The Neurobiology of Chronic Pain in Children

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Maria Fitzgerald

Keywords
Nociceptor • Central sensitization • Cortex and chronic pain • Dorsal horn • Early pain exposure and long term effects

Chronic pain arises from plastic changes in the peripheral and central nervous system. These changes are triggered and may be maintained by an insult to tissues, organs or to the nervous system itself. Because neural connections within the sensory and nociceptive systems have been altered, pain can take on a 'life of its own' and no longer require the presence of tissue damage. As a result, chronic pain will often persist beyond the resolution of the original injury. Thus, chronic pain has a clear biological origin, but that origin lies within the nervous system itself and if we are to prevent or treat it effectively, we need to understand these neural changes. The poor pain recovery following the resolution of a physical insult can lead to the conclusion that patients, especially children, are catastrophizing or have aberrant health beliefs, while in fact defined neurobiological changes in neural pain pathways are the source of the problem.

M. Fitzgerald (✉)
Department of Neuroscience, Physiology and Pharmacology, University College London, London, UK
e-mail: m.fitzgerald@ucl.ac.uk

Chronic Pain Mechanisms

Neural Plasticity and Chronic Pain

Several excellent reviews cover the neural basis of chronic pain in adults (Woolf 2004; Latremoliere and Woolf 2009; Costigan et al. 2009; Sandkuhler 2009). These reviews explain the biological basis for long-lasting changes that can occur in pain pathways following a peripheral trauma. Many of these reviews focus on trauma that involves damage to a peripheral nerve which can result in neuropathic pain, a particularly unpleasant chronic pain which is especially difficult to treat. Figures 2.1–2.3 illustrate some of the key changes that occur in the peripheral and central nervous system following tissue injury that contribute to chronic pain. Figure 2.1 shows how prolonged activation or sensitization of nociceptor and mechanosensitive sensory neurons can arise from the local peripheral immune reaction and release of cytokines, increased sympathetic activity within the dorsal root ganglion and upregulation of ion channels and receptor molecules in the cell bodies and terminals of damaged sensory neurons. All these changes cause increased action potentials or altered

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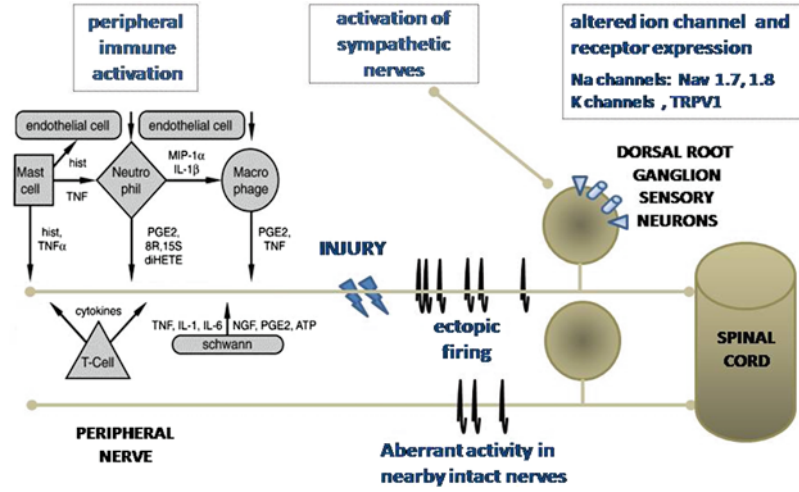

Fig. 2.1 Peripheral events that contribute to the generation and maintenance of chronic pain following nerve injury

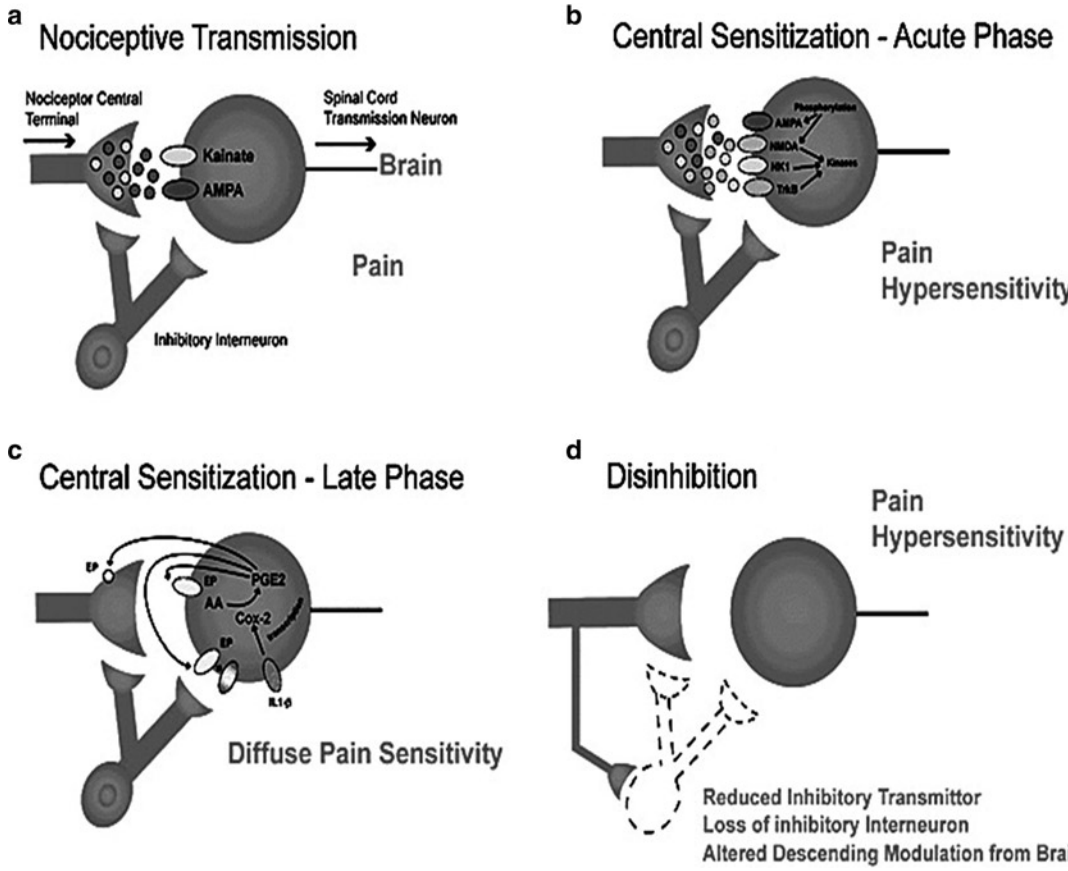

Fig. 2.2 Different synaptic mechansims underlying nociception, acute and chronic pain. (**a**) Normal nociceptive transmission in the spinal cord is carried out by glutamate released from central nociceptive terminals acting on AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) and NMDA (*N*-methyl-d-aspartic acid) receptors on central sensory neurons, controlled by inhibitory neurons. (**b**) Strong nociceptor input, such as follows tissue trauma, involves other neurotransmitter receptors, NK1 (neurokinin 1) and trkB (tyrosine kinase B) to activate intracellular kinases that phosphorylate ion channels and receptors, altering their distribution and function and increasing excitability and thereby pain sensitivity. (**c**) Longer lasting pain arises when changes in transcription in dorsal horn neurons occur, such as the induction of cyclooxygenase 2 (Cox-2) via interleukin (IL1β), arachidonic acid (AA) and prostaglandin E2 (PGE2) acting on prostaglandin receptors (EP). (**d**) After peripheral nerve lesions, there is also a reduction in the activity of inhibitory interneurons which increases nociceptive signals across the synapses (From Woolf 2004)

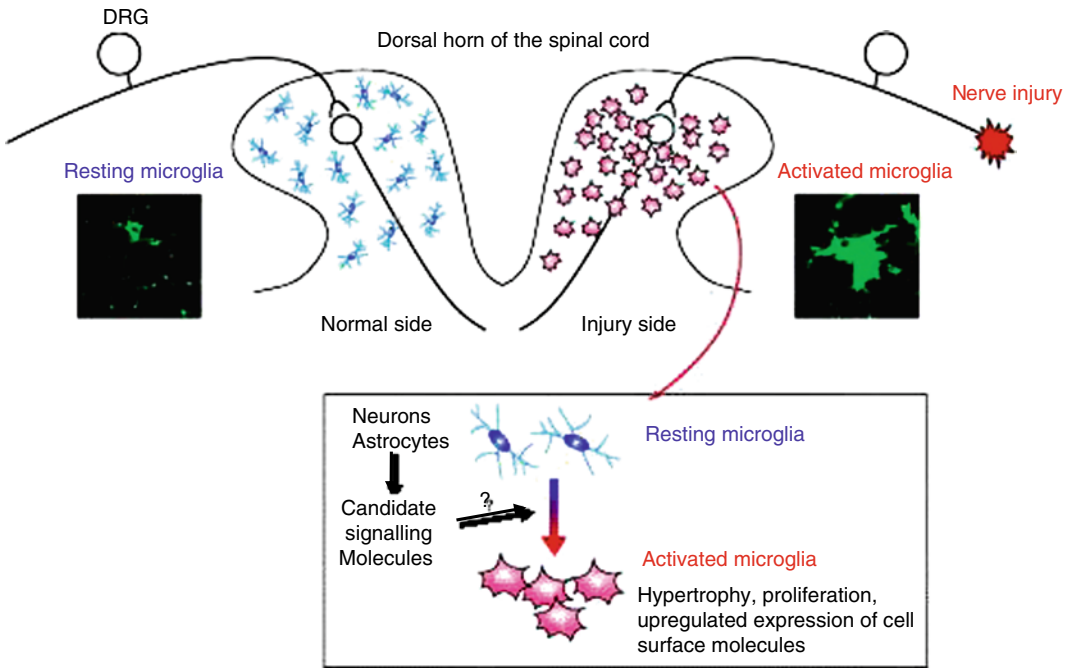

Fig. 2.3 Processes causing activation of microglia in the dorsal horn of the spinal cord following injury to a nerve in the periphery. On the normal side of dorsal horn, microglia have small somas, bearing thin and branched processes, and are homogeneously distributed (i.e. they are 'resting microglia'). After peripheral nerve injury, microglia in the spinal cord ipsilateral to the nerve injury transform from the resting to the 'activated microglia' phenotype, which is characterized by hypertrophy, proliferation and expression of cell-surface molecules (e.g. CR3, CB2, CD14, MHC proteins, TLR4 and the P2X4 receptor). Photographs show resting (*left*) and activated (*right*) microglia staining for CR3. Activation of microglia in the dorsal horn occurs predominantly in the central projection area of the injured peripheral nerve, which implies contribution of signals from injured nerve and/or affected dorsal horn neurons or astrocytes. Candidate signalling molecules include MCSF, IL-6, CD200, ATP, substance P and fractalkine (From Tsuda et al. 2005)

patterns of action potentials in the damaged nerves and in nearby undamaged nerves, which will, in turn, cause aberrant neuronal firing in the central nervous system (CSN) and pain.

Chronic pain also has a major central component. Unlike other sensory stimuli, relatively brief trains of activity in peripheral nociceptors have the ability to trigger long-term changes in CNS circuitry and cause prolonged states of hypersensitivity. This 'central sensitization' contributes to an amplification of the noxious input and a spread of pain into areas outside the original damaged region (hyperalgesia) and the onset of pain from normally innocuous stimuli (allodynia). The central sensitization arises from prolonged increases in membrane excitability, strengthened excitatory synaptic inputs, and reduction of inhibitory interneuronal activity, which in turn are regulated by shifts in gene expression, the production and trafficking of key receptors, channels and downstream neuronal signalling pathways. It may be relatively short-lasting but in cases of chronic pain, new mechanisms come into play that act to maintain this central sensitization for prolonged periods or even permanently. Figure 2.2 shows some of the mechanisms by which this can occur.

All these changes contribute to an increase in the number and pattern of action potentials generated by spinal nociceptive circuits which, when transmitted to higher centres in the brain, increase pain sensitivity.

Major Shifts in CNS Function in Chronic Pain

Recent evidence suggests that the cellular, synaptic and molecular events underlying central

sensitization and chronic pain, illustrated in Fig. 2.2, are driven by several major shifts in CNS function.

One shift is in the functional activity of pain-modulating circuits in the brainstem that normally control nociceptive processing in the spinal cord (Heinricher et al. 2009; Porreca et al. 2002; Gebhart 2004; Suzuki et al. 2004; Vanegas and Schaible 2004). A defined area of the medullary brainstem, called the rostroventral medulla (RVM), plays a key role in this descending brainstem control. The neurons in the region receive afferent input from spinal cord sensory projection neurons and, in turn, send projections back down to spinal sensory circuits, forming a powerful feedback loop. The RVM is itself controlled by higher brainstem and subcortical areas such as the periaqueductal grey (PAG), the amygdala and the hypothalamus, thus making it a strong candidate for mediating the modulatory effects of stress, attention and reward upon pain perception and behaviour. The ability of the RVM to suppress nociceptive transmission is well-documented but at some intensities and sites, stimulation of RVM can also be facilitatory. In normal animals, the balance of RVM descending control is inhibitory, but the situation changes in persistent pain states when the balance of RVM activity becomes facilitatory, probably due to a change in the balance of activity from sub-populations of RVM neurons. Thus, there is an altered balance of inhibition/facilitation or pro-nociceptive/anti-nociceptive mechanisms in chronic pain sates. Evidence for this has been found in both animal models and human imaging studies (Bingel and Tracey 2008). The potential importance of this cannot be overstated; normal CNS pain processing depends upon a system of endogenous control that modulates nociceptive activity through descending fibres and endogenous opioids that represent a homeostatic feedback mechanism of control. These descending and endogenous pain modulatory pathways controls are the mechanisms by which factors such as anticipation, distraction, suggestion, context and past experience can influence pain responses (Fairhurst et al. 2007). If the balance of this mechanism is shifted, then pain processing may effectively become ‘out of control’.

The second important shift is in the cellular immune system. While it is well-established that neuronal circuits are sensitized in chronic pain, it has recently become evident that central glia and immune cells also play a key role in chronic pain states (Scholz and Woolf 2007; Milligan and Watkins 2009; DeLeo et al. 2004; Tsuda et al. 2005). The CNS normally contains resident, quiescent, microglial cells, but tissue and nerve injury outside the CNS changes this situation. Resident microglia become swollen and activated and new microglia infiltrate and migrate through the neuropil to join them; all focused upon CNS areas of intense neural activity. Activation of microglia by chemokines, purines, cytokines and complement anaphylotoxins (DeLeo et al. 2004; Tsuda et al. 2005; DeLeo and Yezierski 2001; Watkins et al. 2001; Griffin et al. 2007) leads to release of signal molecules which alter excitability or synaptic transmission in the dorsal horn which leads to ongoing pain and hypersensitivity. As yet it is not known exactly what signals lead to central glial activation after injury and how exactly they cause pain, but there is no doubt that this is an important mechanism (Wei et al. 2008). Indeed it has been argued that neuropathic pain has many features of a neuroimmune disorder and that immunosuppression and blockade of the reciprocal signalling pathways between neuronal and non-neuronal cells may be a successful approach to the management of pain (Scholz and Woolf 2007).

The Cortex and Chronic Pain

Pain is an emotional/affective process requiring higher-level cortical activity. As such, the neural pathways under consideration go beyond circuits in the spinal cord and brain stem and require the involvement of specific regions of the cortex and other higher brain centres. Extensive research on the central mechanisms regarding the sensory-discriminative dimensions of pain have revealed a complex network of cortical and subcortical brain structures involved in the transmission and integration of pain, the so-called pain matrix, and there is evidence from imaging studies that chronic pain is associated with changes in this central matrix for pain processing (Bingel and Tracey 2008; Seifert and Maihofner 2009; Apkarian 2008). Chronic pain appears to involve

both structural and functional changes in the matrix. Thus, an important component of the pain involves a change in wiring of cortical networks in addition to and perhaps in consequence of the peripheral, spinal cord and brainstem plasticity described above (Zhuo 2008).

Individual Variation in Chronic Pain

Thus far the reader might be forgiven for concluding that everyone who suffers a peripheral injury, especially if it involves a peripheral nerve, will automatically develop maintained hypersensitivity and chronic pain. In reality this is not so. The individual variability in the incidence of chronic pain is very great. While acute post-operative pain is followed by persistent pain in 10–50% of individuals after common operations, chronic pain is severe in only about 2–10% of these patients (Kehlet et al. 2006). Striking interindividual variability in pain sensitivity, the propensity to develop chronic pain conditions and the response to analgesic manipulations, is currently a major focus of chronic pain research. The explanation is likely to be a classic genetic–environmental interaction; that is, the injury itself, an earlier history of injury (see below) and an innate propensity act together to increase the chance of an acute pain changing into a chronic one. The advances, problems and pitfalls of human pain genetic research have recently been discussed in an excellent review by Mogil (Lacroix-Fralish and Mogil 2009). The next few years will no doubt provide a clearer picture of the genetic components of chronic pain.

Much of our knowledge of chronic pain mechanisms is extrapolated from inbred rat and mouse strains, chosen for study because of behavioural signs of long-lasting mechanical hypersensitivity or allodynia, guarding or withdrawal of the affected area and behavioural anxiety and altered decision- making in the presence of tissue or nerve injury. While providing information on the physiology of pain, they cannot model the full human pain experience. The strengths and limitations of these animal models have been recently reviewed (Mogil 2009) and we should not forget, especially with respect to higher pain processing, that ‘a rat is not a monkey is not a human’ (Craig 2009).

Chronic Pain in Children

While the neurobiology of chronic pain in adults has been the subject of intensive research over the last two decades, the neural mechanisms underlying chronic pain in children have received little attention. Many of the neural mechanisms may be similar to those in adults, but the fundamental differences in the immature and mature pain systems suggest that a number of key differences are likely to arise in the incidence, pattern, time course and treatment of chronic pain in children. Paediatric pain pathways are not simply less efficient forms of adult pathways – they function differently, undergoing a series of transitional functional states before reaching maturity (Fitzgerald 2005). This affects nociceptive and acute pain (Fitzgerald and Walker 2009) and thus is likely to impact on the natural history of chronic pain in childhood as well.

Figure 2.4 shows a developmental time line for laboratory rats to help interpret data from young laboratory animals and translate the findings to children. It shows that data from the first two post-natal weeks in rats are likely to be relevant to human infancy, while post-natal day (P) 21–35 are especially relevant to childhood. It is taken from an excellent review that discusses how CNS developmental changes can be qualitative or quantitative in nature, involving gradual changes, rapid switches, or inverted U-shaped curves. Thus, single phenomena may be governed by different mechanisms at different ages in an ongoing process that does not end with puberty (McCutcheon and Marinelli 2009).

Below we focus on some developmental changes that occur over this period and which are likely to affect chronic pain.

Maturation of Brainstem Descending Control Systems

It has been known for some time from the study of young rats that there is little descending inhibitory tone from higher CNS centres in the first weeks of life and that no analgesia is produced from brainstem stimulation until post-natal day

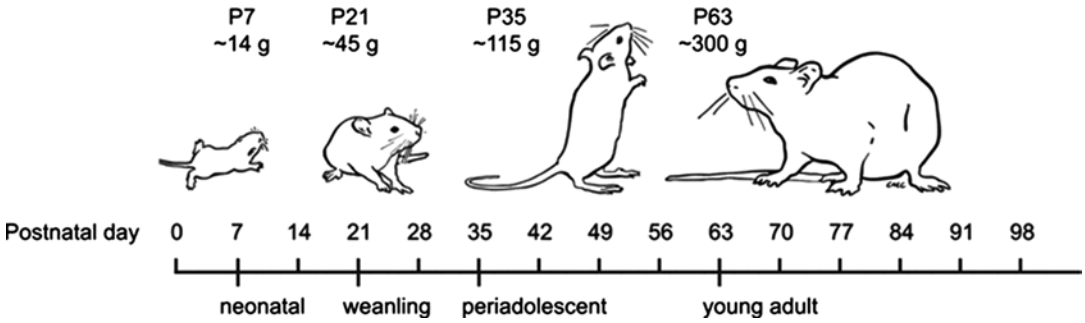

Fig. 2.4 Developmental stages of a laboratory rat (From McCutcheon and Marinelli 2009)

21 (P21) (van Praag and Frenk 1991; Fitzgerald and Koltzenburg 1986). Recent research has shown that the rostroventral medulla (RVM), which is the main output nucleus for brainstem descending control, undergoes a remarkable maturational switch after P2 (Hathway et al. 2009). Both lesioning and electrical stimulation of RVM at different post-natal ages reveal that RVM control over spinal nociceptive circuits switches from being entirely facilitatory before P21 to inhibitory at older ages. Between P25 and P35, descending inhibition begins to dominate but it is not as powerful as in the adult until P40. This gradual change is observed in the changing influence of the RVM over spinal nociceptive reflexes and dorsal horn neuronal activity over this critical periadolescent developmental period.

Childhood may therefore represent a time when the normal balance, rather than the absolute onset, of descending brainstem controls are established. A lack of balance or stability between inhibitory and excitatory supraspinal controls in early life may mean that young children are less able to mount effective endogenous control over noxious inputs compared to adults (Fig. 2.5).

Maturation of Neuroimmune Interactions

While microglia in the dorsal horn of adult animals contribute to the generation of neuropathic pain, through processes that involve their recruitment, proliferation and activation, laboratory data show that in the dorsal horn of young rats, the microglial response to peripheral nerve injury is considerably less than that in adults (Moss et al. 2007; Vega-Avelaira et al. 2007). This may contribute to differences in pain-like hypersensitivity in young and adult animals (Moss et al. 2007; Vega-Avelaira et al. 2007). The absence of a strong neuroimmune response in young animals is not due to a general inability of immature dorsal horn neurons to respond to immune activation. Microglial activation and significant allodynia can be evoked by spinal injections of lipopolysaccharide, glutamate receptor agonists or the intrathecal application of exogenous ATP stimulated microglia at young ages when peripheral nerve injury has no effect (Moss et al. 2007). These data suggest that the resident immune system in young animals is capable of activation but fails to do so in response to peripheral nerve injury. Neuropathic pain does appear to be less prevalent in young children compared to adults (Howard 2003; Howard et al. 2005) and this could be one reason why. The differing status of the immune system and its interactions with CNS neurons in the face of peripheral injury is likely to be an area of important research in children's chronic pain in the future (Fig. 2.6).

Maturation of Cortical Pain Processing

Pain is processed at the level of the cortex at a very young age. Specific cortical haemodynamic and electrical EEG responses can be recorded from pre-term and term infants in response to noxious heel lance suggesting that nociceptive connections

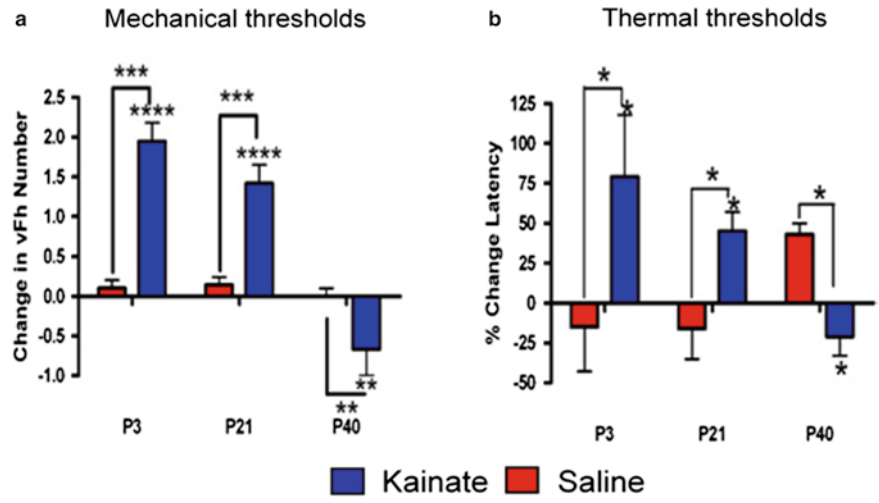

Fig. 2.5 Descending inhibition from the brainstem to the spinal cord. Excitotoxic lesioning of the rostroventral medulla (RVM) with kainate increases hindpaw mechanical and thermal thresholds in P3 and P21 rats but significantly decreases them in adult animals (P40). *Bars* indicate mean values ± s.e.m. $*P<0.05$, $**P<0.01$, $***P<0.001$ and $****P<0.0001$, $n=6$–12 in each group. *Asterisks* immediately above bars indicate significant change from baseline whilst those between bars indicate differences between open bars saline-treated and between filled bars kainate-treated animals within an age group (**a**) Mechanical thresholds, (**b**) Thermal thresholds (From Hathway et al. 2009)

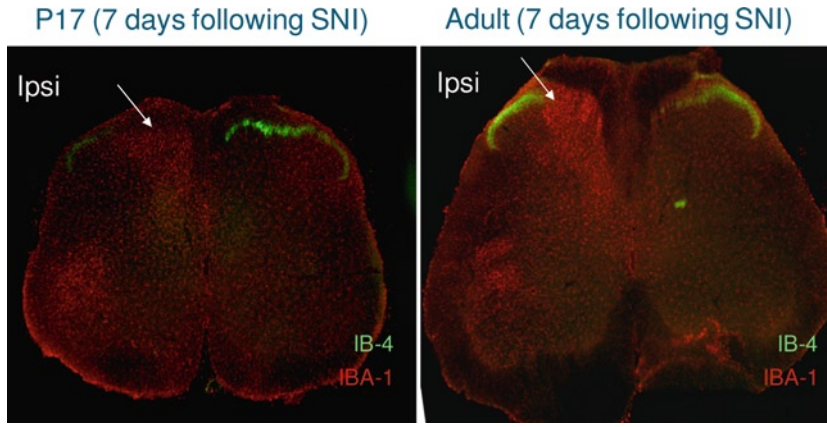

Fig. 2.6 Sections of rat lumbar spinal cord immunostained for microglia with IBA-1 (*red*) and C fibre terminals with IB-4 (*green*). In both cases the sciatic nerve on the left was cut 7 days earlier. *Left*: the nerve section was performed when the rat was 10 days old (P10). *Right*: the same lesion was performed in the adult rat. Note the great increase in microglia on the operated side in the adult but not the P10 rat (From Moss et al. 2007)

are formed with cortical neurons at an early stage (Slater et al. 2006, 2010). Nothing is known about the maturation of the pain matrix over infancy and childhood and it is not known whether chronic pain is processed centrally in young children in the same way that it is in adults.

There is evidence, however, that the presence of chronic pain does alter central processing in children as well as in adults. Two studies of cortical processing in children aged 10–15 years, one with migraine (Zohsel et al. 2008) and one with recurrent abdominal pain (Hermann et al. 2008) show evidence of an automatic attentional bias towards painful and potentially painful somatosensory stimuli. Such an attentional bias could constitute an important mechanism for these

pains becoming a chronic problem. Another study of paediatric patients with complex regional pain syndrome (CRPS) suggested significant changes in CNS circuitry had taken place. CNS activation in response to mechanical (brush) and thermal (cold) stimulation during an active period of pain (CRPS(+)) and after symptomatic recovery (CRPS(−)) was evaluated using fMRI. Stimuli were applied to the affected region of the involved limb and the corresponding mirror region of the unaffected limb. The data suggest pain-induced activation of endogenous pain modulatory systems in the children's brains which persist even after nearly complete elimination of evoked pain. In addition, the 'CRPS brain' responded differently to normal stimuli applied to unaffected regions (Lebel et al. 2008). Future fMRI studies in children with chronic pain will tell us more about cortical plasticity in response to acute and chronic pain in the developing brain and how it differs from the adult, although there are specific concerns related to the imaging of pain in children (Sava et al. 2009).

The Long Term Effects of Early Pain

One possible factor in the development of chronic pain is that there is already a 'memory trace' of pain, laid down perhaps at a younger age. While this is speculation at this stage, there is some epidemiological evidence to support it (Jones et al. 2009). What is becoming increasingly clear is that early pain experience does alter mechanical and thermal nociceptive pain thresholds and acute pain sensitivity in children when they have grown up (Hermann et al. 2006; Zohsel et al. 2006; Walker et al. 2009). A feature of the immature somatosensory and nociceptive system, in both animals and man, is that it is vulnerable to excessive noxious stimulation in early life (Fitzgerald 2005; Fitzgerald and Walker 2009; Schmelzle-Lubiecki et al. 2007). Exposure to pain early in life significantly impacts upon pain experience in childhood (Grunau et al. 2006). In animal models, long after an initial tissue damaging insult to cutaneous, subcutaneous or visceral tissue has healed, animals display a widespread reduction in their baseline noxious and innocuous sensitivity across the body combined with an enhanced hyperalgesia to repeat damage at the original site (Ren et al. 2004). The injury must be performed within the first weeks of life in order for this to occur. These data are supported by follow-up studies in children that have undergone intensive care procedures or surgery as neonates, who also display widespread hyposensitivity to noxious and innocuous stimuli accompanied by enhanced hyperalgesia and sensitization to inflammatory or surgical injury (Walker et al. 2009; Peters et al. 2005). The local hyperalgesia may arise from local peripheral or central sensitization, but the global threshold changes are likely to be centrally mediated. While the local hyperalgesia to repeat injury appears soon after the initial injury is performed, the global hyposensitivity is apparent only after the animal has reached its second month – which, interestingly, is exactly the time when the RVM switches its influence over the dorsal horn (Fig. 2.7).

Many of the post-natal developmental changes in nociceptive processing are dependent upon a normal balance of neural sensory activity and fail to occur if the patterns of activity are disrupted. In rat pups where spinal NMDA receptors are chronically blocked and in mutant mice where the CaMkIIα enzyme does not autophosphorylate, nociceptive processes remain immature (Beggs et al. 2002; Pattinson et al. 2006). Furthermore, maturation is delayed by blockade of low-threshold sensory afferents by peripheral anaesthetic (Waldenstrom et al. 2003) and is altered by tissue injury (Torsney and Fitzgerald 2003; Li et al. 2009). Thus dorsal horn nociceptive circuits are not fixed or preset at birth, but are in a plastic or transitory stage, responsive to the sensory experience (Granmo et al. 2008). In this way, early tissue injury may lead to changes in somatosensory processing, pain signalling and hence future analgesic responsiveness.

Both clinical and pre-clinical studies demonstrate the complexity and diversity of persistent changes in pain responses. It is too simplistic at this stage to expect that early pain experience will reliably increase the chance of developing chronic pain in childhood as multiple contributory factors may interact to influence nociceptive processing and/or the behavioural response to

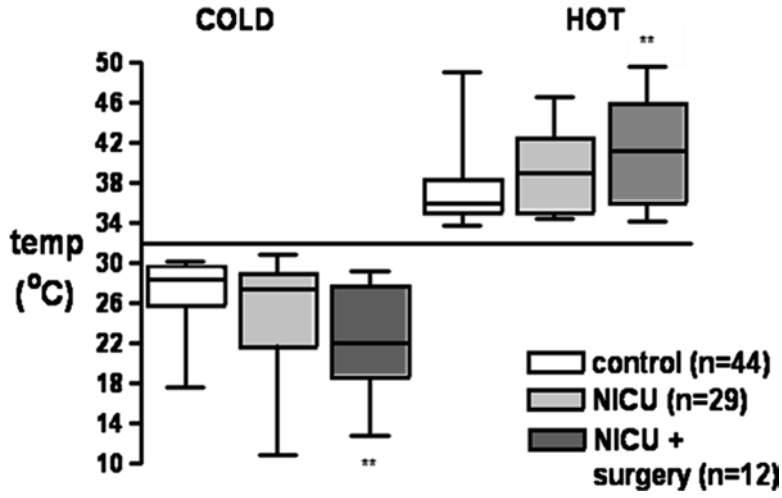

Fig. 2.7 Effect of neonatal surgery on the baseline thermal thresholds measured on the thenar eminence of 9–12-year-old children. The temperature at which the sensations of cold and hot (0 C) were perceived on the thenar eminence of the non-dominant hand are plotted for full-term control ($n=44$), extremely preterm children requiring neonatal intensive care (NICU) treatment ($n=29$) and extremely premature children who also underwent surgical operations in the neonatal period (NICU + surgery, $n=12$). $^{**}P<0.01$ one way ANOVA with Tukey's post hoc comparison (From Walker et al. 2009)

pain. Nevertheless, future neurobiological and clinical research into the relationship between past history and current pain in children will provide important insight into the long term plasticity that underlies chronic pain.

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