Shared mechanisms between chronic pain and neurodegenerative disease

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Accumulating evidence indicates that chronic pain provokes morphological changes in the central nervous system. Animal models of neuropathic pain have revealed that degeneration of inhibitory interneurons in the dorsal horn of the spinal cord contributes to persistent pain after peripheral nerve injury. Brain imaging in patients with chronic pain demonstrates a decrease in neocortical gray matter and in brain metabolites, a sign of reduced neuronal density. Shared disease mechanisms suggest that chronic pain should be considered a neurodegenerative disorder.

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Introduction

Acute (nociceptive) pain serves as a warning device that indicates imminent tissue damage. Chronic pain lacks such protective function as it persists for months or years after injury without reflecting the severity of a lesion or disease, nor does chronic pain necessarily respond to treatment of the underlying disease cause.

Chronic pain is associated with a variety of diseases (Box 1). More than 90% of patients with cancer, for example, experience persistent pain; in 21% of these patients, the pain is linked to tumor therapy [1]. Once pain has become chronic, it is difficult to provide satisfactory relief. Ongoing pain, however, has a major impact on daily life. Pain impairs social interaction, reduces the ability to work, and causes sleep deprivation and depression. Both, treatment-related costs and the loss of workforce that is caused by insufficient pain control create an enormous economic burden for society.

Multiple factors contribute to the development of clinical pain

Mechanical force, chemical, or thermal stimulation causes activation of nociceptors, which convey information about the nature and extent of the stimulus to the dorsal horn of the spinal cord [2]. Dorsal horn interneurons and descending pathways from brainstem nuclei regulate the transmission of nociceptive input to the brain.

This balance between excitation, facilitation and inhibition is lost in conditions of chronic inflammatory pain or pain caused by a lesion or functional disorder of the nervous system (neuropathic pain) [3]. Tissue damage and inflammation elicit the release of multiple mediators including serotonin, bradykinin and prostaglandins. Binding of these ligands to G-protein-coupled receptors leads to the phosphorylation of receptors and ion channels, causing nociceptor terminals to respond with increased excitation to noxious stimuli (peripheral sensitization) [4].

Peripheral nerve injury prompts an immediate barrage of action potentials (injury discharge) that is followed by sustained spontaneous (ectopic) activity. In injured neurons, membrane excitability changes owing to increased transcription and altered trafficking of voltage-gated sodium channels and a decrease in potassium channels. Altered regulation of

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Box 1. Conditions commonly associated with chronic pain

Osteoarthritis, rheumatoid arthritis
Myofascial pain, fibromyalgia
Low back pain
Inflammatory diseases of the gut (e.g. reflux oesophagitis, gastroduodenal ulcer, Crohn's disease, ulcerative colitis) or other visceral organs (chronic pancreatitis)
Irritable bowel syndrome
Urogenital conditions (dysmenorrhea)
Neuropathic pain
Complex regional pain syndrome I
Cancer
Postoperative pain

Box 2. Etiology of neuropathic pain

Peripheral neuropathic pain

- Nerve injury or compression (carpal tunnel syndrome, radicular low back pain)
- Polyneuropathies (diabetes mellitus, Guillain–Barré syndrome, HIV)
- Herpes zoster, postherpetic neuralgia
- Cancer-related neuropathies (tumor invasion, paraneoplastic, treatment-related)
- Complex regional pain syndrome II
- Cranial neuralgias

Central pain

- Stroke
- Multiple sclerosis
- Injury of the brain or spinal cord
- Syringomyelia, syringobulbia
- Parkinson's disease
- Brain tumors
- Epilepsy

Phantom pain

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the expression of numerous proteins results in a modification of the chemical phenotype of primary afferents.

Increased afferent input after inflammation or peripheral nerve damage enhances the responsiveness of the central nervous system. Recruitment of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors to the post-synaptic membrane and the opening, phosphorylation and increased synthesis of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors lead to central sensitization [5]. Normally innocuous stimuli begin to provoke a painful effect (allodynia), because synapses form between low-threshold sensory fibers and transmission neurons for nociceptive information. Brain-derived neurotrophic factor (BDNF) released from activated microglia contributes to the development of mechanical allodynia by causing a shift in the anion gradient of a sub-population of neurons in dorsal horn lamina I so that in these neurons the normal inhibitory effect of γ-aminobutyric acid (GABA) is lost [6].

Mechanisms of neurodegenerative disease

Acute energy depletion or disruption of ion homeostasis causes neuronal necrosis, whereas less severe insults that impair the survival conditions of neurons elicit programmed cell death. Apoptosis is a particular form of programmed cell death that occurs in neurodegenerative disorders such as Alzheimer's, Parkinson's or Huntington's disease, amyotrophic lateral sclerosis and stroke. Apoptosis depends on the maintenance of intracellular energy supply and the synthesis of effector proteins including caspases, a family of proteases involved in the self-destruction of cells. Triggers of neuronal apoptosis in neurodegenerative disorders are toxic amyloid β-peptide and aggregates of Tau filaments in Alzheimer's disease, oxidative or metabolic stress, excess levels of the neurotransmitter glutamate and death receptor activation by cytokines [7,8].

Apoptosis of dorsal horn neurons in chronic neuropathic pain

Diseases of the nervous system that are associated with chronic pain (Box 2) usually involve a primary lesion of a peripheral nerve or central pathway conveying sensory information. Pathological findings in the spinal cords of patients who had suffered from postherpetic neuralgia during their lifetimes first indicated that secondary neurodegeneration along nociceptive pathways might occur after peripheral nerve injury. In patients with persistent pain after herpes zoster, the dorsal horn of those spinal segments that were supplied by sensory fibers from the affected dermatomes exhibited marked 'atrophy'. By contrast, the dorsal horn was unchanged in the spinal cord of patients after herpes zoster, who did not develop ongoing pain [9].

Cell death in the dorsal horn has now been observed in several animal models of peripheral neuropathic pain [10,11]. Within days after nerve injury, apoptotic cell profiles occur in the superficial dorsal horn (laminae I–III), where nociceptive fibers terminate. The number of apoptotic profiles is small at any time, indicating a slow process of degeneration. However, apoptosis induction continues over a period of several weeks after injury [12], indicating that, over time, many cells might be lost.

Nerve injury-induced cell death in the dorsal horn involves neurons and is linked to activation of the executioner caspase-3. A stereological study has provided a quantitative assessment of neuronal loss in the rat dorsal horn after spared nerve injury (SNI) [12]. SNI is a model of partial sciatic nerve injury, which produces persistent behavioral changes in rats and mice that are equivalent to the essential features of neuropathic pain in humans: an abnormally low pain threshold (allodynia) for mechanical or cold stimuli, and an increased response to painful mechanical stimuli (hyperalgesia) [13,14]. Four weeks after SNI, more than 20% of neurons in dorsal horn laminae I–III were lost, including interneurons that expressed glutamic acid decarboxylase (GAD) (Fig. 1).

Figure 1. Neurodegeneration in the spinal cord. (a) Apoptotic cell profiles in the dorsal horn of the spinal cord seven days after spared nerve injury (SNI), a rat model of persistent neuropathic pain. (b) Four weeks after SNI, the number of dorsal horn neurons (immunolabeled for neuronal nuclear protein; NeuN) was substantially reduced. Stereological counts revealed that the cumulative loss of neurons in laminae I–III was more than 20%. (c) GABAergic inhibitory interneurons (labeled by *in situ* hybridization of glutamic acid decarboxylase (GAD) 67 mRNA) decreased by $24.2 \pm 2.7\%$ in laminae I-II and $25.0 \pm 2.5\%$ in lamina III, compared with the contralateral side ($p < 0.001$). Continuous administration of the caspase inhibitor benzyloxycarbonyl-Val-Ala-Asp(OMe)-fluoromethylketone (zVAD) for four weeks after SNI prevented the loss of GABAergic interneurons, indicating that caspase-dependent apoptosis caused the degeneration of interneurons. Scale bars in (a) 100 μm (left panel) and 5 μm (right panels); 100 μm in (b) and (c). Modified after [12]; copyright 2005 by the Society for Neuroscience.

GAD catalyzes the synthesis of γ-aminobutyric acid (GABA) and is a marker of GABAergic inhibitory interneurons. Continuous intrathecal treatment with benzyloxycarbonyl-Val-Ala-Asp(OMe)-fluoromethylketone (zVAD), a peptide that blocks caspase activity, reduced the number of dying cells in the dorsal horn and prevented the loss of GABAergic interneurons, demonstrating that caspase-dependent apoptosis was responsible for the nerve injury-induced degeneration of these neurons [12].

Loss of GABAergic interneurons results in spinal disinhibition

Whole cell patch clamp recordings from lamina II neurons of the rat dorsal horn have demonstrated that the inhibitory control of sensory transmission in the spinal cord is compromised after peripheral nerve injury [15]. Normally, primary afferent input activates inhibitory interneurons and transmission neurons in parallel. Release of GABA and glycine from inhibitory interneurons provides negative feedback for primary afferents (presynaptic inhibition) and regulates the activity of transmission neurons (postsynaptic inhibition). Afferent activity-evoked inhibitory postsynaptic currents (IPSCs) are usually recorded from more than 95% of lamina II neurons in uninjured rats. Following SNI or chronic constriction of the sciatic nerve, however, inhibitory currents were no longer present in 30% of the neurons. In the remaining neurons, amplitude and duration of GABAergic inhibitory currents were substantially reduced. Glycinergic inhibition, which remained largely intact [12,15], is insufficient to sustain inhibitory control. In the absence of GABAergic inhibitory

control, polysynaptic excitation of dorsal horn neurons rises sharply [16] and pain sensitivity is increased [17].

Blocking caspase activity after SNI prevented the decrease in inhibitory currents after nerve injury and reduced neuropathic pain-like behavior [12]. Consequently, the nerve injury-induced loss of GABAergic spinal inhibition had to be caused by the apoptosis of interneurons. The attenuation of pain hypersensitivity persisted after termination of the treatment, suggesting that the irreversible degeneration of interneurons is involved in the development of chronic pain.

Transsynaptic induction of apoptosis

Apoptosis induction in the dorsal horn after peripheral nerve injury was dependent on afferent activity. As pointed out earlier, nerve injury gives rise to two forms of abnormal spontaneous activity in primary sensory neurons. Axotomy evokes an immediate discharge of high-frequency action potentials; this discharge is of short duration, terminating after 1 or 2 min [18]. However, within hours a second wave of ectopic discharges arises in injured and neighboring intact nerve fibers, which is sustained for weeks [18]. Blocking afferent input from an injured nerve with bupivacaine efficiently decreased the number of apoptotic profiles in the dorsal horn, indicating that the degeneration of dorsal horn neurons is triggered by a transsynaptic mechanism [12]. The protective effect lasted only for the duration of the nerve block. Apoptosis set in again as soon as the local anesthetic had vanished. Consequently, cell death must be produced by the sustained form of ectopic afferent activity. Considering also the delayed onset of apoptosis after nerve lesion, the
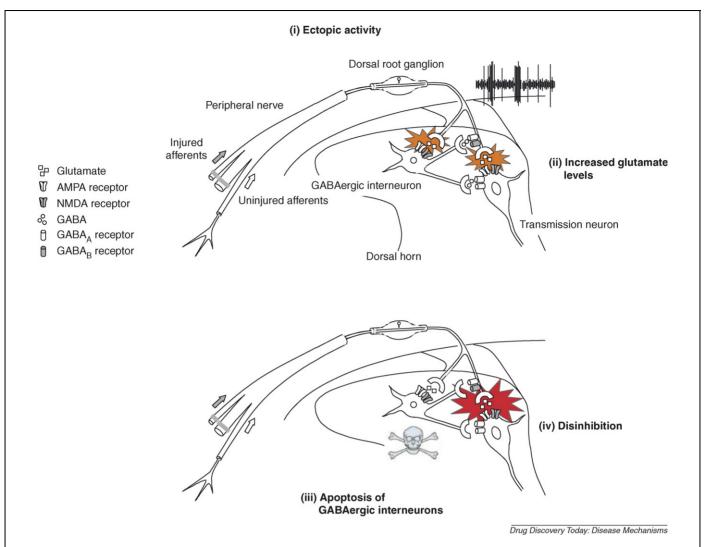
Figure 2. Mechanisms of neurodegeneration in the spinal cord associated with chronic pain. (1) Abnormal ectopic activity arising from injured and neighboring uninjured primary afferents generates increased extracellular glutamate levels in the dorsal horn (2). Excess activation of N-methyl-D-aspartate (NMDA) glutamate receptors leads to a rising influx of Ca^{2+} into dorsal horn neurons, which over time exhausts the buffering capacity of mitochondria. (3) Apoptosis is induced in GABAergic interneurons. (4) As a result, the γ-aminobutyric acid (GABA)-mediated pre- and postsynaptic inhibition of sensory transmission is diminished so that input from nociceptive and non-nociceptive afferents is conveyed without adequate control. Response to noxious stimulation becomes exaggerated (producing hyperalgesia) and normally innocuous stimuli begin to produce pain (allodynia).

injury discharge alone is unlikely to play a major role in the induction of transsynaptic neurodegeneration.

Ectopic activity after injury may produce excitotoxic levels of glutamate, because glutamate is the main transmitter released by nociceptive and non-nociceptive primary afferents. Toxic glutamate receptor activation is, for example, involved in neuronal death after hypoxia (ischemia) or trauma. In these conditions, a rapid rise in extracellular glutamate primarily causes necrosis, whereas apoptosis is associated with insults that produce slower and less extensive increases in glutamate. Glutamate excitotoxicity is caused by excess Ca^{2+} influx into the cell following AMPA or NMDA receptor activation. The higher affinity of glutamate to NMDA receptors and the long decay (several hundreds of milliseconds) of NMDA receptor currents, which allows temporal and spatial summation, increase the risk of toxic Ca^{2+} influx

mediated by NMDA receptor activation. Mitochondria can buffer a gradual rise in intracellular Ca^{2+}, but once their capacity is exhausted, Ca^{2+} overload causes leakage of proapoptotic factors such as cytochrome c through the mitochondrial membrane, followed by caspase activation and cell death.

Apoptosis after SNI was reduced by the NMDA receptor antagonist dizocilpine (MK-801) [12], supporting the hypothesis that glutamate-mediated excitotoxicity is a major cause of neurodegeneration in the dorsal horn after nerve injury (Fig. 2). Compared with other forms of excitotoxic insult, the time course of apoptosis induction is delayed and protracted.

Evidence for supraspinal neurodegeneration in chronic pain comes from human brain imaging studies

Neurodegeneration in the spinal cord, which changes the topography as well as the gain for nociceptive signal

transmission, likely provokes parallel reorganizations in supraspinal pathways. Human brain imaging studies are beginning to address this question in relation to specific chronic pain conditions [19,20].

A particular brain activity pattern associated with acute painful stimuli has emerged in functional imaging studies using positron emission tomography, single photon emission tomography (SPECT) or magnetic resonance imaging have established. This pattern has been replicated across a large number of labs and for multiple stimulus modalities [19,20]. The activation is primarily attributed to second order projections of nociceptive responsive spinal cord neurons through the classic spinothalamic pathway [21]. However, the extent of the involvement of this pathway in clinical chronic pain remains unclear because most functional imaging studies in clinical conditions indicate decreased brain activity in many components of the brain circuitry identified for acute pain [19]. It should be added that the majority of studies in clinical pain have examined responses to acute painful stimuli on top of the already present pain, which may not be the best approach for studying chronic pain [22,23].

Thalamic activity in chronic pain

In contrast to experimentally induced pain in normal subjects, chronic clinical pain conditions are consistently associated with decreased baseline activity or decreased stimulus-related activity in the thalamus [19]. Interpretations of these results, though, are often hampered by inadequate controls. The most elegant study on the topic so far has been a SPECT blood flow experiment [24] showing a strong relationship between time of onset of complex regional pain syndrome (CRPS) and thalamic activity. The ratio between contralateral and ipsilateral thalamic perfusion was greater then 1.0 (indicating hyperperfusion) for patients with symptoms for only 3–7 months, and smaller than 1.0 (indicating hypoperfusion) for patients with longer-term symptoms (24–36 months), with a correlation coefficient of 0.97 (normal subjects had a thalamic perfusion ratio of about 1.0). These results suggested that thalamic activity undergoes adaptive changes in the course of CRPS, indicating the transition of from an acute to a chronic state. Unfortunately, there are no biological markers for pain that would define standard time lines for the transition from acute to chronic pain. This ambiguity complicates interpreting the thalamic adaptive changes seen in CRPS. Early hyperperfusion in the thalamus might be a consequence of central sensitization or spinal disinhibition because of the apoptosis of interneurons. Increased polysynaptic excitation after the removal of GABAergic inhibitory control may prompt a vicious circle, causing the degeneration of more dorsal horn neurons including nociceptive transmission neurons, which would explain long-term thalamic hypo-perfusion.

Regional brain activation with experimental pain in humans is usually interpreted in relation to the spinothalamic pathway. Decreased thalamic signaling in chronic pain poses a puzzling dilemma from this viewpoint, suggesting that nociceptive pathways outside of this projection may be more important in chronic pain. Given the thalamic activity changes seen in CRPS [24], one possible explanation would be an early activation of the spinothalamic pathway, which at longer time periods becomes hypoactive, compensated by enhanced activity in other nociceptive pathways, like spino-parabrachial-amygdala, spino-basal ganglia, spino-prefrontal and spino-hypothalamic pathways.

Decreased metabolism in thalamus and cortex

In most human neurodegenerative conditions, such as Alzheimer's or Parkinson's diseases, proton magnetic resonance spectroscopy (MRS) shows decreased levels of brain metabolites, primarily of N-acetyl-aspartate (NAA) either in absolute terms or in relation to internal markers such as creatine, phosphocreatine, inositol or choline. Because NAA is found mainly in neuronal cell bodies, it has become accepted as a parameter for neuronal density and a tool with which neurodegeneration can be studied noninvasively. Recent studies indicate that NAA levels discriminate between amyotrophic lateral sclerosis patients and healthy controls with 71% sensitivity and 93% specificity and predict survival outcomes in this population [25,26]. In Alzheimer's disease (AD), parietal lobe NAA levels are reported as predictive of positive treatment outcome [27]. Levels of NAA apparently correlate with AD disease progression as strongly as the rate of ventricular expansion [28]. Such metabolic changes are detected in pre-symptomatic AD mutation carriers, where the magnitude of change seems related to proximity of expected age of onset of symptoms [29,30].

In chronic pain, NAA decreases in the dorsolateral prefrontal cortex (DLPFC) of patients with chronic back pain [31]. The concentration of NAA in DLPFC correlated with the pain intensity as well as affective dimensions of back pain. A follow-up study showed that the NAA concentration in the DLPFC relates to the character of the back as assessed using the Short Form of McGill Pain Questionnaire. By contrast, NAA in orbitofrontal cortex was not associated with particular pain descriptors but correlated with state and trait anxiety parameters [32]. The association of decreased thalamic NAA levels and pain intensity has also been observed in patients with central pain after spinal cord injury [33] and in patients with CRPS or postherpetic neuralgia [34]. Decreased concentrations of metabolites such as glucose or inositol have been found in the cerebrospinal fluid of patients with back pain caused by disc herniation or spinal stenosis [35].

Table 1. Potential targets for therapeutic intervention to prevent neuronal loss in neuropathic pain

Neuropathic pain mechanism	Target	Intervention	Available drugs
Ectopic activity of primary sensory neurons	VGSCs[a]	Non-selective sodium channel blockers or selective blockers for TTX[b]-resistent VGSCs	Local anesthetics, carbamazepine, lamotrigine, mexiletine
	Potassium channels	Potassium channel activators	
	Purinoceptors	Purinoceptor (e.g. $P2X_3$) antagonists	
Reduced threshold of nociceptor activation	Trp[c] channels (TrpV1, TrpV2, TrpA1, TrpM8)	Trp channel antagonists	Capsaicin cream (leads to nociceptor desensitization)
	NGF[d]	Antibodies against NGF or TrkA[e]	
Synaptic reorganization in the dorsal horn	TrkA	NGF	
	GFR-1(2)[f]	GDNF[g]	
Abnormal stimulus integration	Wind-up	NMDA[h]-receptor antagonists	Ketamine, dextromethorphan, amantadine
	Temporal summation		
	Long-term potentiation	NK1[i] antagonists	
Increased excitability of sensory transmission neurons	Kainate receptor	Kainate receptor antagonists	
	mGluRs[j]	mGluR antagonists	
	NMDA receptor	NMDA-receptor antagonists	Ketamine, dextromethorphan, amantadine
	PKCγ[k]	PKCγ inhibitors	
	NK1	NK1 antagonists	
	nNOS[l]	nNOS inhibitors, GTP[m]-cyclohydrolase or sepiapterin reductase inhibitors	
	MAPK[n]	MAPK inhibitors	
	VGCC[o] ($\alpha2\delta$-subunit)		Gabapentin, pregabalin
	N-type Ca^{2+} channels	N-type-specific Ca^{2+} channel blockers	Ziconotide
Reduced inhibition	GABA[p]	$GABA_A$ and $GABA_B$ receptor agonists	Baclofen
	μOR[q]	μ-Opioid agonists	Morphine, oxycodone
	Cannabinoid-1 receptor	Cannabinoids	
	α2-Adenoreceptor	α2-Adenoreceptor agonists	Clonidine
	Monoamine reuptake	Tricyclic antidepressants	Amitriptyline, imipramine, clomipramine
		Noradrenaline and serotonin reuptake blockers	
		Noradrenaline and dopamine reuptake blockers	Duloxetine, venlafaxine
	Adenosine receptor	Adenosine receptor agonists	Bupropion
Excitotoxic death of inhibitory dorsal horn interneurons	GABA receptors	$GABA_A$ and $GABA_B$ receptor agonists	Baclofen
	NMDA receptor	NMDA-receptor antagonists	Ketamine, dextromethorphan, amantadine
	Caspases	Upstream inhibitors of caspase activation (e.g. Hsp27[r])	
		Caspase inhibitors	
Microglia activation	Purinoceptors	$P2X_4$ antagonists	
	Microglia	Fluorocitrate, metothrexate, minocycline	
	Cytokines, for example, TNFα[s]	Antibodies against TNFα, TNF receptor-fusion proteins	Infliximab, adalimumab, ethanercept

[a] Voltage-gated sodium channel.
[b] Tetrodotoxin.
[c] Tansient receptor potential.
[d] Nerve growth factor.
[e] Tropomyosin-related kinase A.
[f] GDNF family receptor.
[g] Glial cell line-derived neurotrophic factor.
[h] N-Methyl-D-aspartate.
[i] Neurokinin 1 receptor.
[j] Metabotropic glutamate receptor.
[k] γ-Isoform of protein kinase C.
[l] Neuronal nitric oxide synthase.
[m] Guanosine triphosphate.
[n] Mitogen-activated protein kinase.
[o] Voltage-gated Ca^{2+} channel.
[p] γ-Aminobutyric acid.
[q] μ-Opioid receptor.
[r] Heat shock protein 27.
[s] Tumor necrosis factor α.

Reduction of cerebral gray matter

Automated techniques to study human brain morphology provide a powerful tool with which subtle changes in brain anatomy can be studied across different subject and patient populations. This technique has provided novel insights into age-related changes of the human brain, addiction, depression, anxiety, schizophrenia and bipolar disorder. Only recently it was applied to the study of chronic pain. Given the baseline activity pattern and metabolic changes in the brain that have been found in functional imaging studies, one would expect a decrease in neocortical gray matter volume and regional gray matter density in the thalamus and the DLPFC. Such changes were in fact the main observation of the first morphometric study contrasting the morphology of chronic back pain patients to sex- and age-matched healthy control subjects [36] (Fig. 3). Total neorcortical gray matter volume was negatively correlated with the duration of chronic pain. Every year of living with the condition decreased the cortical volume by an additional 1.5 cm^3 beyond the decrease in volume attributable to normal aging. The specificity of the outcome is corroborated by the fact that the magnitude of DLPFC gray matter changes in patients with spinal nerve root injury differed from that in patients with non-neuropathic back pain. Furthermore, gray matter variability correlated with sensory and affective dimensions of back pain. A recent independent study replicated most of these results [37]. Specific changes in regional gray matter density have also been found in patients with tension headache [38], CRPS and fibromyalgia (abstracts at 2006 Human Brain Mapping meeting). Details of the morphological changes may be specific to particular chronic pain states, potentially providing biological parameters that allow a differentiation of chronic pain conditions.

The results imply that chronic pain is accompanied by cerebral atrophy. Yet, the mechanisms underlying this atrophy remain to be elucidated. Cortical neurodegeneration may occur secondarily to spinal cord neurodegeneration, or reflect stress impinging on neurons that are trying to cope with increased afferent input. Genetic factors may render subjects vulnerable to chronic pain, either because they have genetically determined lower gray matter density in brain regions such as the DLPFC, or because neurons in brain regions at risk of chronic pain-related degeneration are more susceptible to stress, for example increased excitatory input. Brain atrophy in chronic pain may be because of an irreversible loss of neurons or volume changes that could recover when chronic pain is properly treated. The extent of reversibility of brain atrophy in chronic pain is a crucial issue and its relationship to successful therapy deserves to be investigated.

Conclusion

Animal studies indicate that transsynaptically induced degeneration of dorsal horn neurons is involved in the
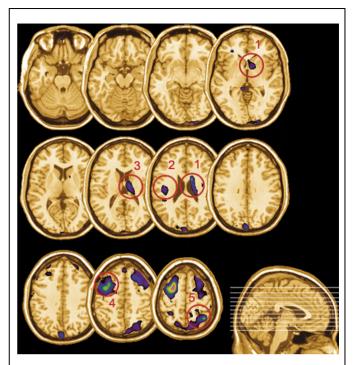

Figure 3. Brain regions exhibit decreased gray matter density in patients with chronic back pain, compared to age- and sex-matched healthy controls. The figure is derived from the data reported in [36]. Here, however, the difference was determined using parametric statistics (*t*-test). Brain regions that show either significant or borderline-significant gray matter decreases in contrast to the control subjects are numbered (red circles). In the original study only dorsolateral prefrontal cortex (DLPFC) (number 4) and thalamus (number 3) were reported, because they showed greater decreases in gray matter density and were significant in nonparametric statistical tests. Additional areas highlighted in the present figure include: caudate (number 1); secondary somatosensory cortex (number 2); and posterior parietal cortex (number 5). Distinct chronic pain conditions may be associated with specific profiles of cortical atrophy.

development of chronic pain. Human studies suggest neurodegeneration in the cerebral cortex. The risk of irreversible neuronal loss demands early intervention. Glutamate antagonists may reduce the transsynaptic apoptosis of dorsal horn neurons after nerve injury; however, treatment with glutamate antagonists carries the risk of producing severe side effects, because glutamate is the major excitatory neurotransmitter of the central nervous system. Likewise, a sustained blockade of apoptosis would interfere with the physiological cell turnover that takes place in many tissues. Safe and efficient strategies for neuroprotection need to be established (Table 1). They may create a unique opportunity to modify the course of pain-related disorders, by averting the loss of neurons and interrupting the development of chronic pain.

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