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The deeper you look, the more you realize just how much we do not understand about pain. For those who favour the simple feed-forward model, three observations need to be considered. First, there is no ‘pain cortex’: even though regions light up beautifully and reproducibly in response to pain during functional brain imaging experiments, direct stimulation of any single cortical region fails reliably to reproduce the sensation of pain (see Mazzola et al., 2012: page 640 in this issue). Secondly, information travels the wrong way: a recent study of placebo analgesia showed modulation of activity primarily in the dorsal horn (Eippert...
et al., 2009), indicating that beliefs concerning the higher-order modulation of pain may depend as much on the spinal cord as our prefrontal cortex. Lastly, lesions of the classical pain pathway (such as peripheral nerve, spinal cord or thalamus) often result in chronic pain not chronic analgesia (see Borsook, 2012: page 320 in this issue). Based on a pain system that must involve reciprocally connected, multiple and multi-level regions of the nervous system, theories of chronic pain seem ever more elusive.

Given the state of ignorance, therefore, new insights into the pathogenesis of chronic pain are sorely needed. What is essential is an account of how the system (mal)adapts in patients with chronic pain: that is, a neurophysiological account of the dynamic mechanisms of plasticity that take place at different levels of the neuroaxis in response to injury. This issue of Brain reports two studies that mark important additions to our knowledge. Both relate to how increased neuronal excitability might develop in certain circumstances and thereby predispose to chronic pain.

Zeilig and colleagues (2012; see page 418) present longitudinal clinical neurophysiological data from a population of patients who suffered acute lesions of the spinal cord (for example, following a road traffic accident). Their aim is to identify physiological predictors for the subsequent development of chronic pain—which followed injury in roughly half the patients, typically within a few months. What they find is that patients who display a phenotype of progressive allodynia and hyperpathia, in concert with a reduced ability to detect thermal threshold stimuli in the weeks following injury, tend to be those who go on to develop clinically significant pain. This suggests that a damaged spinothalamic tract is accompanied by nociceptive hypersensitivity stemming from the lesion; and, if severe enough, this predicts the subsequent development of a chronic pain state. This is not merely a non-specific increase in ‘gain’ of the system, since function above the level of the lesion remains normal.

This result is important for two reasons: first, it shows that hyperactivity within localized regions of the pain system precedes chronic pain; something which had often been hypothesized, but not previously shown. Secondly, it allows the identification of patients for whom preventative treatments can be considered.

Beggs and colleagues (see page 404) present a very different type of maladaptation: so-called ‘neuro-immune priming’. The work represents the next chapter of what has been one of the most intriguing research areas in chronic pain: the idea that neonatal pain exposure may cause fundamental and long-term changes in pain pathways, which result in susceptibility to chronic pain in adult life (Anand and Hickey, 1987; Ruda et al., 2000). The notion of a ‘critical period’ of plasticity is well-recognized in other sensory modalities, but pain is not much like other sensory modalities. Although well-controlled epidemiological studies have been difficult to come by, there is an emerging literature in clinical populations that suggests that there may be some truth in the hypothesis—for instance, school-aged children who required intensive-care treatment as infants were recently found to have both enhanced behavioural and neurophysiological responses to pain (Hohmeister et al., 2010).

As a result, there has been fervent interest in the possible structural changes that underlie this effect. However, Beggs and colleagues (2012) focus on a different possibility—that altered neuroimmune responses amplify the normal mechanisms of post-injury central sensitization in the dorsal horn. This draws on increasing evidence that neuroglial interactions play a role in chronic pain (Gosselin et al., 2010). Here, the authors administered small hindpaw injuries (skin incisions) to newborn rats, and then studied the behavioural and dorsal horn inflammatory response to a similar injury during adulthood. They show amplified microglial responses in the neonatal injury group, mirrored by increased hyperalgesia. Administration of minocycline (which inhibits microglial activity) into the dorsal horn selectively reduced hyperalgesia, compared to controls, thereby implicating primed neuroimmune coupling in mediating the enhanced hyperalgesic response.

This is fascinating, since it provides clear evidence for a neuroimmune ‘memory’ that extends from the neonatal period into adulthood; and further demonstrates the existence and complexity of mechanisms underlying a critical period of plasticity in the pain system. The result is clinically interesting since although neonatal injury alone might have only a subtle effect on adult pain (which seems to be the case), it may predispose to chronic pain due to other causes later in life—something that has been less well studied.

Ultimately, chronic pain remains widespread and enormously difficult to treat across clinical specialties. But an understanding of its diverse pathogenesis is especially important to neurologists, since highly specific phenotypes of chronic pain arise as a complication of a wide variety of neurological diseases. David Borsook (see page 320) presents an excellent translational review of this topic, in which the startling frequency by which chronic pain exists in many disorders not commonly linked with pain is also highlighted.

Borsook also notes an important quasi-philosophical problem: pain is an inherently private experience, and the physician has no way of getting inside the patients’ minds to know exactly what they are feeling. It is difficult to underestimate how much of a problem this really is; doctors often have a morbid fear of being tricked by patients for secondary gain. When this reserve is coupled with the complex phenomenology of pain, the not infrequent difficulty of relating pain to identifiable lesions of the nervous system, and the refractory nature of many pain disorders, it is no surprise that pain often becomes chronic and intractable. Two things may relieve this impasse in the future: new neurophysiological methods that correlate objective data with the experience of pain [such as structural and functional imaging (Apkarian et al., 2004; Baliki et al., 2010)]; and a better understanding and ability to predict when chronic pain is likely to occur. In each respect, papers on pain in the current issue represent a welcome advance in our understanding of why chronic and pathological pain may replace the physiological processes that serve normally to protect us from injury.

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Migraine is a common, complex and certainly fascinating disorder of the brain (Lipton et al., 2001; Goadsby et al., 2002), which most active clinicians would agree needs more treatments (Goadsby and Sperner, 2010). Over the last two decades we have seen substantial advances in migraine therapeutics with the development of triptans, serotonin 5-HT_{1B/1D} receptor agonists (Ferrari et al., 2001), gepants, calcitonin gene-related peptide (CGRP) receptor antagonists (Ho et al., 2010), and most recently ditans, serotonin 5-HT_{1F} receptor agonists (Ferrari et al., 2010). Each targets, among other sites the trigeminovascular system, the trigeminal afferent innervation of the pain-producing meninges (Feindel et al., 1960; McNaughton and Feindel, 1977) that projects to second order afferents in the trigeminocervical complex (Akerman et al., 2011). This issue of *Brain* illustrates yet another target, weaving a very engaging tale of biology, herbalism and therapeutics (Nassini et al., 2012).

Nassini and colleagues (2012) studied a candidate compound, the monoterpane ketone umbellulone, a volatile component of the leaves of the California Bay Laurel (*Umbellularia californica*). The tree is said by the authors to be a ‘headache tree’ since inhalation of its vapours can cause headache, a story reminiscent of the origins (Laws, 1898) of the now well established concepts on the role of nitric oxide in migraine (Thomsen and Olesen, 2001). It is remarkable that the tree is said to both headache provoking, and used to relieve headache by binding the leaves and twigs around the head (Barrett and Gifford, 1933). The latter fact is cited by Wikipedia on the same page that already cites Nassini and colleagues (http://en.wikipedia.org/wiki/Umbellularia), a sobering thought concerning the modern dissemination of knowledge. The authors then set out to study what umbellulone may target to produce headache.

They hypothesized, based on its rapid binding of thiols, an action on the transient receptor potential ankyrin 1 (TRPA1) channel located on peptidergic, nociceptive trigeminovascular neurons. TRPA1 is part of the temperature-sensitive transient receptor (release) potential (TRP) ion channel family (Story et al., 2003), which is crucially involved in thermal detection. First identified by the pioneering work of Julius and colleagues, the capsaicin receptor was heat-activated (Caterina et al., 1997), and called the vanilloid receptor, before being renamed the TRPV1 receptor. It has been known for some time that these receptors are involved in pain as well as thermal sensation (Tominaga et al., 1998). Of the nearly 30 TRP channels, eight sense hot or warm temperatures (TRPV1–4, TRPM2, 4 and 5) and two are activated by cold (TRPA1 and TRPM8), covering a remarkable range of temperatures from 10°C to 53°C (Ramsey et al., 2006).

The TRPV1 channel has been considered as a therapeutic target in migraine (Levy, 1995) and cluster headache (Sicuteri et al., 1989; Fusco et al., 1994), although effective blinding of studies has been very problematic (Marks et al., 1993). Moreover, using an antagonist approach with SB-705498 (Rami et al., 2006), which was not found useful in the laboratory using a different compound (Summ et al., 2011), a clinical trial was conducted (http://clinicaltrials.gov/ct2/show/NCT00269022), which seems to have been finished for more than 2 years without any announcement or progress report—it seems likely to have failed. On this background the new findings are all the more encouraging and exciting.

Nassini et al. (2012) show that umbellulone selectively activates the TRPA1 channel as expressed in HEK293 cells but not in untransfected cells. They describe activation of rat trigeminal ganglion neurons that can be blocked by the TRPA1 receptor.