Vanilloid receptors (TRPV1) are located predominantly on nociceptive afferent fibers, and can be activated by CAPSAICIN. Physiologically, this receptor senses noxious heat (>43 °C).[16] After partial nerve injury, and in rats with streptozotocin-induced diabetes, the situation changes dramatically: the lesion triggers a TRPV1 downregulation on many damaged afferents, but novel expression of TRPV1 on uninjured C-fibers and A-fibers

(Figure 2B, and see below).[17,18] Recent studies also provide evidence for an upregulation of TRPV1 in medium and large injured DRG cells.[19] The observation that TRPV1-deficient mice do not develop heat hyperalgesia after tissue inflammation[16,20] supports the idea that these changes might contribute to the development of C-nociceptor sensitization and the associated symptom of heat hyperalgesia.[21] TRPV1 does not seem to be the only transduction mechanism for thermal sensitization after nerve injury, however: after partial sciatic nerve ligation, wild-type and *TRPV1*-null mice exhibited comparable persistent enhancement of mechanical and thermal nociceptive responses.[16]

In taxol-induced small-fiber painful polyneuropathy, TRPV4, which is normally activated by temperatures of >30 °C, seems to play a crucial role in producing taxol-induced mechanical hyperalgesia. Spinal administration of ANTISENSE OLIGODEOXYNUCLEOTIDES to TRPV4, which reduces receptor expression in sensory nerves, abolished mechanical hyperalgesia in rats.[22]

In postherpetic neuralgia patients with heat hyperalgesia, the acute topical application of histamine or capsaicin enhances pain, indicating abnormal sensitivity of nociceptors to capsaicin and histamine in the affected skin area,[23,24] probably owing to expression of a novel receptor pattern. In a few patients with erythromelalgia and characteristic signs of nociceptor sensitization (burning pain and heat hyperalgesia), microneurographic recordings have confirmed that C-nociceptors are sensitized.[25]

Investigations into temperature-sensitive excitatory ion channels also identified a cold- and menthol-sensitive TRP channel (TRPM8) that is activated in the 8–28 °C range.[26] This receptor is expressed in small-diameter DRG neurons.[27] Upregulation or gating of this channel after injury might lead to the peripheral sensitization of cold-sensitive C-nociceptors, resulting in the sensory phenomenon of cold hyperalgesia.[28]

The transduction process for mechanical stimuli is still unresolved, although acid-sensing ion channels (ASICs) have been proposed as candidates for involvement in static mechanical hyperalgesia.[29]

Experimental nerve injury also triggers the expression of functional α_1-adrenoceptors and α_2-adrenoceptors on cutaneous afferent fibers (Figure 2B). Consequently, these neurons develop adrenergic sensitivity. The concept of a pathological adrenergic coupling between sympathetic postganglionic fibers and afferent neurons forms the conceptual framework for the use of sympathetic blocks in pain syndromes such as CRPS.[30,31]

Several observations support the idea that noradrenergic sensitivity of human nociceptors is present after partial or complete nerve lesion. In amputees, the perineuromal administration of norepinephrine induced intense pain.[32] In patients with postherpetic neuralgia, CRPS II and post-traumatic neuralgias, application of norepinephrine in physiological doses into a symptomatic skin area evoked or increased spontaneous pain and dynamic mechanical hyperalgesia.[33,34] In patients with CRPS I, spontaneous pain and mechanical hyperalgesia were augmented when sympathetic cutaneous vasoconstrictor neurons were activated physiologically by cold stress.[35] By contrast, no adrenergic sensitivity of primary afferent neurons could be found in polyneuropathies.[36]

Novel drugs that specifically block temperature-sensitive receptors or adrenoreceptors on nociceptive neurons would be ideal for tackling specific symptoms, such as temperature-induced and sympathetically-induced pain types.

There is increasing evidence that uninjured fibers that intermingle with degenerating fibers in a partially lesioned nerve might also participate in pain signaling.[37] Products such as nerve growth factor that are associated with WALLERIAN DEGENERATION and are released in the vicinity of spared fibers might trigger the release of tumor-necrosis factor-α (TNF-α), as well as channel and receptor expression (sodium channels, TRPV1 receptors, adrenoreceptors; Figure 2B) thereby altering the properties of uninjured afferents.[17,38] Future research should focus on the variety of changes that might occur in uninjured axons, as these neurons are still connected with their peripheral organs and could have a pivotal role in the generation of neuropathic pain.

Inflammation in neuropathic pain

After nerve lesion, activated macrophages infiltrate from endoneural blood vessels into the nerve and DRG, releasing proinflammatory CYTOKINES, in particular TNF-α.[39] These mediators induce ectopic activity in both injured and adjacent uninjured primary afferent nociceptors at the lesion site.[40]

GLOSSARY

ANTISENSE OLIGODEOXYNUCLEOTIDES
DNA sequences complementary to transcribed RNA sequences that result in translational attenuation or messenger-RNA degradation

WALLERIAN DEGENERATION
Degeneration of the distal segment of a peripheral nerve fiber after it has been severed from the cell body

CYTOKINES
Intercellular soluble proteins that activate and regulate inflammatory and immune responses through interactions with specific receptors

In patients with inflammatory neuropathies—such as vasculitic neuropathies or HIV neuropathy—deep proximal aching and paroxysmal pain are characteristic phenomena. COX2 and proinflammatory cytokines were found to be upregulated in nerve biopsy specimens of these patients.[41] In the affected extremities of CRPS patients, the fluid of artificially produced skin blisters contain significantly higher levels of IL-6 and TNF-α than the uninvolved extremity.

Central sensitization

Sensitization in the spinal cord

As a consequence of peripheral nociceptor hyperactivity, dramatic secondary changes occur in the spinal cord dorsal horn. Peripheral nerve injury leads to an increase in the general excitability of multireceptive spinal cord neurons (wide-dynamic-range neurons with multiple synaptic inputs from the nociceptive as well as the non-nociceptive system [orange neuron in Figure 2C]). This hyperexcitability is manifested by increased neuronal activity in response to noxious stimuli, expansion of neuronal receptive fields and spread of spinal hyperexcitability to other segments. This so-called central sensitization is initiated and maintained by activity in pathologically sensitized C-fibers. These fibers sensitize spinal cord dorsal horn neurons by releasing glutamate, which acts on postsynaptic N-methyl-D-aspartate (NMDA) receptors (Figure 2C), and the neuropeptide substance P. Postsynaptically, second-order dorsal horn neurons abnormally express $Na_v1.3$ after peripheral nerve injury.[42] Several intracellular cascades contribute to central sensitization, in particular the mitogen-activated protein kinase system (MAPK).[43] If central sensitization is established, normally innocuous tactile stimuli become capable of activating spinal cord pain-signaling neurons via Aδ and Aβ low-threshold mechanoreceptors (blue neurons in Figure 2C).[44] Central neuronal voltage-gated N-calcium channels located at the presynaptic sites on terminals of primary afferent nociceptors have an important role in central sensitization, through the facilitation of glutamate and substance P release. These channels are overexpressed after peripheral nerve lesion.[45]

Dynamic mechanical allodynia in patients is also conveyed by Aβ low-threshold mechanoreceptors, pointing to central sensitization as the underlying mechanism. Reaction-time measurements show that dynamic allodynia in patients is signaled by afferents with conduction velocities that are appropriate for large myelinated axons. Also, transcutaneous or intraneural stimulation of nerves that innervate the allodynic skin can evoke pain at stimulus intensities that only produce tactile sensations in healthy skin.[46] Furthermore, differential nerve blocks can abolish dynamic allodynia at time points when tactile sensation is lost but other modalities remain unaffected.

Physiologically, dorsal horn neurons receive a strong inhibitory control by γ-aminobutyric acid (GABA)-releasing interneurons (Figure 2A,C). In rodents, partial peripheral nerve injury promotes a selective apoptotic loss of GABA-releasing inhibitory neurons in the superficial dorsal horn of the spinal cord,[47] a mechanism that further increases central sensitization. An alternative mechanism of intraspinal disinhibition following peripheral nerve injury was recently proposed, however. This mechanism involves a trans-synaptic reduction in the expression of the potassium–chloride exporter KCC2 in lamina I neurons, which disrupts anion homeostasis in these neurons. The resulting shift in the transmembrane anion gradient causes normally inhibitory anionic synaptic currents to be excitatory. The effect is that GABA release from normally inhibitory interneurons now paradoxically exerts an excitatory action on lamina I neurons, again increasing central sensitization.[48]

Dorsal horn neurons receive a powerful descending modulating control from supraspinal brainstem centers (inhibitory as well as facilitatory)[49] (Figure 2A,C). It was hypothesized that a loss of function in descending inhibitory serotonergic and noradrenergic pathways contributes to central sensitization and pain chronification. This idea nicely explained the efficacy of serotonin and noradrenalin reuptake blocking antidepressants in neuropathic pain. In animals, however, mechanical allodynia after peripheral nerve injury depended on tonic activation of descending pathways that facilitate pain transmission, indicating that structures in the mesencephalic reticular formation—possibly the nucleus cuneiformis and the periaqueductal gray—are involved in central sensitization in neuropathic pain.[50] Interestingly, advanced functional MRI (fMRI) techniques showed that the same brainstem structures were active in humans with allodynia.[51] Because descending facilitation and inhibition are triggered simultaneously in most animal pain models, it

will be important to elucidate why inhibition predominates in some neuronal pools, whereas facilitation predominates in others. Therapies that enhance descending inhibition and/or attenuate descending facilitation are an important target for future research.

Central sensitization might also be augmented by non-neural glial cells in the spinal cord. Peripheral nerve injury activates spinal cord glia and causes these cells to enhance pain by releasing neuroexcitatory glial proinflammatory cytokines and glutamate (Figure 2D).[52]

Changes in the brain

Most animal experiments have concentrated on the dorsal horn as the location of central sensitization. In rodents, however, sensitized neurons are also found in the thalamus and primary somatosensory cortex after partial peripheral nerve injury.[53] Furthermore, magneto-encephalography (MEG), positron emission tomography (PET) and fMRI studies demonstrate fundamental changes in the somatosensory cortical representation and excitability in patients with phantom limb pain, CRPS and central pain syndromes,[54–58] as well as in experimental pain models.[59,60] Interestingly, these changes correlated with the intensity of the perceived pain and disappeared after successful treatment of the pain.[61,62]

Deafferentation: hyperactivity of central pain transmission neurons

Although the above data convincingly support a role for peripheral and central sensitization in the generation of neuropathic pain, in some patients there is a profound cutaneous deafferentation of the painful area with no significant allodynia. Assuming that the DRG cells and the central afferent connections are lost in such patients, their pain must be the result of intrinsic CNS changes. In animal studies, following complete primary afferent loss of a spinal segment, many dorsal horn cells begin to fire spontaneously at high frequencies,[63,64] and there is some evidence that a similar process might underlie the pain that follows extensive denervating injuries in human. Recordings of spinal neuron activity in a pain patient whose dorsal roots were injured by trauma to the CAUDA EQUINA revealed high-frequency regular and paroxysmal bursting discharges.[65] The patient complained of spontaneous burning pain in a skin region that was rendered anesthetized by the lesion (a phenomenon that is termed anesthesia dolorosa).

QUANTITATIVE SENSORY TESTING AS A DIAGNOSTIC TOOL IN NEUROPATHIC PAIN

The modern theoretical concept of a mechanism-based therapy assumes that a specific symptom predicts a specific underlying mechanism.[1,66] This approach carries certain important caveats, however. Clinical experimental studies indicate that a specific symptom might be generated by several entirely different underlying pathophysiological mechanisms, so a specific symptom profile rather than a single symptom might be required to predict the underlying mechanism. To translate these ideas into the clinical framework, it is important to characterize the somatosensory phenotype of a patient as precisely as possible.

In 2002, the German Research Network on Neuropathic Pain was founded with the aim of building a database of phenotypically characterized patients with various neuropathic pain states, and to perform research studies and clinical trials in this cohort of patients. A standardized QST protocol was introduced, including 13 parameters that encompass thermal as well as mechanical testing procedures for the analysis of the somatosensory phenotype. To judge plus or minus symptoms in patients, an age- and gender-matched database for absolute and relative QST reference data for several body regions in healthy human subjects was established.[67]

Currently, this nationwide multicenter trial comprises complete sensory profiles of 180 healthy human subjects and more than 1,000 patients with various types of neuropathic pain. For genetic analysis, blood samples of all patients are collected and stored. Skin biopsies to quantify epidermal nerve-fiber density are taken from subgroups of patients.

Precise phenotypic mapping with QST is an important step in determining a future mechanism-based treatment strategy for neuropathic pain. If symptoms are closely related to mechanisms, clinical assessment of the symptoms might give an idea of the interplay between distinct mechanisms that operate in any individual patient. This knowledge might lead to an optimal polypragmatic therapeutic approach, with drugs that address the specific combination of mechanisms occurring in each patient.

Several approaches are particularly interesting, and should be investigated in future trials. First, standardized QST profiling should be used to detect phenotype subgroups in neuropathic pain patients to learn more about

GLOSSARY

CAUDA EQUINA
The bundle of nerve roots caudal to the lumbar end of the spinal cord

pathophysiological mechanisms. Second, precisely classified phenotype subgroups should be entered into proof-of-concept trials. Last, a simplified QST protocol should be elaborated to enable inclusion of simple-to-use QST in large multicenter trials.

GENETICS OF PAIN PERCEPTION AND RESPONSE TO TREATMENT

It is well known that sensitivity to painful stimuli, the risk of developing chronic pain and the responses to analgesics vary considerably between individuals. Classical genetic techniques have been used to describe differences in pain perception in genetically different mouse strains, and have shown that pain traits are indeed influenced by genetic factors.[68] Furthermore, polymorphisms of the endogenous opioid system are likely to account for individual differences in human nociception,[69] and differences in the individual response to certain analgesics might be related to polymorphisms in drug-metabolizing enzymes.

Future research should focus on several issues. Genetic studies should be performed to define the influence of the individual genotype on the predisposition to pain chronicity and the response to treatment. It will also be necessary to identify and characterize specific molecular targets (ion channels, enzymes and regulators of gene transcription) and to evaluate the use of biotechnological approaches (gene therapy, stem cells) for pain therapy.

CONCLUSION

Neuropathic pain due to lesions or disease of the nervous system represents an important neurological challenge; treatment of patients with neuropathic pain has been largely neglected by neurologists in the past. Existing trials only provide general pain relief values for specific etiologies, which might partially explain the failure to obtain complete pain relief in neuropathic pain conditions. Increased knowledge of pain-generating mechanisms and their translation into symptoms and signs in neuropathic pain patients should allow a dissection of the mechanisms that are at play in each patient. If a systematic clinical examination of the neuropathic pain patient and a precise phenotypic characterization is combined with a selection of drugs that act on those particular mechanisms, it should be possible to design optimal treatments for individual patients.

KEY POINTS

- Neuropathic pain syndromes are chronic pain disorders caused by lesion or disease of the parts of the nervous system that normally signal pain
- A disease- and anatomy-based system is often insufficient to classify neuropathic pain conditions, and analysis on the basis of underlying mechanisms provides an alternative approach
- Molecular mechanisms that underlie the sensitization of primary afferent nociceptors include upregulation of voltage-gated sodium channels and various receptor proteins, and the release of growth factors from degenerating nerve fibers
- As a consequence of peripheral nociceptor hyperactivity, dramatic secondary changes occur in the spinal cord dorsal horn, and there is also evidence of sensitization of neurons in the brain
- A single symptom may be generated by several different mechanisms, so a specific symptom profile might be required to predict the underlying mechanism
- By combining a systematic clinical examination and a precise phenotypic characterization with a selection of drugs that act on particular mechanisms, it should be possible to design optimal treatments for individual patients

References

1 Jensen TS and Baron R (2003) Translation of symptoms and signs into mechanisms in neuropathic pain. *Pain* **102:** 1–8
2 Woolf CJ *et al.* (1998) Towards a mechanism-based classification of pain? *Pain* **77:** 227–229
3 Dworkin RH *et al.* (2003) Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* **60:** 1524–1534
4 Baron R (2000) Peripheral neuropathic pain: from mechanisms to symptoms. *Clin J Pain* **16:** S12–20
5 Janig W and Baron R (2003) Complex regional pain syndrome: mystery explained? *Lancet Neurol* **2:** 687–697
6 Bouhassira D *et al.* (2004) Development and validation of the Neuropathic Pain Symptom Inventory. *Pain* **108:** 248–257
7 Cruccu G *et al.* (2004) EFNS guidelines on neuropathic pain assessment. *Eur J Neurol* **11:** 153–162
8 Rasmussen PV *et al.* (2004) Symptoms and signs in patients with suspected neuropathic pain. *Pain* **110:** 461–469
9 Lai J *et al.* (2003) The role of voltage-gated sodium channels in neuropathic pain. *Curr Opin Neurobiol* **13:** 291–297
10 Wood JN *et al.* (2004) Voltage-gated sodium channels and pain pathways. *J Neurobiol* **61:** 55–71
11 Amir R *et al.* (2002) Oscillatory mechanism in primary sensory neurones. *Brain* **125:** 421–435
12 Jacobs JM *et al.* (1976) Vascular leakage in the dorsal root ganglia of the rat, studied with horseradish peroxidase. *J Neurol Sci* **29:** 95–107
13 Nystrom B and Hagbarth KE (1981) Microelectrode recordings from transected nerves in amputees with phantom limb pain. *Neurosci Lett* **27:** 211–216

14 Dib-Hajj SD *et al.* (2005) Gain-of-function mutation in $Na_v1.7$ in familial erythromelalgia induces bursting of sensory neurons. *Brain* **128:** 1847–1854
15 Meier T *et al.* (2003) Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain* **106:** 151–158
16 Catarina MJ *et al.* (2000) Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* **288:** 306–313
17 Hudson LJ *et al.* (2001) VR1 protein expression increases in undamaged DRG neurons after partial nerve injury. *Eur J Neurosci* **13:** 2105–2114
18 Hong S and Wiley JW (2005) Early painful diabetic neuropathy is associated with differential changes in the expression and function of vanilloid receptor 1. *J Biol Chem* **280:** 618–627
19 Ma W *et al.* (2005) Medium and large injured dorsal root ganglion cells increase TRPV-1, accompanied by increased α2C-adrenoceptor co-expression and functional inhibition by clonidine. *Pain* **113:** 386–394
20 Davis JB *et al.* (2000) Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. *Nature* **405:** 183–187
21 Baron R (2000) Capsaicin and nociception: from basic mechanisms to novel drugs. *Lancet* **356:** 785–787
22 Alessandri-Haber N *et al.* (2004) Transient receptor potential vanilloid 4 is essential in chemotherapy-induced neuropathic pain in the rat. *J Neurosci* **24:** 4444–4452
23 Petersen KL *et al.* (2000) Capsaicin evoked pain and allodynia in post-herpetic neuralgia. *Pain* **88:** 125–133
24 Baron R *et al.* (2001) Histamine-induced itch converts into pain in neuropathic hyperalgesia. *Neuroreport* **12:** 3475–3478
25 Orstavik K *et al.* (2003) Pathological C-fibres in patients with a chronic painful condition. *Brain* **126:** 567–578
26 Patapoutian A *et al.* (2003) ThermoTRP channels and beyond: mechanisms of temperature sensation. *Nat Rev Neurosci* **4:** 529–539
27 McKemy DD *et al.* (2002) Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature* **416:** 52–58
28 Wasner G *et al.* (2004) Topical menthol—a human model for cold pain by activation and sensitization of C nociceptors. *Brain* **127:** 1159–1171
29 Price MP *et al.* (2001) The DRASIC cation channel contributes to the detection of cutaneous touch and acid stimuli in mice. *Neuron* **32:** 1071–1083
30 Baron R *et al.* (1999) Causalgia and reflex sympathetic dystrophy: does the sympathetic nervous system contribute to the generation of pain? *Muscle Nerve* **22:** 678–695
31 Price DD *et al.* (1998) Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. *Clin J Pain* **14:** 216–226
32 Raja SN *et al.* (1998) Role of α-adrenoceptors in neuroma pain in amputees. *Anesthesiology* **89:** A1083
33 Choi B and Rowbotham MC (1997) Effect of adrenergic receptor activation on post-herpetic neuralgia pain and sensory disturbances. *Pain* **69:** 55–63
34 Ali Z *et al.* (2000) Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. *Pain* **88:** 161–168
35 Baron R *et al.* (2002) Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: a case-control study. *Lancet* **359:** 1655–1660
36 Schattschneider J *et al.* (2005) No adrenergic sensitization of afferent neurons in painful sensory neuropathy. *J Neurol* [doi: 10.1007/s00415-005-0976-8]
37 Wasner G *et al.* (2005) Postherpetic neuralgia: topical lidocaine is effective in nociceptor-deprived skin. *J Neurol* **252:** 677–686
38 Wu G *et al.* (2001) Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. *J Neurosci* **21:** RC140
39 Sommer C (2003) Painful neuropathies. *Curr Opin Neurol* **16:** 623–628
40 Marchand F *et al.* (2005) Role of the immune system in chronic pain. *Nat Rev Neurosci* **6:** 521–532
41 Lindenlaub T and Sommer C (2003) Cytokines in sural nerve biopsies from inflammatory and non-inflammatory neuropathies. *Acta Neuropathol (Berl)* **105:** 593–602
42 Hains BC *et al.* (2004) Altered sodium channel expression in second-order spinal sensory neurons contributes to pain after peripheral nerve injury. *J Neurosci* **24:** 4832–4839
43 Ji RR and Woolf CJ (2001) Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. *Neurobiol Dis* **8:** 1–10
44 Tal M and Bennett GJ (1994) Extra-territorial pain in rats with a peripheral mononeuropathy: mechano-hyperalgesia and mechano-allodynia in the territory of an uninjured nerve. *Pain* **57:** 375–382
45 Luo ZD *et al.* (2001) Upregulation of dorsal root ganglion $\alpha_2\delta$ calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. *J Neurosci* **21:** 1868–1875
46 Gracely RH *et al.* (1992) Painful neuropathy: altered central processing maintained dynamically by peripheral input. *Pain* **51:** 175–194
47 Moore KA *et al.* (2002) Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. *J Neurosci* **22:** 6724–6731
48 Coull JA *et al.* (2003) Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain. *Nature* **424:** 938–942
49 Vanegas H and Schaible HG (2004) Descending control of persistent pain: inhibitory or facilitatory? *Brain Res Brain Res Rev* **46:** 295–309
50 Ossipov MH *et al.* (2000) Spinal and supraspinal mechanisms of neuropathic pain. *Ann NY Acad Sci* **909:** 12–24
51 Zambreanu L *et al.* (2005) A role for the brainstem in central sensitisation in humans: evidence from functional magnetic resonance imaging. *Pain* **114:** 397–407
52 Wieseler-Frank J *et al.* (2005) Central proinflammatory cytokines and pain enhancement. *Neurosignals* **14:** 166–174
53 Guilbaud G *et al.* (1992) Primary somatosensory cortex in rats with pain-related behaviours due to a peripheral mononeuropathy after moderate ligation of one sciatic nerve: neuronal responsivity to somatic stimulation. *Exp Brain Res* **92:** 227–245
54 Flor H *et al.* (1995) Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* **375:** 482–484
55 Pleger B *et al.* (2004) Mean sustained pain levels are linked to hemispherical side-to-side differences of primary somatosensory cortex in the complex regional pain syndrome I. *Exp Brain Res* **155:** 115–119
56 Maihofner C *et al.* (2005) Brain processing during mechanical hyperalgesia in complex regional pain syndrome: a functional MRI study. *Pain* **114:** 93–103
57 Willoch F *et al.* (2000) Phantom limb pain in the human brain: unraveling neural circuitries of phantom limb sensations using positron emission tomography. *Ann Neurol* **48:** 842–849

Acknowledgments
R Baron is supported by the Deutsche Forschungsgemeinschaft (DFG Ba 1921), the German Ministry of Research and Education, German Research Network on Neuropathic Pain (BMBF, 01EM01/04) and an unrestricted educational grant from Pfizer, Germany.

Competing interests
The author declared competing interests; go to the article online for details.

58 Willoch F *et al.* (2004) Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [^{11}C]diprenorphine PET study. *Pain* **108:** 213–220
59 Baron R *et al.* (1999) Brain processing of capsaicin-induced secondary hyperalgesia: a functional MRI study. *Neurology* **53:** 548–557
60 Baron R *et al.* (2000) Activation of the somatosensory cortex during Aβ-fiber mediated hyperalgesia: a MSI study. *Brain Res* **871:** 75–82
61 Maihofner C *et al.* (2004) Cortical reorganization during recovery from complex regional pain syndrome. *Neurology* **63:** 693–701
62 Pleger B *et al.* (2005) Sensorimotor retuning in complex regional pain syndrome parallels pain reduction. *Ann Neurol* **57:** 425–429
63 Fields HL *et al.* (1998) Postherpetic neuralgia: irritable nociceptors and deafferentation. *Neurobiol Dis* **5:** 209–227
64 Lombard MC and Larabi Y (1983) Electrophysiological study of cervical dorsal horn cells in partially deafferented rats. In *Advances in Pain Research and Therapy*, 147–154 (Ed Bonica JJ) New York: Raven Press
65 Loeser JD *et al.* (1967) Chronic deafferentation of human spinal cord neurons. *J Neurosurg* **29:** 48–50
66 Woolf CJ and Mannion RJ (1999) Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet* **353:** 1959–1964
67 Rolke R *et al.*: Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain*, in press
68 Mogil JS *et al.* (1999) Heritability of nociception I: responses of 11 inbred mouse strains on 12 measures of nociception. *Pain* **80:** 67–82
69 Zubieta JK *et al.* (2003) COMT *val^{158}met* genotype affects μ-opioid neurotransmitter responses to a pain stressor. *Science* **299:** 1240–1243