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REVIEW ARTICLE

Neurological diseases and pain

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Chronic pain is a frequent component of many neurological disorders, affecting 20–40% of patients for many primary neurological diseases. These diseases result from a wide range of pathophysiologies including traumatic injury to the central nervous system, neurodegeneration and neuroinflammation, and exploring the aetiology of pain in these disorders is an opportunity to achieve new insight into pain processing. Whether pain originates in the central or peripheral nervous system, it frequently becomes centralized through maladaptive responses within the central nervous system that can profoundly alter brain systems and thereby behaviour (e.g. depression). Chronic pain should thus be considered a brain disease in which alterations in neural networks affect multiple aspects of brain function, structure and chemistry. The study and treatment of this disease is greatly complicated by the lack of objective measures for either the symptoms or the underlying mechanisms of chronic pain. In pain associated with neurological disease, it is sometimes difficult to obtain even a subjective evaluation of pain, as is the case for patients in a vegetative state or end-stage Alzheimer's disease. It is critical that neurologists become more involved in chronic pain treatment and research (already significant in the fields of migraine and peripheral neuropathies). To achieve this goal, greater efforts are needed to enhance training for neurologists in pain treatment and promote greater interest in the field. This review describes examples of pain in different neurological diseases including primary neurological pain conditions, discusses the therapeutic potential of brain-targeted therapies and highlights the need for objective measures of pain.

Keywords: brain imaging; Parkinson's disease; complex regional pain syndrome; migraine; brain trauma

Abbreviations: CRPS = complex regional pain syndrome

Introduction

Recent advances in basic and clinical neuroscience suggest the brain plays a pivotal role in the chronic pain state. Recent advances in pain research, fuelled by neuroimaging studies, have engendered a transformation in our understanding of how pain affects the brain. As a result, the notion that changes in sensory systems are the predominant process in chronic pain has been replaced by a conceptualization of chronic pain as a very complex CNS state in which patterns of sensory system activation are integrated aberrantly with activity in other brain systems, including emotional, cognitive and modulatory processes. Obvious causes such as peripheral nerve injury-induced pain (neuropathic pain) affect a large number of brain regions with a wide range of other functions such as the anterior cingulate cortex, insular cortex, ventrolateral orbitofrontal area, amygdala, striatum, thalamus, hypothalamus, rostral ventromedial medulla, periaqueductal grey, pons (locus coeruleus), red nucleus, medulla oblongata and other less obvious causes of pain including those associated with primary depression where there is no injury or prior pain condition. More recently, clinicians and researchers have come to the conclusion that, in many cases, chronic pain is a direct result of the neurological disease, or may even be considered an integral part of the underlying disease. Perhaps the best example of this is Parkinson's disease, where 40–60% of patients report chronic pain (Simuni and Sethi, 2008; Ford, 2010). Table 1 shows the prevalence of pain in many neurological diseases,

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Table 1 Pain and neurological diseases

Disease	Prevalence of pain	Pain symptoms	Co-morbid depression
Degenerative			
Parkinson's disease	40–60% (Simuni and Sethi, 2008; Ford, 2010)	Musculoskeletal Dystonic Radicular Central neuropathic	15–30% (Vanderheyden *et al.*, 2010) 45% (Lemke, 2008)
Huntington's disease	Unknown	Myopathic pain Central pain?	40% (Paulsen *et al.*, 2005)
Alzheimer's disease	57% (Pautex *et al.*, 2006)	Musculoskeletal Other	35% (Pautex *et al.*, 2006) 20.5% (Arbus *et al.*, 2010) 87% (Strober and Arnett, 2009)
CNS damage			
Post-stroke (thalamic)	8–14% of all stroke patients (Kumar *et al.*, 2009)	Sensory loss and signs of hypersensitivity/allodynia in the painful area. Spontaneous (e.g. burning) or evoked pain in 85% of patients; intermittent shooting pains. Abnormalities to cold and pinprick in >90% (Vestergaard *et al.*, 1995; Klit *et al.*, 2009)	36% (Bour *et al.*, 2010)
Multiple sclerosis	50–86% (O'Connor *et al.*, 2008; Bermejo *et al.*, 2010)	Extremity pain, trigeminal neuralgia, Lhermitte's sign, painful tonic spasms, back pain and headache.	50% (Siegert and Abernethy, 2005)
Syringomyelia	Pain present in most (Aghakhani *et al.*, 2009) 37% (Milhorat *et al.*, 1996)	Burning pain Hyperaesthesia (Milhorat *et al.*, 1996) Typical neuropathic pain (Hatem *et al.*, 2010)	Unknown
Spinal cord injury[a]	64.9% (Modirian *et al.*, 2010)		10.7–19.7% (Krause *et al.*, 2009) 11.4% (Bombardier *et al.*, 2004)
Traumatic brain injury	57.8%—Headache 51%—Chronic pain with mild traumatic brain injury (Nampiaparampil, 2008) 12% CRPSNIH (Office of Communications and Public Liaison, 2003)	Continuous headache Autonomic dyscontrol Chronic pain – direct or related to Rx – CRPS, neuropathic pain.	35% (Busch and Alpern, 1998) 10–77% (Alderfer *et al.*, 2005)
Metabolic			
Fabry's disease	81% (males); 65% (females) (Hoffmann *et al.*, 2007)	Hands > feet > whole body	60% (Schermuly *et al.*, 2010) 46% (Cole *et al.*, 2007)
Diabetic neuropathy[a]	63% (Davies *et al.*, 2006)	19% non-neuropathic 36% painful neuropathy 7% mixed pain 37% no pain (Davies *et al.*, 2006) 8% painful neuropathy (Wu *et al.*, 2007)	41% with diabetes (Raval *et al.*, 2010)
Neuromuscular			
Amyotrophic lateral sclerosis	15% (Franca *et al.*, 2007) 20% (de Castro-Costa *et al.*, 1999)	Arms > other parts (de Castro-Costa *et al.*, 1999)	6–28% (Atassi *et al.*, 2010) 9–11% (Kurt *et al.*, 2007)
Guillaine-Barre[a]	Often present (van Doorn *et al.*, 2008) 89% (Moulin *et al.*, 1997) 36% pain before motor changes 66% pain in acute phase 38% after 1 year (Ruts *et al.*, 2010)	Acute chronic neuropathic paraesthesias Numbness (van Doorn *et al.*, 2008) 5–10% Neuropathic pain persists after motor recovery (Moulin *et al.*, 1997)	18% Extreme depression (Khan *et al.*, 2010)
Tumours			
NF2 Schwannomatosis Schwannomas	>60% pain (MacCollin *et al.*, 2005)	Pain as presenting symptoms Schwannomas—thumb, forearm and digits	Unknown
Peripheral nerve			
Complex regional pain syndrome	100% 61–81% Female 44–61% Upper extremity	Spontaneous pain Hyperaesthesia Shooting pain Allodynia	41% (Ciccone *et al.*, 1997)

(continued)

Table 1 Continued

Disease	Prevalence of pain	Pain symptoms	Co-morbid depression
	39–51% Lower extremity (Ghai and Dureja, 2004)		
Post-herpetic neuralgia[a]	PHN in 20% of HZ patients; 90% of these have pain (Johnson *et al.*, 2010)	Neuropathic Burning Shooting	44% (Atkinson *et al.*, 1986)
Back pain[a]	2–40% (Verhaak *et al.*, 1998) 66.9% (young adults) (Mallen *et al.*, 2005) 54–80% (lifetime) (Manchikanti *et al.*, 2009)	Nociceptive Neuropathic	5–54% (Sullivan *et al.*, 1992)
Post-surgical neuropathic pain[a]	10–50% of surgeries (Kehlet *et al.*, 2006)	Classic neuropathic symptoms	2% (Kalliomaki *et al.*, 2009)
Migraine (episodic)	26% of the population (Cooke and Becker, 2010) 11.7% (17.1% female, 5.6% male) (Lipton *et al.*, 2007)	Headache Hypersensitivity (e.g. light, sound, allodynia) Autonomic features (e.g. nausea)	28.5% (McWilliams *et al.*, 2004) 14–47% (Antonaci *et al.*, 2011)
HIV/AIDS	30–90% (Hewitt *et al.*, 1997)	Distal symmetrical Polyneuropathy Mononeuropathy multiplex (Verma, 2001)	8–45% (Perkins *et al.*, 1994)
Idiopathic/unknown aetiology			
Fibromyalgia[a]	2–4% of the population (Staud, 2009) 5–10% of all female patients (Russell and Raphael, 2008)	Widespread pain Extremity dysaesthesias	20–80% (Fietta and Manganelli, 2007)

a Not discussed in this article. HZ = herpes zoster; PHN = post-herpetic neuralgia.

including some that are primary pain disorders commonly seen by neurologists, and the rates are striking. As noted in Fig. 1, pain produces changes throughout the CNS with particular effects on emotional processing. The latter interaction is complex, for example, pain causes depression and depression causes pain (Lepine and Briley, 2004; Borsook *et al.*, 2007; Husain *et al.*, 2007; Maletic and Raison, 2009; Elman *et al.*, 2011). The prevalence of co-morbid depression is high in many chronic neurological diseases (Table 1).

Damage to either the peripheral or CNS is a well-defined cause of neuropathic pain. Considering the altered patterns of brain activity in neurological disease with pain may provide insight into pain processing in the brain in chronic disease. In contrast to the many neurological diseases with associated pain symptoms, some neurological conditions are associated with diminished pain or no pain (i.e. congenital insensitivity to pain). The underlying pathology and regional changes in brain systems are well described for some of these disorders, and examining them may also shed light on how alterations in the central circuitry of the brain produce chronic pain. In this article, we define chronic pain as a brain disease based on significant changes in function, anatomy (see discussion below on morphological changes in chronic pain) and chemistry, which occur following pathophysiological alterations in pain pathways. These changes occur in areas of the brain involved in sensory, emotional and modulatory systems and are 'brain-wide' [e.g. including regions not normally associated with pain such as the cerebellum (Moulton *et al.*, 2010)]. These changes are a direct consequence of pain or secondary to comorbid changes such as depression or anxiety (Elman *et al.*, 2011).

The changes in brain activity that underlie chronic pain may result in changes in central circuits that manifest as pain in the absence of the peripheral trigger. 'Centralization' of pain, here defined as 'the persistent static or dynamic brain functional state that contributes to or causes the behavioural responses to pain (e.g. depression increased sensitivity to stimuli, ongoing pain)', occurs as a result of altered brain dynamics not only in specific sensory systems, but also in other brain systems including emotional, cognitive and motor systems. This altered state results in a cognitive, sensory and emotional experience of pain, whether the initial instigating process is in the peripheral (perhaps including muscle) or CNS, as a result of primary brain disease, or secondary to afferent input as a result of nerve or spinal cord damage. Figure 2 summarizes known alterations in brain systems in chronic pain, including functional, anatomical and chemical changes. Specific examples are referenced.

While a number of recent reviews cover neuropathic pain (Baron *et al.*, 2010), the primary focus here is on specific neurological conditions that have pain as a co-morbid condition (defined as the presence of pain in addition to the primary neurological disorder), with a discussion of the potential insights into pain neurobiology provided by what we know about each disease state (Fig. 3). The section 'Neurological disease and pain' summarizes links between neurological disease, disease markers and genetic traits that may contribute to the pathophysiology of pain in neurological diseases. In section, 'Brain-based restorative approaches for chronic pain', novel therapies that target brain systems are discussed as opportunities for neurologists to take the lead role in chronic pain treatment and clinical research. In the final section, 'Smarter tools for objective diagnosis

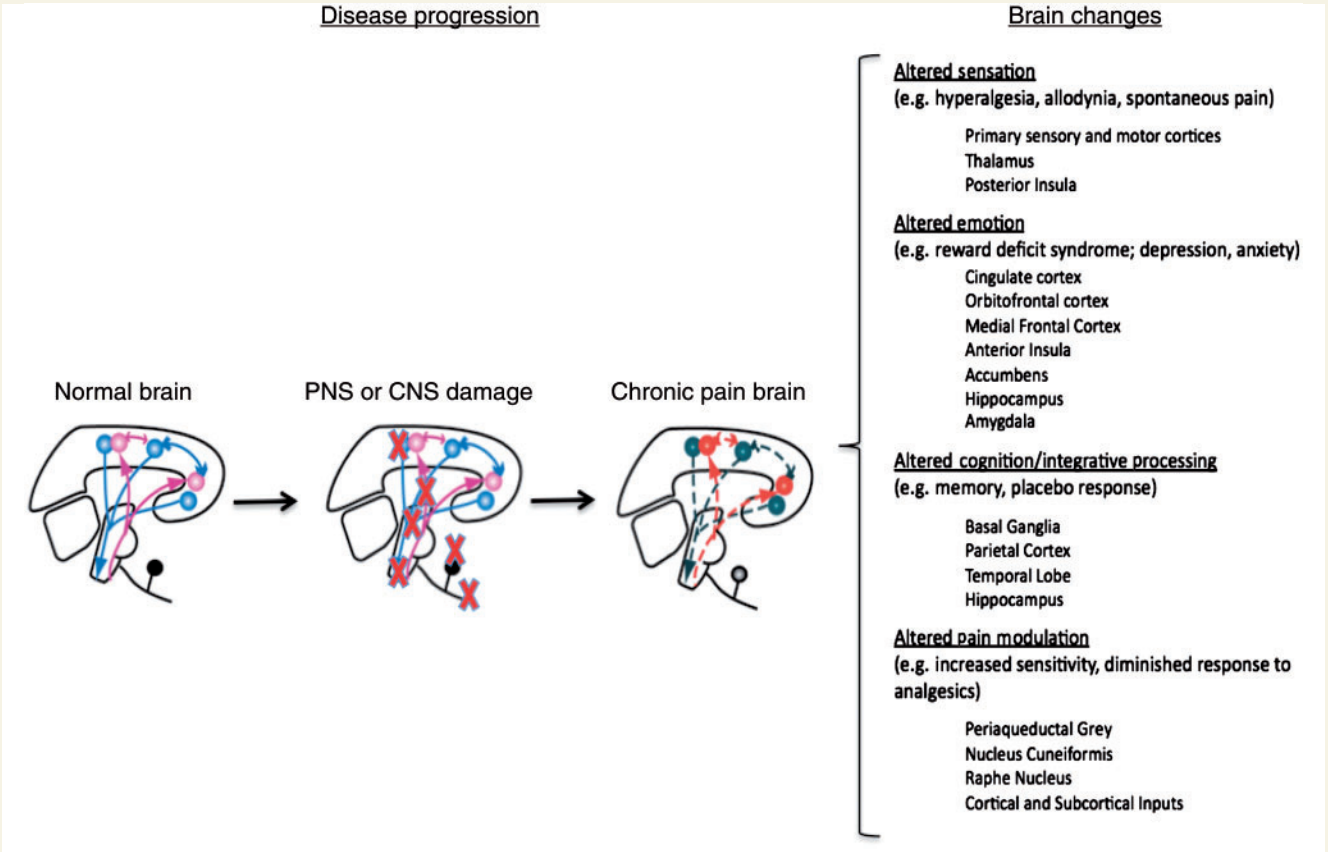

Figure 1 Brain changes in chronic pain. The figure summarizes two concepts that relate to the development of chronic pain following damage to either peripheral or CNS pathways involved in pain. (i) The first is that following injury (red crosses) progressive changes take place in the brain: the normal brain is altered in a manner that produces changes in function and structure in the chronic pain state; (ii) the second, noted in the text on the right, indicates that multiple brain regions involved in sensation, emotion, cognition and pain modulation may manifest in varied behavioural symptoms from ongoing pain to anxiety and depression. While it is easy to conceptualize altered systems, altered circuitry is best considered in the context of interactive brain processes that are disrupted in chronic pain. Both central and peripheral origins of pain are noted; the peripheral sources are clearly important in producing or maintaining central changes whether these are part of a disease affecting both central and peripheral systems or not.

of pain' section, we briefly discuss the need for objective markers for pain.

Understanding potential links between pain pathophysiology and neurological disease

Recent advances have greatly increased our understanding of pain mechanisms. Although much of this work has been in peripheral systems and lower CNS areas—peripheral nerve, the spinal cord and brainstem (Dubner, 2004), research focused on higher brain centres is increasing rapidly (Woolf, 2011), including neuroimaging of pain in humans (Tracey and Mantyh, 2007). Pain may be a sentinel marker of disease (e.g. acute back pain, acute shingles) or a consequence of disease (e.g. post-herpetic neuralgia, thalamic stroke, spinal cord injury). Neuroimaging has identified states of activation that associate with pain; however, it is unclear if the initial pain-related state markers (usually transient) transform into trait markers (usually enduring) of a neurological disease. In some primary neurological diseases, pain contributes to the course of the condition; this is perhaps most obvious in back pain, but is significantly less clear in other neurological conditions with pain (e.g. Parkinson's disease). Where pain contributes to the course of disease, this may be a direct result of pain-related CNS changes or may be the result of associated processes such as immune response. Conversely, the immune response may modulate pain, thereby affecting disease course (Ren and Dubner, 2010; Austin and Moalem-Taylor, 2010).

Only a few studies have examined genetic, neurobiological and behavioural factors in specific neurological diseases with a focus on pain. However, some of these have identified potential genetic markers of the risk of developing chronic pain, including the GTP-cyclohydrolase 1, encoded by GCH1 pain-protective gene haplotype, which decreases pain levels (Tegeder *et al.*, 2006); the potassium channel alpha subunit KCNS1 that associates with several chronic pain conditions e.g. back pain, amputation (Costigan *et al.*, 2010);

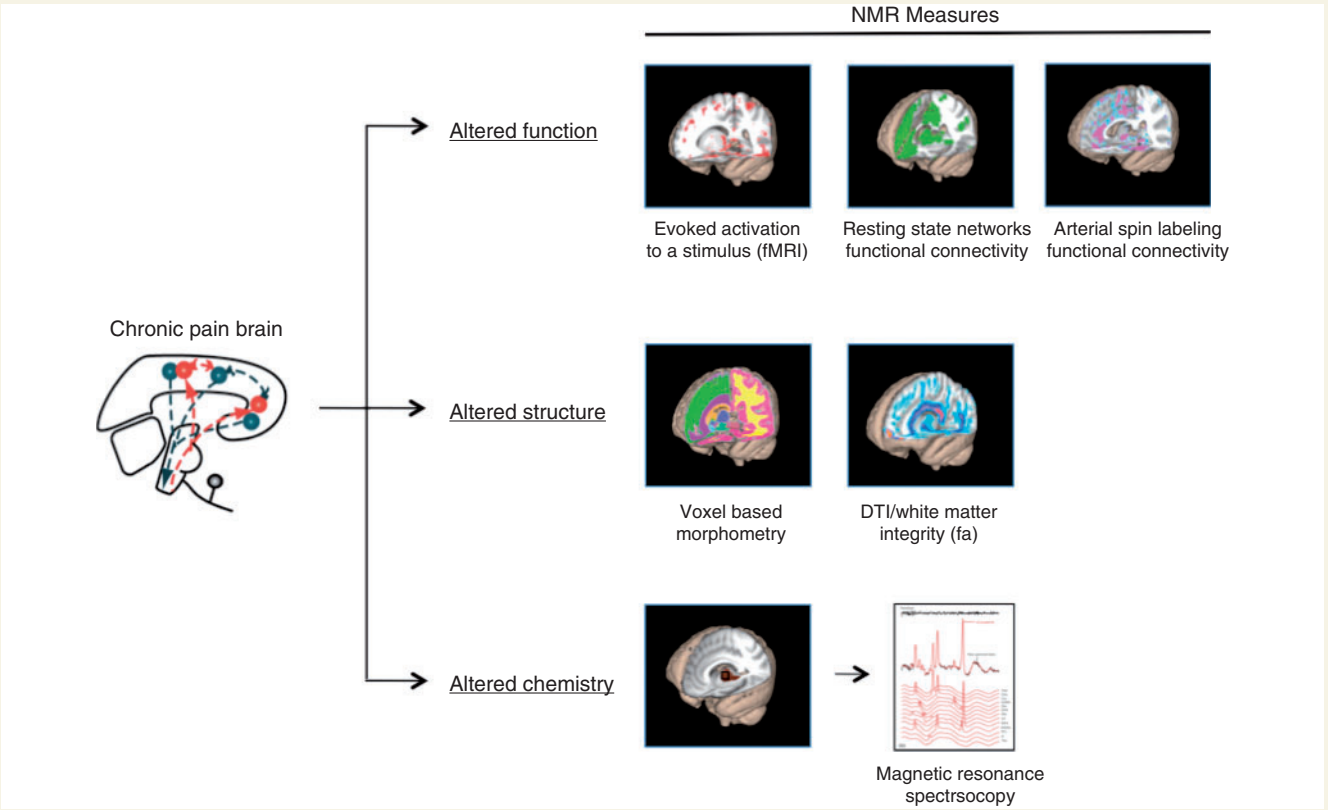

Figure 2 Changes in function, structure and chemistry in chronic pain. Chronic pain alters the brain (*left*) and produces alterations in function [e.g. increased activation as in central sensitization (Lee *et al.*, 2008)]; altered resting state networks (Apkarian *et al.*, 2004); and altered chemistry [e.g. changes in excitatory and inhibitory amino acids, (Gussew *et al.*, 2011)]. While the example of nuclear magnetic resonance (NMR) approaches for evaluating alterations in the brain in pain conditions (Borsook *et al.*, 2007; Borsook and Becerra, 2011) is provided, other approaches have been employed to measure pain-related alterations in brain systems including electroencephalography (Brinkmeyer *et al.*, 2010), magnetoencephalography (Maihofner *et al.*, 2010) and near infrared spectroscopy (Slater *et al.*, 2006; Becerra *et al.*, 2008). fa = fractional anisotropy; fMRI = functional MRI.

and the calcium channel gamma subunit gene *CACNG2*, a protein intimately involved in the trafficking of glutamatergic α-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptors that is implicated in susceptibility to chronic pain (Nissenbaum *et al.*, 2010). We are unaware of any twin studies that have evaluated trait markers that may contribute to the relationship between pain and primary neurological conditions. Clearly, genome-wide association studies are the way forward to define clinically relevant genetic markers that predict pain susceptibility, severity and treatment responses in neurological conditions. Insights into genetic mutations that prevent pain may open new opportunities to understanding pain in neurological conditions and their treatment (Oertel and Lotsch, 2008). Characterization of pain endophenotypes through measures including functional brain imaging may allow us to connect genetic findings with defined biomarkers underlying pain-related processing (Tracey, 2011).

Neurological diseases and pain

This section discusses examples of neurological diseases that have pain as a co-existing or co-morbid process. This is not intended to be an exhaustive review of pain in neurological disease but to illustrate how commonly pain presents with neurological disease across a spectrum of underlying pathologies and to provide some insight into how the pathophysiologies of each disease may facilitate or synergize with brain mechanisms involved in chronic pain. For many of these diseases, the underlying pathophysiology is not clear, so our discussion of the potential interaction is necessarily brief and is intended to spark interest rather than present definitive connections. For most neurological conditions not discussed in this article, there are already excellent reviews of the literature on pain as related to the condition: fibromyalgia (Brederson *et al.*, 2011; Smith *et al.*, 2011); phantom pain occurring in missing limbs (Flor, 2002; Grüsser *et al.*, 2003; Ketz, 2008) but also many other body regions (Holland *et al.*, 1994); post-traumatic painful neuropathy occurring in significant numbers (10–50%) of patients following surgery (Kehlet *et al.*, 2006); chronic back pain (Manchikanti *et al.*, 2009) including failed back surgery (Chan and Peng, 2011); peripheral neuropathic pain such as painful diabetic neuropathy and small fibre neuropathies (Vaillancourt and Langevin, 1999; Sommer, 2003); and post-herpetic neuralgia (Hempenstall *et al.*, 2005; Philip and Thakur, 2011).

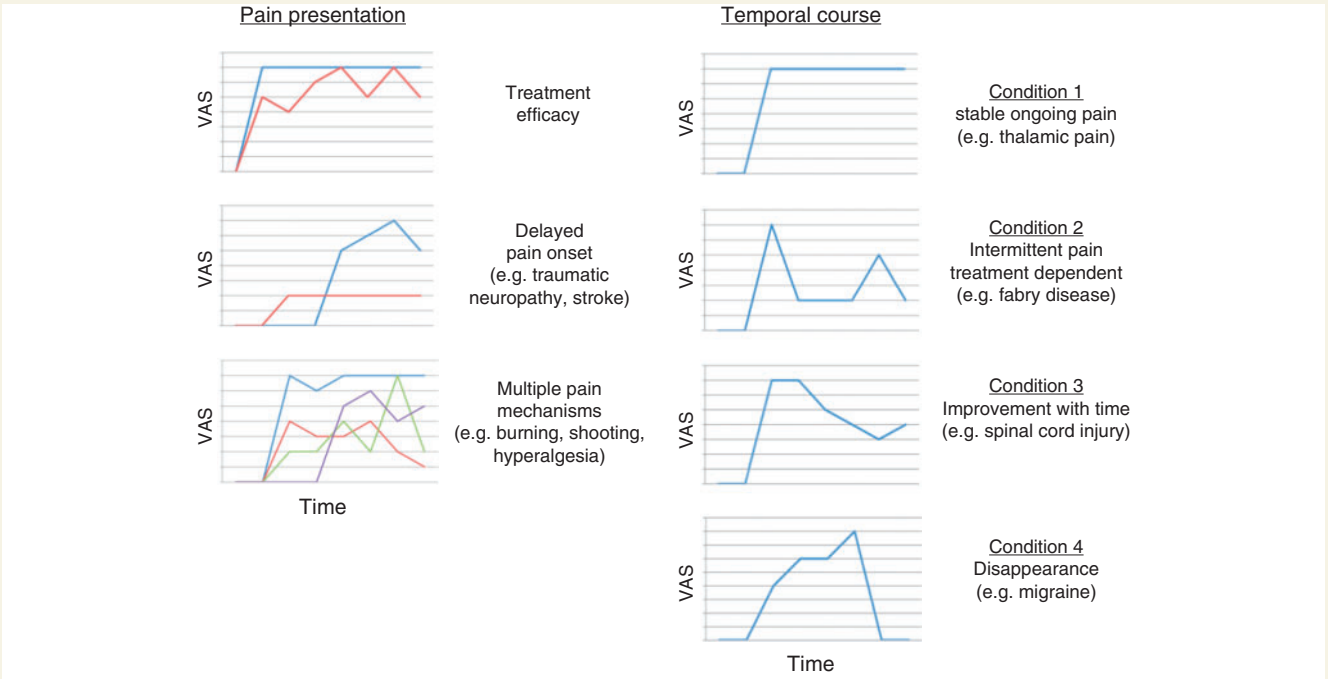

Figure 3 Chronic pain symptoms and variations in temporal course. Chronobiological effects of pain, treatment effects, environmental changes (e.g. barometric pressure) activity all may contribute to a variation in pain over time (Auvil-Novak, 1999; Lake, 2005; Odrcich *et al.*, 2006; Dworkin *et al.*, 2007; Kloss-Brandstatter *et al.*, 2011). *Left*: Examples of features of pain presentation. (i) Relatively small effect of therapy (red line) versus pain (blue line) [pain is rated by patients on an 11-point (0–10) Likert's scale (VAS)] usually decreases by just two points on this scale; on average most pharmacological treatments decrease pain by 20–30% in population placebo controlled studies; (ii) the onset of pain may be variable and even be delayed following disease onset (red line)—this is more easily observed with specific PNS or CNS damage (i.e. traumatic neuropathy or thalamic stroke); (iii) most conditions have more than one pain (lines in different colours representing different pains) that can be defined mechanistically—e.g. shooting pain due to ectopic activity; burning pain due to inhibitory neuron dropout (Baron *et al.*, 2010). *Right*: Representative examples of different temporal courses for pain from constant (Condition 1) to intermittent or dependent on specific treatment (Condition 2) to a natural course of improvement (Condition 3) to complete remission (Condition 4). The colours are used to differentiate time courses where multiple plots are used.

Central nervous system degenerative diseases

Parkinson's disease and pain

Parkinson's disease is perhaps the best example of co-morbid pain as an integral part of a neurodegenerative disease. Between 40 and 60% of patients with Parkinson's disease have chronic pain that frequently includes more than one type of pain (Giuffrida *et al.*, 2005; Simuni and Sethi, 2008; Ford, 2010). Using the Brief Pain Inventory to assess average pain over a 24-h period, patients with Parkinson's disease reported an average pain level of 2.85, significantly greater than the general population, with >50% of patients reporting one, 24% reporting two and 5% reporting three pain types. Of these, musculoskeletal pain was noted in 70%, dystonic pain in 40%, radicular–neuropathic pain in 20% and central neuropathic pain in 10%. Around 34% of patients in this study were on analgesic medication. Pain was significantly higher (83%) in those with dystonic symptoms (Beiske *et al.*, 2009). Pain in Parkinson's disease correlates with age, disease duration and severity, and, as with many pain conditions, female gender is a significant predictor of pain. In addition, chronic use of analgesic prescription drugs is highly prevalent in Parkinson's disease (Brefel-Courbon *et al.*, 2009): patients with Parkinson's disease received more prescriptions for analgesics than the general population (82% versus 77%), but fewer than patients with osteoarthritis (82% versus 90%). As a comparison, no significant difference in analgesic use was found between Parkinson's disease and diabetic patients, a patient group traditionally used to evaluate analgesics in clinical trials. Clearly, pain is a problem in Parkinson's disease and the growing interest in Parkinson's disease and pain over the past two decades is reflected by the increase in publications related to pain and Parkinson's disease and by increased efforts to manage pain symptoms (Fig. 4).

Specific changes in psychophysical measures of pain have been detected clinically in Parkinson's disease. For example, using heat and laser pinprick paradigms in patients with Parkinson's disease in the OFF condition, patients with Parkinson's disease with central pain had lower thresholds for heat pain and laser pinprick than patients with Parkinson's disease with no central pain or control subjects. These effects were attenuated with L-DOPA treatment (Schestatsky *et al.*, 2007). Similarly, another report showed that

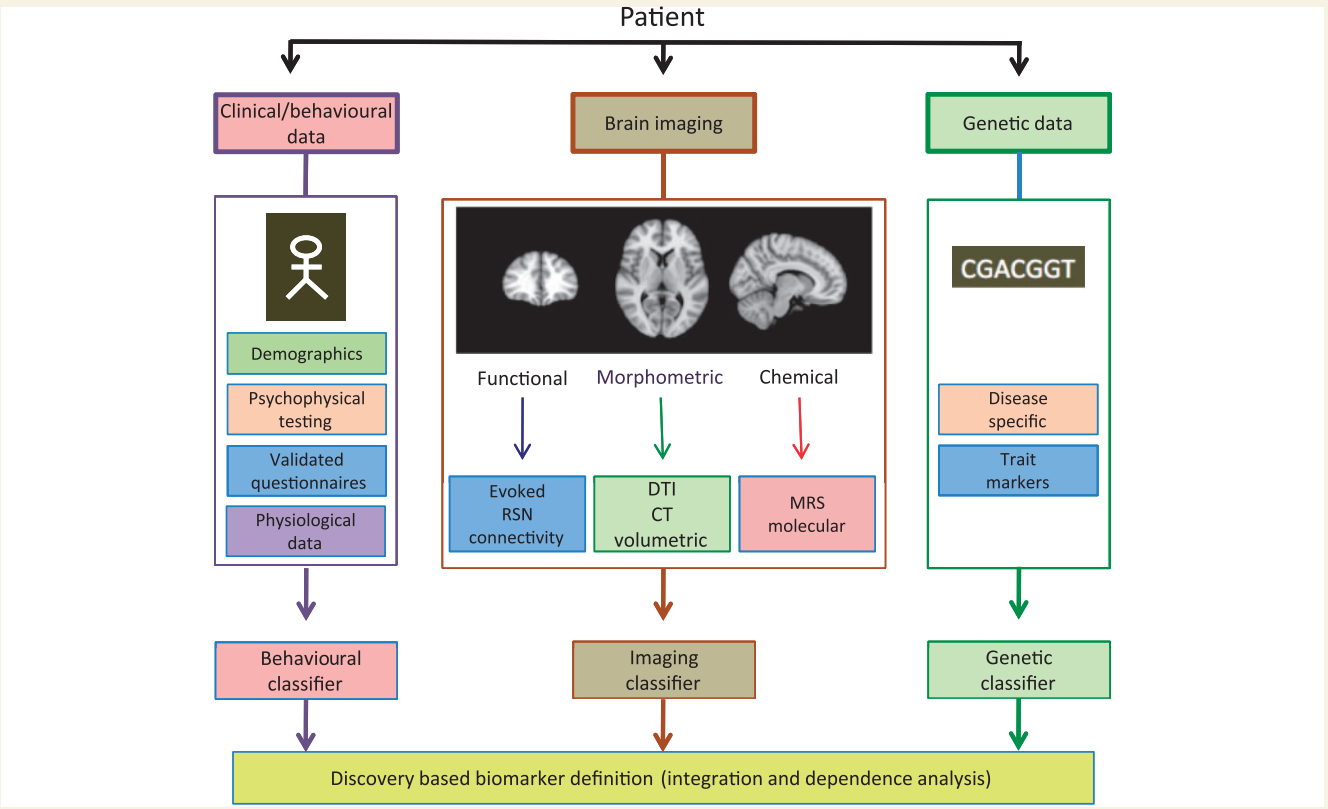

Figure 4 Objective imaging assays. Current research for pain biomarkers includes brain imaging (Borsook *et al.*, 2011*a*, *b*), clinical/behavioural approaches (Freynhagen *et al.*, 2006; Scholz *et al.*, 2009) and genetic markers (Tegeder *et al.*, 2006). Each of these approaches has yielded some promising results, suggesting that specific classifiers can be defined that may be used alone or, more likely, in combination, as pain biomarkers. DTI = diffusion tensor imaging; RSN = resting state network; MRS = magnetic resonance spectroscopy.

L-DOPA increases the pain threshold in Parkinson's disease as assessed by the RIII nociceptive flexion reflex (Gerdelat-Mas *et al.*, 2007). Patients with Parkinson's disease also exhibited facilitation of temporal summation, a process in which the response to repeated painful stimuli is greater than to a single stimulus of the same intensity. Temporal summation is frequently enhanced in chronic pain, and is often used as an indicator of central sensitization. Patients with Parkinson's disease are more sensitive than normal controls to repeated painful stimuli, suggesting alterations in supraspinal inputs to pain modulatory systems (Perrotta *et al.*, 2010).

Dopaminergic systems are involved in the modulation and integration of sensory information and the response to pain (Wolters, 2009; Juri *et al.*, 2010). Pain symptoms increase and decrease with dopaminergic fluctuation. For example, in a Parkinson's disease patient cohort of >200, 47% reported pain and 45% therapy patients reported decrease (sensitivity 59.5% and specificity of 65% and a negative predictive value of 75%) in pain level with dopaminergic therapy (Stacy *et al.*, 2010). Patients with Parkinson's disease reported increased unpleasantness in response to heat pain but only while ON medication, compared with the OFF state (Nandhagopal *et al.*, 2010). Significantly, pain may be alleviated by adjustments of L-DOPA medications (Letro *et al.*, 2009; Nebe and Ebersbach, 2009). Central pain may also be a result of dopaminergic loss, as is reported during dopamine agonist withdrawal: patients with Parkinson's disease who have their dopamine agonist stopped exhibit a withdrawal syndrome that is dose-dependent and includes pain (Rabinak and Nirenberg, 2010). Studies looking at other pain syndromes also support the role of dopaminergic systems in pain. The dopamine agonist pramipexole, a dopamine 3 receptor agonist, improved symptoms of patients with fibromyalgia (Holman and Myers, 2005). In addition, genetic variants of catechol-O-methyltransferase (COMT), which inactivates catecholamines including dopamine, are associated with different responses to acute and chronic pain (Andersen and Skorpen, 2009; Belfer and Segall, 2011).

Dopamine is centrally involved in CNS reward systems and reward and pain are at opposite ends of a behavioural motivational spectrum. Depression is common in pain conditions and vice versa. Depression has been reported to affect ~45% of patients with Parkinson's disease, but prevalence varies across studies (Burn, 2002; Lemke, 2008). Thus, depression may also be a contributing factor to the pain symptoms reported in patients with Parkinson's disease (Lohle *et al.*, 2009). A complex link exists between pain and emotions, and there is an overlap in pathways involved in reward and pain (Zubieta *et al.*, 2001; Scott *et al.*, 2006; Borsook *et al.*, 2007). Dopamine regulated neurons have been implicated in motivational control both in reward and

aversion and in defining motivational salience as it relates to rapid detection of important sensory information (Martin *et al*., 2010). Dopaminergic systems are implicated in both reward and pain (Zubieta and Stohler, 2009). The neuroanatomical and functional overlap between pain and brain circuitry involved in emotion/reward/motivation brain suggests integration and mutual modulation of these systems (Elman *et al*., 2011). As noted above, catechol-O-methyltransferase polymorphisms contribute to the interindividual variability in human pain phenotypes. Such genes may alter the brain's mesolimbic reward circuitry (Chen *et al*., 2009). Alterations in dopamine levels may contribute to alterations in reward function in chronic pain resulting in a 'reward deficit state' (Comings and Blum, 2000).

Alzheimer's disease and pain

Pain processing may be altered in dementias (Scherder *et al*., 2003; Schmidt *et al*., 2010) including Alzheimer's disease (Pickering *et al*., 2000). The issue is complicated by patients' diminished ability to report pain because of cognitive deficits (Schmidt *et al*., 2010). A recent brain imaging study reports that pain perception and processing are not diminished in Alzheimer's disease (Cole *et al*., 2006). This is consistent with reports that sensory-discriminative components of pain are preserved even in advanced stages of Alzheimer's disease (Benedetti *et al*., 2004), while pain tolerance increases with disease severity (Benedetti *et al*., 1999). Other studies report similar findings: in studies comparing patients with Alzheimer's disease to age-matched subjects without dementia, patients with Alzheimer's disease consistently report lower pain intensity in response to painful stimuli, and have diminished pain affect (Scherder *et al*., 2001). Although there are data suggesting that the threshold for pain tolerance is markedly increased and the autonomic pain reaction is diminished in Alzheimer's disease (Rainero *et al*., 2000; Kunz and Lautenbacher, 2004), these results need to be evaluated in the context of altered autonomic function (Toledo and Junqueira, 2010) and delayed ability to respond. The prevalence of pain in the elderly in nursing homes is estimated to be between 40% and 80%; however, pain prevalence is difficult to assess in Alzheimer's disease because of the difficulty in measuring pain when there is cognitive impairment.

Alzheimer's disease is a double-edged sword when it comes to pain assessment. Pain affects cognitive function (Lee *et al*., 2010; Moriarty *et al*., 2011) and cognitive function also affects pain assessment and pain treatment because the primary method for pain assessment is still patient reporting (Licht *et al*., 2009). Thus, it is difficult, if not impossible, to obtain reliable subjective measures of pain in subjects with advanced Alzheimer's disease. As discussed in the section 'Pain in the unconscious or non-communicative patient' below, the same difficulty is present in treating or studying pain in patients who are neurologically compromised for other reasons (i.e. non-communicative brain injured patients, vegetative state) (Owen *et al*., 2006; Boly *et al*., 2007) and in preverbal infants. However, as noted above, new data obtained from imaging studies of experimental pain in patients with Alzheimer's disease show that presumed pain perception (involvement of sensory and emotional systems) is not diminished despite morphological and functional changes in cortical regions. Indeed, there is a greater amplitude and duration of pain-related activity in sensory, affective and cognitive processing regions in patients with early onset Alzheimer's disease compared with age matched controls (Cole *et al*., 2006). Regions of the brain like the thalamic nuclei (Rudelli *et al*., 1984) and the overall sensory/discriminative cortex appear relatively unaffected by Alzheimer's disease (Farrell *et al*., 1996). However, loss in limbic structures, hippocampus and prefrontal cortex (Hyman *et al*., 1984) may explain the deterioration of affective aspects and emotions in cognitively impaired elderly adults suffering from Alzheimer's disease (Pickering *et al*., 2000; Greicius *et al*., 2003). Thus, assessing pain at different stages of Alzheimer's disease progression may provide an opportunity to differentiate between pain-related activation in sensory systems (i.e. intensity) and emotional processing (i.e. affect, unpleasantness) of pain. Altered pain processing may also reflect diminished modulation of pain at the level of regions such as the periaqueductal grey (Parvizi *et al*., 2000), which could explain the perseveration of brain responses reported in imaging studies (Cole *et al*., 2006). Thus, patients with Alzheimer's disease may not be able to remember, interpret, respond to, or report pain in a normal fashion and may exhibit abnormal behaviours as a result, including agitation, aggression and other affective changes (Benedetti *et al*., 2004; Shega *et al*., 2007).

Without objective tests or biomarkers, evaluating pain in any population is complex and variable. In the Alzheimer's disease group, because of the added complication of diminished cognitive processing, pain assessment is even more difficult, with about a third of subjects unable to complete a number of pain assessment tools (Krulewitch *et al*., 2000). A number of instruments have been developed to measure pain in patients with decreased cognitive function including evaluating facial grimacing (Shega *et al*., 2008), pain intensity scale (Krulewitch *et al*., 2000); Mahoney Pain Scale (Mahoney and Peters, 2008) and Pain Assessment in Advanced Dementia (Zwakhalen *et al*., 2011). These are all subjective measures.

Huntington's disease and pain

The prevalence of pain in Huntington's disease is unknown. An initial case report describes severe pain in two patients with this condition (Albin and Young, 1988). In a more recent study, 11 of 19 patients with Huntington's disease had pain, with altered pain perception to pinprick, touch and temperature in some subjects (Scherder and Statema, 2010). In Huntington's disease, alterations in peripheral tissue (muscle) may be due to alterations in mitochondrial dysfunction and energy metabolism (Sassone *et al*., 2009). Exercise-induced muscle pain has been described in a marathon runner who subsequently developed Huntington's disease (Kosinski *et al*., 2007), suggesting that it may be an early unrecognized symptom of the disease. Significantly, there is a 10–25% prevalence of diabetes in patients with Huntington's disease (Farrer, 1985); diabetes is a relatively common cause of neuropathic pain in a subset of diabetics, but we are unaware of any reports related to how this may impact

patients with Huntington's disease. As discussed above, pain and depression are frequently co-morbid conditions; the prevalence of severe depression is twice as high in Huntington's disease as in the general population, reportedly as high as 40% (Folstein *et al.*, 1985; Paulsen *et al.*, 2005).

Huntington's disease is an autosomal dominant progressive neurodegenerative disorder (Ross and Tabrizi, 2011) that affects the brain, primarily the basal ganglia where there is extensive atrophy of the caudate, globus pallidus and putamen, with consequent changes in motor, cognitive, and emotional functioning (Grove *et al.*, 2003). The disease also affects the thalamus (particularly the ventrolateral nucleus), a region considered to play a role in sensory perception (Ro *et al.*, 2007). The basal ganglia are involved in both acute and chronic pain processing (Borsook *et al.*, 2010) and have a prominent role in sensorimotor integration, which is altered in Huntington's disease, in which these regions may actually become deafferented (Abbruzzese and Berardelli, 2003). Basal ganglia activations are common in functional imaging studies of pain (Borsook *et al.*, 2010), thus it would not be surprising if the compromised function of the basal ganglia in Huntington's disease led to alterations in pain processing. Abnormal cortical and subcortical activation in patients with Huntington's disease following passive sensory stimulation as evaluated by functional PET studies (Boecker *et al.*, 1999). Although there are no published studies of pain processing in Huntington's disease, it is known that experimental lesions of the caudate impair pain avoidance, indicating impaired pain processing (Koyama *et al.*, 2000).

Ataxia and pain

Machado–Joseph disease is the most common spinocerebellar ataxia, also known as spinocerebellar ataxia type 3 (Rub *et al.*, 2008) and is a neurodegenerative disease that includes ataxia, opthalmoplegia and peripheral neuropathy (D'Abreu *et al.*, 2010). Although classically described as affecting the cerebellum, it affects a number of other brain regions including brainstem, basal ganglia, thalamus and cerebral cortex (D'Abreu *et al.*, 2010). In a small study, nearly 50% of patients reported chronic pain including muscle cramps (Franca *et al.*, 2007). Muscle excitability abnormalities occur in >80% of these patients and peripheral nerve damage correlates with the extent of muscle fasciculations (Franca *et al.*, 2008). In addition, widespread neurodegeneration is observed in somatosensory (although pain is not specifically delineated) as well as primary sensory systems with alterations in dopaminergic and cholinergic systems (Rub *et al.*, 2008). Sensory symptoms including pain are observed across subtypes of spinocerebellar ataxia, with 48% of subjects complaining of pain or discomfort (Schmitz-Hubsch *et al.*, 2008).

One emerging concept is that the cerebellum may play a role in chronic pain (Moulton *et al.*, 2010), based on its complex role in cognitive and affective processing (Stoodley and Schmahmann, 2010). Current data suggest that the cerebellum is an integrator of multiple effector systems including affective processing, pain modulation, as well as sensorimotor processing.

Neuromuscular diseases

Amyotrophic lateral sclerosis

Chronic pain is common in neuromuscular diseases, including amyotrophic lateral sclerosis (Wijesekera and Leigh, 2009), where the prevalence is 15–20% (Franca *et al.*, 2007). In a small case series of amyotrophic lateral sclerosis, pain was the first symptom manifested in >20% of patients (de Castro-Costa *et al.*, 1999), with the arms as the primary affected region. Cases of chronic central pain have also been reported in patients with amyotrophic lateral sclerosis (Drake, 1983). One study reported mild (29% of patients) and severe (6%) depression in amyotrophic lateral sclerosis (Atassi *et al.*, 2010), which may be a major contributor to the pain manifestations in this disease.

Although amyotrophic lateral sclerosis predominantly affects the motor system, sensory changes are present, including paraesthesias. A multi-centre European study reported generalized sensory changes in amyotrophic lateral sclerosis (Pugdahl *et al.*, 2007), but made no specific reference to pain. Quantitative sensory testing performed to evaluate function in unmyelinated fibre systems using heat stimuli for thresholds of cold and warm sensation found no differences between amyotrophic lateral sclerosis and control subjects in cold or warm thresholds (Deepika *et al.*, 2006); however, no suprathreshold testing was performed.

Is the underlying disease in amyotrophic lateral sclerosis a cause of pain? Both the animal (Chen *et al.*, 2010) and human (Gerber *et al.*, 2011) literature suggest that a muscle neuropathic-like pain syndrome exists in amyotrophic lateral sclerosis. Imaging studies have reported functional deficits in secondary/higher order sensory processing areas in amyotrophic lateral sclerosis (Lule *et al.*, 2010), but the authors do not describe changes in response to pain.

Central nervous system damage

Stroke

It is well-documented that strokes affecting the CNS, particularly the structures along the spino-thalamocortico-tract (spinothalamic tract, lateral thalamus, thalamic–parietal projections), produce central pain syndromes (central post-stroke pain) (Bowsher *et al.*, 1998). Despite the fact that the classic description of thalamic stroke producing pain was published >100 years ago (Dejerine and Roussy, 1906), the mechanisms underlying the severe, spontaneous, burning pain that occurs with thalamic stroke remain unclear. However, it is clear that damage to specific regions of the brain produces central pain. In operculo-insular pain, a central pain syndrome resulting from posterior parasylvian lesions, thermal and pain sensations are altered and laser-evoked potentials to thermo-nociceptive stimuli are abnormal (Garcia-Larrea *et al.*, 2010). A pseudothalamic syndrome, producing pain asymbolia (absent or inadequate emotional responses to painful stimuli) (Berthier *et al.*, 1988), results from a stroke producing damage to the posterior insula region (Masson *et al.*, 1991). This is consistent with evidence indicating a significant role of the posterior insula in processing of thalamic pain (Craig, 2000).

A number of important findings related to central pain shed light on pain processing: (i) damage to the classic pain sensory systems (spinothalamic tract) seems to be pivotal in producing central pain syndromes resulting from stroke (Hong *et al.*, 2010). Loss of grey matter in chronic pain has been well described and the altered connectivity resulting from either direct damage or indirect changes may contribute to a central pain syndrome. In contrast, most patients with a loss of cortical sensory evoked potentials and a CT scan finding of ischaemic lesion of the posterolateral thalamus do not exhibit central pain (Wessel *et al.*, 1994); (ii) in thalamic pain, there is increased excitability of thalamic regions. Although there may be diminished activation in the thalamus at rest, hyperactivity (including bursting activity) is found in central post-stroke pain, suggesting derangement of an oscillatory pattern inside a sensory corticothalamocortical reverberatory loop (Lumer *et al.*, 1997); and (iii) other changes including alterations in neural connectivity (deafferentation) (Boivie *et al.*, 1989), decreases in opioid receptor concentrations (Jones *et al.*, 2004; Maarrawi *et al.*, 2007), damage to lateral nociceptive thalamoparietal fibres (Schmahmann and Leifer, 1992), and altered chemistry (evaluated by magnetic resonance spectroscopy, Veldhuijzen *et al.*, 2007) are present in central pain. Functional imaging studies of a patient with thalamic pain suggest that the release of activity in anterior cingulate and posterior parietal regions is a plausible mechanism for central pain (Seghier *et al.*, 2005). The article provides evidence for specific damage to the thalamoparietal fibres (using 3D diffusion tensor imaging), consistent with clinical studies of thalamic pain (Demasles *et al.*, 2008) and with increased responses to pain in the insula, putamen and parietal lobe on the affected side. The latter have been shown to be involved in analgesia (Borsook *et al.*, 2010; Mhuircheartaigh *et al.*, 2010).

Syringomyelia

Syringomyelia and its sister disorder, syringobulbia, are disorders associated with Arnold–Chiari malformation (Koyanagi and Houkin, 2010) or spinal cord trauma (Schurch *et al.*, 1996). Syringomyelia and syringobulbia frequently produce pain (Todor *et al.*, 2000; Greitz, 2006; Hatem *et al.*, 2010) and result in an increasing cavity of CSF within the spinal cord tissue (i.e. not involving the central canal). Differential alterations in CSF flow and pressure seem to be important components of an underlying mechanism that initiates or potentiates the evolution of the syrinx (Greitz, 2006; Martin *et al.*, 2010). Pain is present when the syrinx presses on the crossing fibres of spinothalamic tracts.

As in thalamic stroke, the disease affects the spinothalamic tract at the level of the spinal cord in the dorsolateral quadrant (or brainstem in syringobulbia). In patients with neuropathic pain, higher average daily pain intensity is correlated with greater structural damage to the spinal cord (Hatem *et al.*, 2010). Pain descriptors (describing spontaneous pain or paraesthesias) were negatively correlated with fibre reconstruction and were clearly different in patients with both spontaneous and evoked pain compared to patients with spontaneous pain only. Patients with spontaneous pain only had more severe spinal cord damage.

Traumatic brain injury

Multiple pain syndromes have been described in different patients following traumatic brain injury with diffuse axonal injury (Raghupathi and Margulies, 2002), including neuropathic pain, central pain, and thalamic pain (Formisano *et al.*, 2009). Pain after traumatic brain injury is common (Walker, 2004). Headache following head trauma is observed in >50% of patients and has received increasing attention as it relates to combat blast-induced injuries (Vargas, 2009; Risdall and Menon, 2011). The prevalence of chronic pain following mild traumatic brain injury (75%) is higher than following severe traumatic brain injury (32%) (Nampiaparampil, 2008). Significantly, in traumatic brain injury, chronic pain is independent of post-traumatic stress disorder and depression, but is frequently associated with other brain changes including auditory and visual deficits (Nampiaparampil, 2008), autonomic dysfunction (Kanjwal *et al.*, 2010), insomnia (Zeitzer *et al.*, 2009) and psychiatric disease (Halbauer *et al.*, 2009). Traumatic brain injury produces diffuse axonal injury. Diffusion tensor imaging of mild blast injury veterans has not shown any differences compared with veterans without a history of traumatic brain injury (Levin *et al.*, 2010). Little information is available on assessing and treating pain in traumatic brain injury (Dobscha *et al.*, 2009).

The aetiology of headache is unknown. Its immediate trigger may be the tearing of trigeminal fibres that innervate the meninges. Small fibre (calcitonin gene related peptide positive) meningeal nerves infiltrate the calvarial bones of the skull and the nerves may be tethered predominantly in the calvarial sutures (Kosaras *et al.*, 2009). With impact producing movement of the meningeal surface, these nerves are stretched or torn. In traumatic brain injury, disturbances in brain perfusion in the frontal and temporal lobes correlate with the headache (Lyczak and Lyczak-Rucinska, 2005).

Multiple sclerosis

Chronic pain is experienced in 40–75% of patients with multiple sclerosis (Kenner *et al.*, 2007; Bermejo *et al.*, 2010; Solaro and Messmer Uccelli, 2010). Multiple sclerosis, an inflammatory, demyelinating autoimmune disease of the CNS, has been associated with multiple pain syndromes including extremity pain, trigeminal neuralgia, Lhermitte's sign, painful tonic spasms, back pain and headache (O'Connor *et al.*, 2008). While it seems as though the presentation of pain should be correlated with sites of demyelination, a study evaluating CNS pathways in patients with multiple sclerosis with and without pain found no association between chronic pain and the site of demyelination. Increased pain in multiple sclerosis correlates with depression, spinal cord involvement at the onset and the presence of spinal cord lesions (Grau-Lopez *et al.*, 2011). Thus the aetiology of pain may involve a more complex phenomenon including local cytokine processes or alterations in white and grey matter integrity of networks that produce pain.

Damage to pain pathways in multiple sclerosis may result from inflammatory processes involving glia and cytokines (Merson *et al.*, 2010), which are also a potential mechanism of central pain (Graeber, 2010; Nakagawa and Kaneko, 2010). Approaches

using anti-cytokine gene therapy reportedly decrease sensory dysfunction in multiple sclerosis (Sloane *et al.*, 2009). Disease modifying medications targeted at the immune system do not seem to provide significant pain relief.

Metabolic diseases

Fabry's disease and pain

Fabry's disease is an X-linked recessive lysosomal disease caused by α-galactosidase A deficiency. Although Fabry's disease-related pain syndromes include migraine (Albano *et al.*, 2010), distal limb pain is a common presenting feature (Pagnini *et al.*, 2011) and is the most common feature in childhood. An important observation is that the gender effect on pain prevalence in Fabry's disease is opposite to that in most kinds of pain: pain is more prevalent in males (80%) than females (65%) with Fabry's disease, although it interfered more with daily activities in females (Hoffmann *et al.*, 2007). In adults, Fabry's disease-associated alterations in brain structure are well established (Nill *et al.*, 2006), including cerebrovascular events relating to accumulation of lysosomes in several tissues, particularly vascular endothelium and smooth muscle cells (Fellgiebel *et al.*, 2006). These vascular events primarily affect the posterior circulation, resulting in damage to periventricular white matter, brainstem, cerebellum, and basal ganglia in particular (Clavelou *et al.*, 2006). In addition, T_1-weighted MRI studies have identified pulvinar calcification in particular as a structure with abnormalities in Fabry's disease (Moore *et al.*, 2003).

The mechanisms by which α-galactosidase A deficiency causes these physiological abnormalities are poorly understood. Small fibre reductions are noted in skin biopsies in symptomatic and asymptomatic individuals (Liguori *et al.*, 2010) as are abnormalities in autonomic function (Moller *et al.*, 2009). Similarly, a mouse model of Fabry's disease exhibits decreased density of both non-myelinated and thinly myelinated fibres (Onishi and Dyck, 1974; Rodrigues *et al.*, 2009). Glycolipid accumulation in the dorsal root ganglion or nerves may explain phenomena such as shooting pains (Gadoth and Sandbank, 1983). Enzyme replacement therapy with α-galactosidase A significantly reduces pain but can take a few years to be effective (Schiffmann *et al.*, 2001; Hoffmann *et al.*, 2007).

Tumours and pain

Neurofibromatosis

Neurofibromatosis is an autosomal dominant neurocutaneous disorder subdivided into neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2) and schwannomatosis (Lu-Emerson and Plotkin, 2009). NF1 is the most common neurogenetic disorder (Lu-Emerson and Plotkin, 2009) where the most common lesion is a benign tumour—the neurofibroma. NF1 tumours may develop anywhere in the nervous system including the skin and PNS and usually produce 'unmanageable pain' (Huson *et al.*, 2011). NF2 tumours occur in the CNS, including bilateral vestibular schwannomas and meningiomas. Schwannomatosis is characterized by multiple non-vestibular, non-intradermal schwannomas and chronic pain. Pain is the most common presenting feature of schwannnomatosis (MacCollin *et al.*, 2005) and paediatric plexiform (51%) neurofibromas (Serletis *et al.*, 2007). There is an increased incidence of itch in NF1, which may be related to increases in mast cells in the skin (Nurnberger and Moll, 1994). Common sites for neurofibromatosis-related tumours include intraspinal, paraspinal, brachial plexus, femoral nerve and sciatic nerve. Pain may become manifest as a result of compression (e.g. with foraminal tumours). These tumours are distinct from benign schwannomas, which are common tumours of peripheral and cranial nerves, also presenting with pain, neurological deficits and enlargement of a pre-existing peripheral nerve sheath tumour in NF1 (Valeyrie-Allanore *et al.*, 2005).

These tumours illustrate two processes involved in pain: (i) compressive neuropathy (Corey, 2006), where there is nerve sheath involvement (Wang *et al.*, 2005); and (ii) the contribution of inflammatory mediators (through mast cells) to pain (Staser *et al.*, 2010). In neurofibromatosis-1, these inflammatory mediators induce vascular changes that may lead to vasculo-occlusive disease (Lasater *et al.*, 2010), producing microinfarcts in the vasa vasorum that may contribute to painful symptoms.

Peripherally initiated changes in central nervous system pain processing

Each of the three clinical examples presented in this section provides insight into how changes in peripheral pain pathways impact CNS pain processing. Complex regional pain syndrome illustrates how peripheral nerve damage may transform brain systems; congenital insensitivity to pain provides a dramatic example of the profound consequences of loss of peripheral pain sensation; and migraine demonstrates that a common neurological disease that involves the trigeminal system is not simply an intermittent manifestation of pain and associated symptoms, but may alter brain systems.

Complex regional pain syndrome

Perhaps no pain condition represents the centralization of pain more clearly than complex regional pain syndrome (CRPS; Janig and Baron, 2002; Bruehl, 2010). Following a peripheral nerve injury, usually trivial, a series of progressive changes may take place that include some or all of the following: (i) spreading pain that may cross the midline and involve the whole body, suggestive of centralization of sensory processing at the thalamus or higher centres (Maleki *et al.*, 2000); (ii) autonomic changes suggestive of hypothalamic changes (Gradl and Schurmann, 2005); (iii) neglect-like symptoms suggestive of parietal lobe dysfunction (Galer and Jensen, 1999); and (iv) in some cases, dystonias or other motor changes suggestive of potential basal ganglia involvement [see review by Maihofner *et al*. (2010)]. Taken together, these findings implicate alterations in CNS processing, a notion supported by functional brain imaging studies that demonstrate reproducible alterations in adult (Geha *et al.*, 2008; Maihofner *et al.*, 2010) and paediatric (Lebel *et al.*, 2008) patients with CRPS.

In CPRS, persistent pain and subsequent progressive changes in the brain (namely automonomic, cognitive, central sensitization, hemineglect) are observed following mild peripheral nerve injury. This and other brain imaging studies suggest that all patients with neuropathic pain have alterations in brain systems that may result in cognitive and other behavioural changes, which may go unrecognized because they are not as prominent as the pain symptoms. Longitudinal MRI studies of paediatric patients with CRPS indicate that the brains of these children continue to exhibit significant differences from normal controls after symptoms resolve (Lebel *et al.*, 2008).

Congenital insensitivity to pain

This is a rare and severe autosomal recessive condition (Rosemberg *et al.*, 1994) that leads to self-mutilation in early life. The underlying pathophysiology is alteration of pain and temperature perception due to involvement of the autonomic and sensory nervous system involving small-calibre (A-delta and C) nerve fibres (Danziger and Willer, 2009). In addition, bone fractures, scars, osteomyelitis, joint deformities, limb amputation and mental retardation are common in individuals with congenital insensitivity to pain (Thrush, 1973). These patients lack nerve growth factor-dependent unmyelinated (C-) and thinly myelinated (Aδ-) fibres (Indo, 2010). Clinically, congenital insensitivity to pain is characterized by insensitivity to all modalities of pain, with the possible exception of neuropathic pain, since some case reports describe patients with congenital insensitivity to pain with burning 'pain' following post-herpetic neuralgia (Tomioka *et al.*, 2002). The disorder results from mutation (deletion) in the *SNC9A* gene, which encodes the Na1.7 channel (Cox *et al.*, 2010; Kurban *et al.*, 2010). This is of interest since activating mutations in SNC9A produces severe pain due to gain of channel function in paroxysmal extreme pain disorder and primary erythermalgia (Choi *et al.*, 2011).

Congenital insensitivity to pain is an important human model for pain genetics, representing a functional 'knockout'. However, the ethics of studying pain in individuals with congenital insensitivity to pain are complex, since profound mental retardation frequently makes it difficult to determine whether or not they suffer even without a behavioural response to pain *per se* (Borsook and Becerra, 2009a, 2009b). In a report on neural correlates of empathy in congenital insensitivity to pain, brain activations to observed pain were reported in the anterior mid-cingulate cortex and anterior insula (regions of the so-called 'shared circuits' for self and other pain).

Migraine/headache

Episodic migraine is one of the common primary headache disorders (Robbins and Lipton, 2010). Until relatively recently, it was considered an episodic pain syndrome without effects on CNS processing. Current evidence suggests that the brains of patients with episodic migraine are significantly different from healthy controls. For example, even during the interictal period, these brains exhibit increased cortical excitability to pain (Moulton *et al.*, 2011), to light (Denuelle *et al.*, 2011), and to smell (Demarquay *et al.*, 2008), as well as altered brainstem processing (Moulton *et al.*, 2008) and associated changes in grey matter volume (May, 2009). Thus, migraine is now considered a brain disease and not simply a recurrent acute pain syndrome. Like many chronic pain syndromes, migraine predominantly affects females.

Migraine provides an interesting pain model: (i) it provides a clear-cut model of gender-related pain issues, generally uncomplicated by prior history that contributes to chronic pain (e.g. post-traumatic stress disorder); (ii) migraine is a disease associated with progression or chronification (Bigal and Lipton, 2011), a process that has an unknown basis except that it may be produced by medication overuse (Jonsson *et al.*, 2011); although chronic daily headache affects a relatively small per cent of the migraine population, it is these patients that most frequently seek medical attention (Manack *et al.*, 2011); (iii) migraine is an ideal model of pain systems involved in central sensitization since with the onset of the headache, progressive central sensitization is associated with allodynia in the face, body and limbs (Burstein *et al.*, 2010) and for understanding altered (ineffective) modulatory circuits in pain (Moulton *et al.*, 2008) that is observed in pain processing in humans (Becerra *et al.*, 2006; Seifert *et al.*, 2009); (iv) diffuse brain systems are involved including the temporal pole (Moulton *et al.*, 2010) and areas involved in modulation of sensory systems that may produce pain [e.g. light (Noseda *et al.*, 2010)]; and (v) cortical spreading depression, a process involved in both stroke and migraine is now understood to drive trigeminovascular pain neurons (Zhang *et al.*, 2011).

Pain in the unconscious or non-communicative patient

Altered states of consciousness pose a huge dilemma in diagnosis (misdiagnosed in 43% of cases) and in determining whether a patient is experiencing pain and suffering (Coleman *et al.*, 2009). Assessing acute and chronic pain in unconscious (comatose) patients or those who cannot communicate is a critical problem. In the USA, between 100 000 and 280 000 patients are believed to be in a minimally conscious state (Strauss *et al.*, 2000). Recent neuroimaging studies have reported conscious awareness and potential cognition in patients in a vegetative state (Owen *et al.*, 2006, 2007; Monti *et al.*, 2010). Less is known about the ability of such patients to perceive pain (as opposed to nociception), and studying this issue presents a clinical and ethical dilemma. In a functional brain imaging study of pain in response to median nerve stimulation in patients in a minimally conscious state, patterns of activation similar to controls were reported (thalamus, S1 and the secondary somatosensory or insular, frontoparietal and anterior cingulate cortices), suggesting that pain perception may be intact in these patients (Boly *et al.*, 2008). Newer technologies may be able to determine patterns of activation in pain networks at the bedside (Becerra *et al.*, 2008, 2009*a*). Recommendations on how to best evaluate and treat such patients have been drawn up by nursing groups (Herr *et al.*, 2006; Pudas-Tahka *et al.*, 2009), anaesthesia/critical care (Gelinas *et al.*, 2006) and neonatologist (Duhn and Medves, 2004) services. However, none of these approaches include objective measures

of pain, and rates of misdiagnosis of patients in the minimally conscious state (motor cortex stimulation; some evidence of awareness of self and environment) or vegetative state (wakefulness without awareness) (Fins *et al.*, 2007). Attempts have been made to provide objective measures of cognition and pain using neuroimaging. PET studies show activation in regions of the pain network (thalamus, S1 and the secondary somatosensory or insular, frontoparietal, and anterior cingulate cortices) in patients with motor cortex stimulation and vegetative state (at a lower level) and demonstrate loss of functional connectivity between S1 and frontoparietal regions in both conditions (Boly *et al.*, 2008). In an earlier study, pain stimulation activated the midbrain (in the same regions activated by somatosensory stimulation), contralateral thalamus, and primary somatosensory cortex in all vegetative state patients, even in the absence of cortical evoked potentials (Laureys *et al.*, 2002). The activation in the primary cortex seems to be isolated and dissociated from higher order associative cortices in vegetative state.

What do these functional MRI studies tell us about pain processing in unconscious/non-communicating patients? Measures of pain processing in the brain across the spectrum from awake/conscious processing to pain processing in unconscious anaesthetized states provide some insight (Brown *et al*., 2010). As noted in the reports above, in comatose patients (vegetative or minimally conscious state), pain stimuli activate well-defined pain pathways in the brain. What is unclear is if the patient comprehends or suffers from pain. Behavioural scales have been used to try to evaluate pain in comatose patients, including the Nociceptive Coma Scale (Schnakers *et al.*, 2010). While neuroimaging studies may provide data relating to brain regions involved in aversion and affective dimensions of pain, currently we can utilize functional MRI methods to define nociceptive processing but not pain itself. These data indicate that a better understanding of pain perception in the minimally conscious or vegetative state is a clinical and ethical imperative. Further studies are required, as well as the development of new neuroimaging modalities that can be applied easily at the bedside.

Pain and strange/unexplained symptoms

There is an unfortunate tendency to define patients as 'crazy' if their pain symptoms are unusual or clinical evaluation yields a non-classical finding. Examples of these atypical presentations include non-dermatomal sensory deficit in patients who have pain (Mailis-Gagnon *et al.*, 2003; Egloff *et al.*, 2009; Mailis-Gagnon and Nicholson, 2010) and altered manifestations of phantom sensations with pain (Borsook *et al.*, 1998). Other more complex phenomena include neglect-like symptoms observed in patients with CRPS and non-CRPS neuropathic pain (Galer and Jensen, 1999; Frettloh *et al.*, 2006). In addition, the evolution of pain in depressed patients with no prior history of pain or non-traumatic post-traumatic stress disorder provides further insight into the complexity of alterations in brain circuits producing pain. Some patients display a recognizable illness without any pathology, making it difficult to determine if the illness is real or simulated. Similarly puzzling are instances of delayed onset of pain following an insult and spontaneous resolution of pain, which may take place over a short time period even if pain has been present for years (Schott, 2001). Finally, the effect of opioids in chronic pain is often counter-intuitive. For example, they have relatively limited efficacy (a decrease of 13 points on a 100 point scale) (Eisenberg *et al.*, 2006), and, in some neurological conditions, opioids either exacerbate pain or diminish future treatment efficacy. For example, opioids induce migraine chronification (Bigal and Lipton, 2009). Opioids clearly alter brain systems (Upadhyay *et al.*, 2010); however, the impact of these changes on chronic pain is not understood. Objective measures of pain would help clarify many of these issues and aid in the assessment of clinical efficacy of analgesics.

Brain-based restorative approaches for chronic pain

Despite trials of a number of approaches, chronic pain is largely refractory to treatment. Chronic pain associated with neurological disease has varied presentations and temporal profiles (Fig. 5) that add to the complexity of treatment approaches. Below, I discuss therapeutic approaches that may be more logical in light of the new understanding that chronic pain is a disease of the brain. The over-riding goal of these approaches is to restore brain networks to states that are adaptive. This discussion is not meant to suggest specific therapies for pain in particular neurological diseases, but rather to spur further exploration of new chronic pain treatment options that represent a fairly radical departure from our previous therapeutic approach.

Motor training

Motor and sensory systems are well integrated (Flor and Diers, 2009). In the setting of chronic pain, a number of 'motor' treatments have been used, including physical therapy, mirror movement in patients with chronic pain including phantom limb pain (Ramachandran and Altschuler, 2009; Ramachandran *et al.*, 2010) and complex regional pain syndrome (Selles *et al.*, 2008), motor cortex stimulation (discussed below) and motor imagery (Moseley, 2006). It has been suggested that phantom limb pain is caused by motor cortex dysfunction that is the result of dissociation between motor and sensory representations (Karl *et al.*, 2001; Sumitani *et al.*, 2010). Through motor training, phantom-limb patients may decrease their pain, presumably by resetting these altered sensory–motor dissociations. Recent work has indicated that mirror movement differentially activates the sensory cortex in amputees with and without phantom pain, further implicating altered functional connectivity (Diers *et al.*, 2010). Related to this is the use of smart limb prosthetics (Marasco *et al.*, 2011) or sensory feedback that may utilize sensory motor feedback loops to decrease phantom limb pain (Weiss *et al.*, 1999; Flor, 2002).

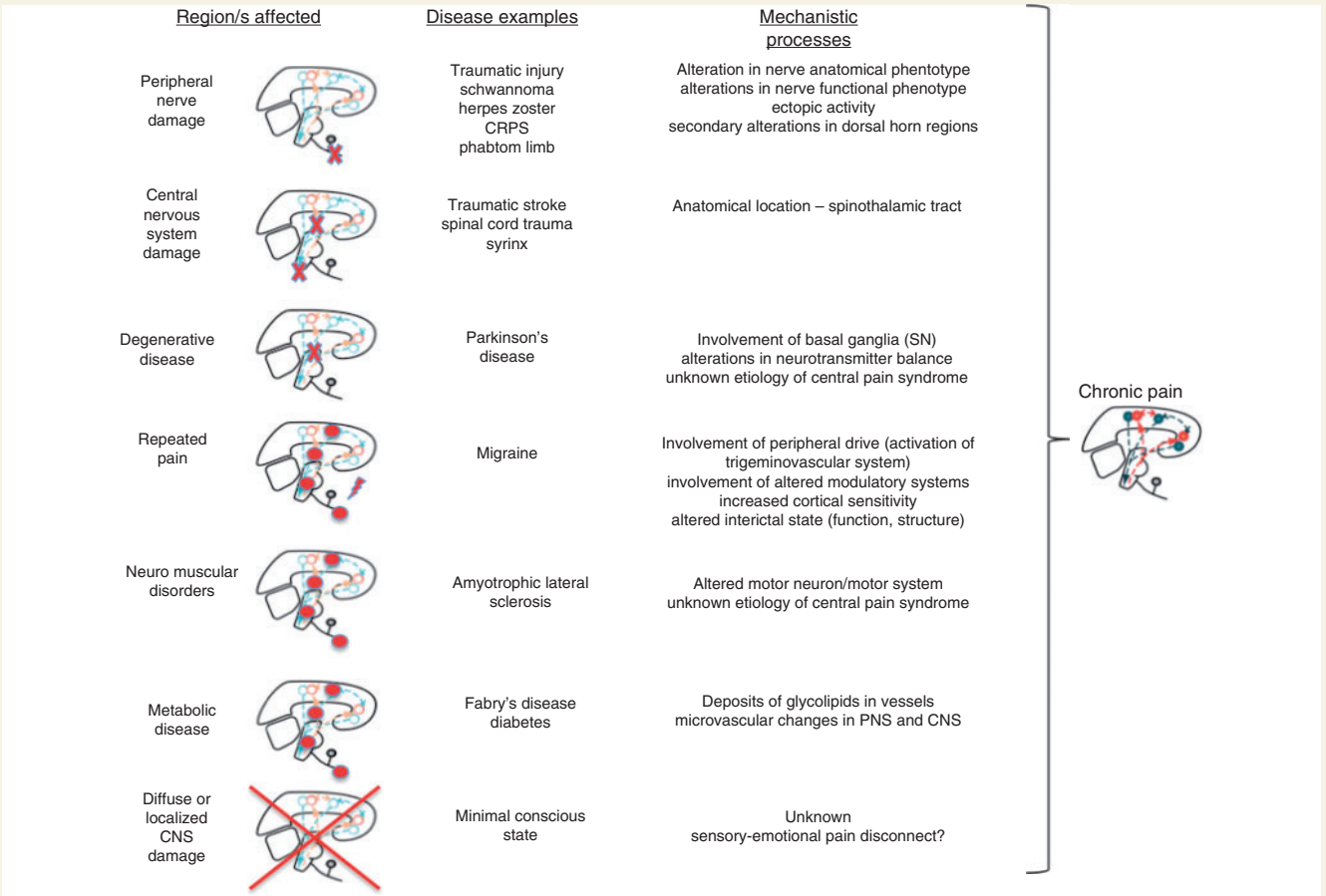

Figure 5 Schematic of altered pain processing in neurological disease. The figure summarizes altered pain processing in examples of neurological disease, as well as underlying mechanisms that contribute to chronic disease-related pain. In most diseases, multiple regions are affected (as opposed to secondary effects such as centralization of pain following a peripheral nerve injury). Whether or not the disease is a primary or secondary cause of pain, pain itself drives an altered brain state (Fig. 1). Damage anywhere along the pain pathway from peripheral nerve to spinothalamic tracts and more central pathways including thalamus and thalamocortical projections may result in neuropathic pain. In the figure, damage as indicated by red crosses or abnormal activation in pain pathways (circles), contributes to other changes in brain systems.

Brain 'shocks'—insights into pain control

Electroconvulsive therapy has been suggested to be of use in chronic neurological diseases such as Parkinson's disease—on both psychiatric manifestations and motor systems (Popeo and Kellner, 2009). Electroconvulsive therapy has also been recommended for chronic pain (Fukui *et al.*, 2002; Wasan *et al.*, 2004; Usui *et al.*, 2006; Suda *et al.*, 2008; Suzuki *et al.*, 2009). Thalamic blood flow is reportedly normalized following electroconvulsive therapy in patients with CRPS (Fukui *et al.*, 2002). The interesting application in many of the neurological orders discussed relates to electroconvulsive therapy's strong antidepressant effects (Merkl *et al.*, 2009), mitigating the use of medications that may produce side-effects.

A possible chemical 'equivalent' of electroconvulsive therapy is the N-Methyl-D-aspartic acid (NMDA) antagonist ketamine. Ketamine has been used to treat chronic pain and depression (Berman *et al.*, 2000; Zarate *et al.*, 2006). In chronic pain, higher doses seem to be more effective and reports have suggested that very high or continued dosing (anaesthetic levels) may reverse conditions such as CRPS (Kiefer *et al.*, 2007; Becerra *et al.*, 2009*b*). Indeed in uncontrolled trials, anaesthetic levels of ketamine reversed pain in 20 patients with chronic pain, producing complete relief in all patients at 1 month; pain relief persisted in 17 of these patients at 3 months, and in 16 at 6 months (Kiefer *et al.*, 2008). Clearly, controlled trials are required to verify these findings, but they raise the exciting possibility that ketamine alters brain systems in a significant manner in a highly resistant population. It remains unclear if the changes are the result of 'reordering' or resetting neural networks or of ketamine-induced lesions at a cellular level that somehow result in recovery. This approach is clearly not recommended in patients with neurodegenerative disease, particularly those with hyperexcitability-related pathogenesis, in which ketamine could potentially exacerbate ongoing neurotoxicity.

Central nervous system lesions—do they inform us more than they provide effective pain control?

Neurosurgical approaches have included stereotaxic surgery (Weigel and Krauss, 2004) and high intensity focused ultrasound of various brain structures including the thalamus (Martin *et al.*, 2009). Cingulotomy is perhaps the classic neurosurgical ablative technique reported to provide pain control (Wilkinson *et al.*, 1999), but like other neurosurgical procedures for pain, claims for its efficacy are based on class III evidence (i.e. possibly effective) (Cetas *et al.*, 2008). Subjects report 'the pain is the same but they don't care', consistent with the proposed role for the cingulate cortex in rank ordering the salience of incoming stimuli in animal (LaGraize *et al.*, 2006) and human studies (Williams *et al.*, 2004). Following cingulotomy (for a non-pain disorder), pain affect in response to noxious heat and cold was altered (Davis *et al.*, 1994), suggesting that either this area is involved in suppression of pain affect or involved in rank ordering stimulus salience (De Martino *et al.*, 2009). In patients undergoing cingulotomy, microelectode single unit measures of cingulate neurons following reward-based stimuli revealed decrease in neuronal activity predicting movement. However, following ablation, patients made more errors (Williams *et al.*, 2004). Morphine has been postulated to have a similar effect on modulation of affect by the cingulate cortex (LaGraize *et al.*, 2006). Clearly any lesion of the brain will alter the dynamics of brain function both at a local (brain region) and at a systems level (through afferent and efferent connections)

Brain stimulation

Stimulation techniques, whether extracranial (e.g. transcranial magnetic stimulation) or intracranial (deep brain stimulation or motor cortex stimulation), have the benefit of being reversible. Although small case studies of deep brain stimulation reported successful outcomes (Owen *et al.*, 2006), these were not prospective. A meta-analysis of deep brain stimulation for pain (Bittar *et al.*, 2005) reported that the long-term pain alleviation rate was highest with deep brain stimulation of the periventricular/periaqueductal grey matter (79%), or the periventricular/periaqueductal grey matter plus sensory thalamus/internal capsule (87%). Stimulation of the sensory thalamus alone was less effective (58% long-term success) (Bittar *et al.*, 2005). In the same meta-analysis, stimulation was successful in ~50% of those with post-stroke pain, and 58% of patients permanently implanted with deep brain stimulation devices achieved ongoing pain relief. Even higher rates of success were seen with phantom limb pain and neuropathies. To date, stimulation sites have included the ventroposterolateral thalamus and the periaqueductal grey region. Motor cortex stimulation has been proposed for the treatment of chronic pain (Lefaucheur *et al.*, 2009). Deep brain stimulation of the subthalamic nucleus has had a landmark effect in Parkinson's disease, but its effects on pain processing also seem potentially useful. In one study, chronic pain was reduced following deep brain stimulation, but pain sensitivity to quantitative sensory testing was unaltered (Gierthmuhlen *et al.*, 2010). In another study, early pain relief was observed in 20 of 23 patients (Kim *et al.*, 2008). Neuroimaging studies have suggested that deep brain stimulation targeting the ipsilateral posterior inferior hypothalamus might be effective for chronic cluster headache; this is now an established treatment for intractable cases (Leone, 2006; Leone *et al.*, 2008).

Motor cortex stimulation is another intracranial approach that has been used to treat refractory neuropathic pain (Lefaucheur *et al.*, 2009) with substantial effects (48% of subjects reported decreased pain intensity). In a 4-year outcome evaluation, 10% of subjects rated the benefit as excellent (>70% pain relief), 42% as good (40–69% relief), 35% as poor (10–39%) and 13% as negligible (0–9%). Intake of analgesic drugs was decreased in 52% of patients in this study (Nuti *et al.*, 2005). Given the interactions between sensory and motor systems and the fact that pain may inhibit motor cortex function (patients may limit their movement) (Farina *et al.*, 2003), such motor function-based approaches may 'unglue' the status quo via mechanisms that may include activation of corticobasal ganglia thalamic loops or modulation of the pain.

A relatively recent approach is the use of transcranial magnetic stimulation for chronic pain (Lefaucheur, 2008), migraine (Lipton and Pearlman, 2010), spinal cord injury pain (Defrin *et al.*, 2007) and traumatic neuropathic pain (Schwenkreis *et al.*, 2010). Transcranial magnetic stimulation is currently US Food and Drug Administration (FDA) approved for depression (Schonfeldt-Lecuona *et al.*, 2010). Experimental use in neurological diseases including Alzheimer's disease (Bentwich *et al.*, 2011) and Huntington's disease (Medina and Tunez, 2010) suggests transcranial magnetic stimulation can induce improvement in some features of these diseases, including depression. In Parkinson's disease (Baumer *et al.*, 2009), cerebellar stimulation resets or improves tremor (Ni *et al.*, 2010), suggesting that transcranial magnetic stimulation may have long-lasting effects on cerebellar outputs/cortical excitability (Popa *et al.*, 2010). Further studies are needed to determine its potential clinical utility in neurological diseases with pain.

Centrally active drugs developed for neurological disease and their potential role in pain therapeutics

Specific pharmacotherapies developed for many of these neurological conditions have been assessed for their ability to treat chronic pain (Finnerup *et al.*, 2010; Haanpaa *et al.*, 2011). The most notably successful are the anti-epilepsy drugs, but antidepressants, membrane stabilizers and opioids have also been used to treat chronic pain, with varying levels of success. Given our new understanding that alterations in grey matter volume correlate with chronic pain, recent trials have investigated drugs with the potential to modify putative underlying disease mechanisms. The major categories of drugs that have been assayed are neuroprotectants, including the excitatory neurotransmitter antagonists (e.g. NMDA), and agonists of inhibitory neurotransmitter systems (e.g. γ-aminobutyric acid, glycine). Examples of

cross-use of therapies for neurological disease in chronic/neuropathic pain are provided below.

Amantidine is a drug originally used in Parkinson's disease. A derivative, memantine, an NMDA antagonist, has been marketed for treatment of Alzheimer's disease and other neurodegenerative disorders (Sonkusare *et al.*, 2005) and has been in trials for use in chronic neuropathic pain. Another example, D-cycloserine, an antibiotic, is a partial agonist of the NMDA receptor. It has been used in preclinical models of CNS degeneration (Ogawa *et al.*, 2003) as well as neuropathic pain, and affects limbic circuitry in rats (Millecamps *et al.*, 2007). Riluzole, an FDA-approved drug for the treatment of amyotrophic lateral sclerosis, can reverse pain behaviour in spinal cord injured rats (Hama and Sagen, 2010). It is thought to act by inhibiting glutamate release. Other examples of therapies directed at primary neurological disease that may be useful for pain include: (i) minocycline, a microglial inhibitor that may be a neuroprotective agent. It has been used in preclinical models of Huntington's disease (Smith *et al.*, 2003) but has some effects in pain models as well (Chang and Waxman, 2010); (ii) propentofylline, a unique methylxanthine with clear cyclic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, phosphodiesterase and adenosine actions, which have neuroprotective and anti-inflammatory effects. It has effects in a number of preclinical CNS-related disease models including chronic pain (Sweitzer and De Leo, 2011).

Smart treatments—targeting through localized delivery

The use of CT or MRI to direct delivery of small amounts of drugs to specific regions or nerves for pain control is gaining increased attention in preclinical models. The amount of drug delivered is small enough that it has no systemic effect. For example, when injected into a nerve in very small quantities, adriamycin can provide pain relief through retrograde transport and killing of the dorsal root ganglion cells of the specific nerves affected (Grant *et al.*, 2008). Another example is the use of small volumes of agents that specifically knock out C-pain fibres. One such agent is resniferatoxin, a capsaicin analogue that inactivates sensory neurons by binding to the vanilloid (TRPV1) receptor and producing a calcium influx (Bates *et al.*, 2010). Although clearly not a preferred solution since it destroys the sensory neurons, targeted delivery of such an agent may be used to control pain in certain conditions, such as cancer affecting the face, when other efforts have failed. Another possible future application of this kind of approach is the targeted treatment of schwannomas based on newly defined preclinical developments (Saydam *et al.*, 2011).

Smarter tools for objective diagnosis of pain

A major issue in pain diagnosis and research is the lack of an objective measurement of pain. Even in patients able to report subjective pain ratings, these are clearly insufficient (Victor *et al.*, 2008; Lin *et al.*, 2011). In cases where patients cannot communicate, the problem is even more complex. There is an urgent need to develop biomarkers for pain. The search for reliable markers of chronic pain has focused on a number of approaches. These include clinical questionnaires (see below) and screening tools such as painDETECT (Freynhagen *et al.*, 2006; Scholz *et al.*, 2009), psychophysical measures (Jaaskelainen *et al.*, 2005; Arendt-Nielsen and Yarnitsky, 2009; Serra, 2010), and potentially, imaging (Borsook *et al.*, 2011*a*, *b*). Questionnaires that have been used in the evaluation of chronic pain attempt to also determine changes that occur in addition to changes in pain intensity [e.g. Leeds Assessment of Neuropathic Symptoms and Signs (LANSS); Neuropathic Pain Questionnaire (NPQ)] as summarized by Bennett *et al*. (2007). Tools adopted from the psychiatric literature, which can be used to evaluate other dimensions of chronic pain, including quality of life, depression, anxiety, catastrophizing and drug-abuse potential, are being included in chronic pain evaluation because of the multi-dimensional nature of the condition (Haythornthwaite, 2010). In addition, psychophysical/neurophysiological measures such as quantitative sensory testing continue to provide additional information on a subject's pain (Jaaskelainen, 2004). These neurophysiological approaches aim to provide a differentiated assessment based on underlying pathophysiology that may include measures of sensitization, abnormal fibre type, sensory loss etc. Given the multidimensional effects of pain on behaviour, inputs on psychological/psychiatric alterations in patients with chronic pain (Borsook *et al.*, 2007; Elman *et al.*, 2011) would probably improve outcomes. Few of these assessment tools are routinely used in current clinical settings.

Aside from diffusion tensor imaging that is currently employed in many institutions to evaluate alterations in white matter integrity, two current imaging technologies may soon be in the clinic for evaluation of patients with pain. The first is measures of grey matter and the second is resting state networks. A defining article by Apkarian *et al.* (2004) reported loss of grey matter in the thalamus and dorsolateral prefrontal cortex in patients with chronic back pain. Since then a number of groups have reported such changes in various neurological conditions including trigeminal neuropathy (DaSilva *et al.*, 2008) and migraine (May, 2009). While it is not yet well-understood, the finding that the grey matter changes revert towards normal with treatment is highly intriguing (Rodriguez-Raecke *et al.*, 2009; Seminowicz *et al.*, 2011). One potential mechanism that has been evaluated in pain models relates to dendritic sprouting/branching and loss (Metz *et al*., 2009). A second approach with potential utility in the clinic is evaluation of resting state networks (Greicius *et al.*, 2009; Uddin *et al.*, 2009). Such networks can differ in disease states (Chen *et al.*, 2011) or drug effects (Boveroux *et al.*, 2010) and may provide a signature for specific pain syndromes such as back pain (Balenzuela *et al*., 2010) or diabetic neuropathy (Cauda *et al*., 2010), fibromyalgia (Napadow *et al*., 2010) or may at least objectively differentiate pain from non-painful conditions. If methodological issues can be ironed out in terms of how best to evaluate the multiple resting state networks of health and disease, the approach is potentially of high value in the clinic as it does not require any intervention with patients during scanning procedures.

Figure 5 summarizes integrative approaches for evaluating pain. Of these, imaging has taken the stage in its ability to evaluate

functional, morphological and chemical changes in disease states and provide a new window of understanding disease neurobiology related to chronic pain. Having markers for chronic pain would allow for a specific diagnosis of pain and for measures of clinical efficacy (given that the current success rates of analgesics for chronic pain are ~30%). The successful development of drug (analgesic) and disease (neuropathic pain) brain signatures and subsequently the validation as biomarkers would allow for objective indices for clinical drug development and for clinical practice. Since brain action provides a basis for behaviour (pain or analgesia) brain imaging holds the promise of defining potential makers that would need to then be shown to be sensitive, reproducible, validated and subsequently adopted by clinicians and regulatory agencies. A number of recent reviews have addressed the current state of imaging the brain state in pain and its potential in providing objective measures of drug and other therapeutic measures (Tracey and Mantyh, 2007; Apkarian, 2008; Borsook and Becerra, 2010).

Conclusions

Pain is common in neurological diseases affecting diverse parts of the PNS and the CNS (Fig. 5) that may have subsequent effects on altered brain circuitry and result in pain. Most neurologists treat patients with chronic pain, but few specialize in the discipline. In fact, when neurologists rate their preference for treating diseases, chronic pain ranks low (with the exception of migraine, which ranks high) (Evans and Evans, 2010). The reasons for this may include: (i) lack of formal training in pain management (Galer *et al.*, 1999); (ii) the fact that pain clinics treat such a broad spectrum of syndromes (with the exception of those treating conditions such as migraine); (iii) a sense that there are few viable treatment options; (iv) the notion that patients with chronic pain are complex to deal with; or (v) the lack of financial incentive.

Thus, there is a high unmet need for chronic pain treatment and for more research into the underlying mechanisms of pain diseases. With current technological advances and investigation into mechanism-based treatment approaches (Finnerup, 2008), we are at a critical juncture in pain research. However, progress will remain slow unless we fully recognize pain as a brain disease and increase the involvement of neurologists in the treatment of and research into chronic pain. The first step towards this goal is to include a comprehensive survey of pain conditions, management and research as part of the standard training of new neurologists.

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