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LECTURE

The Bayliss–Starling Prize Lecture: The developmental physiology of spinal cord and cortical nociceptive circuits

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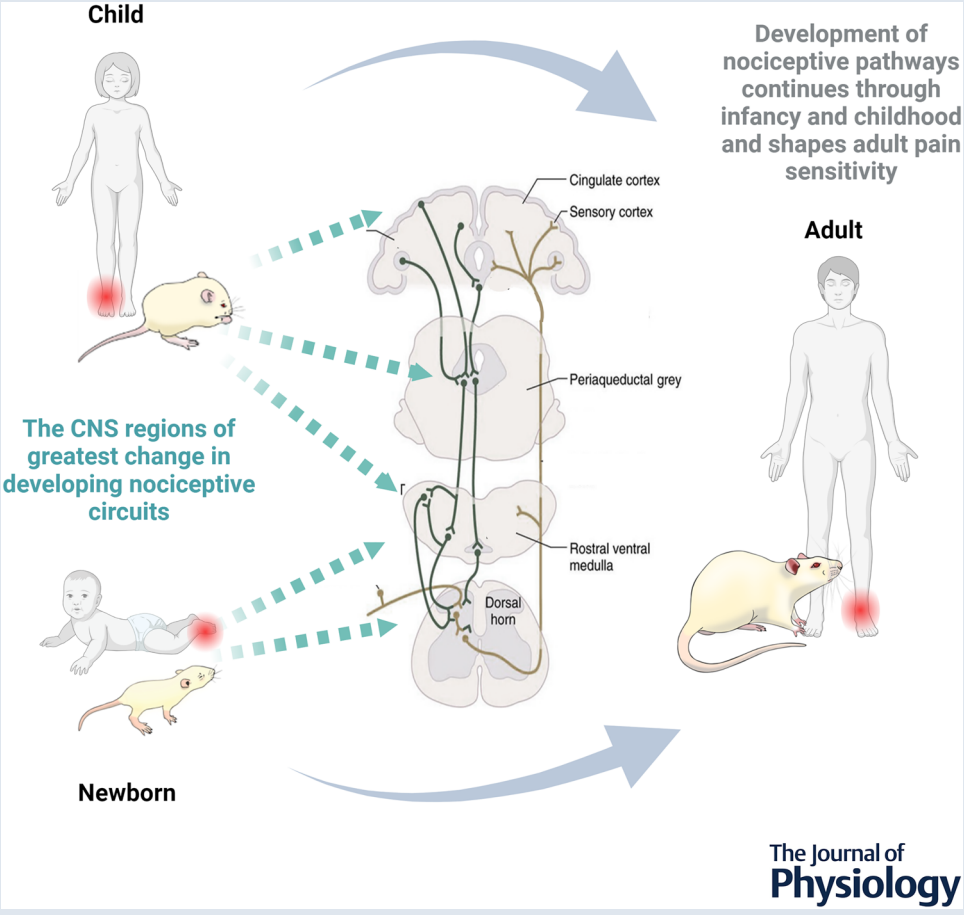

Abstract When do we first experience pain? To address this question, we need to know how the developing nervous system processes potential or real tissue-damaging stimuli in early life. In the newborn, nociception preserves life through reflex avoidance of tissue damage and engagement of parental help. Importantly, nociception also forms the starting point for experiencing and

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learning about pain and for setting the level of adult pain sensitivity. This review, which arose from the Bayliss–Starling Prize Lecture, focuses on the basic developmental neurophysiology of early nociceptive circuits in the spinal cord, brainstem and cortex that form the building blocks of our first pain experience.

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Abstract figure legend Information about a tissue injury or noxious stimulus is processed by nociceptive pathways in the CNS that underlie the perception of pain. These pathways change profoundly over an extended period of postnatal development. From the newborn to the adult, physiological connections in the spinal cord, brainstem and cortex undergo considerable change, such that the transmission and modulation of noxious information are highly age dependent. Much of our understanding of these processes has come from neurophysiological analysis of activity in sensory neurons and networks in the spinal cord, brainstem and cortex at different stages of development in the laboratory rodent. Increasing evidence that untimely tissue injury in early life can cause life-long changes in pain sensitivity has led to a focus on key areas and periods of developmental vulnerability in nociceptive circuit maturation.

Introduction

Brain and spinal cord circuits are responsible for the experience and modulation of acute and chronic pain and, as such, have become the focus of much recent pain research. These circuits develop over a prolonged period, from late fetal and neonatal life through to childhood and adolescence, under the influence of both intrinsic and external factors. If we are to relieve the burden of chronic pain in later life, we must understand the physiological development of these circuits. This review arose from the Bayliss–Starling Prize Lecture. It focuses on the developmental physiology of nociceptive pain, summarizing current knowledge of how noxious potential or real tissue-damaging events are processed by sensory neurons and circuits in the immature CNS and generate pain. The emphasis is on how these circuits change with age, highlighting critical periods of change, when external events can alter the normal course of development and determine future pain sensitivity.

The developmental physiology of spinal cord dorsal horn nociceptive circuits

Almost a century has passed since the first detailed observations of fetal rodent spontaneous and reflex movements were correlated with anatomical growth and maturation of the dorsal horn over the same developmental period (Angulo Y Gonźlez, 1932; Windle & Baxter, 1936). Over the subsequent decades, these studies became increasingly precise and quantitative, mapping cutaneous reflex behaviour across the body from embryonic day (E) 15 to 21 and comparative behavioural and microscopic synaptic analysis in superficial and deep dorsal horn from postnatal day (P) 0 to 21 (Narayanan et al., 1971; Stelzner, 1971). These studies concluded that all induced movements observed in rat embryos and newborns can be explained rationally on the basis of spinal cord structures developed at the time. Twitches detected in earlier stages were proposed to be myogenic, generated directly by the muscle. A picture emerged of a retrograde pattern of synaptogenesis in the early development of the spinal cutaneous reflex pathway, with deeper-lying interneurons making synaptic contacts with motor neurons before synapses are formed between primary sensory neurons and dorsal horn interneurons, in a sequence that is the reverse of the normal flow of nerve impulses through spinal reflex pathways (Saito, 1979; Vaughn & Grieshaber, 1973).

Although these early studies predicted the formation of functional sensory networks in the late fetal spinal cord, the first direct evidence of the prenatal onset of sensory circuit function in the lumbar dorsal horn came from single-cell electrophysiological recording in intact urethane-anaesthetized rat fetuses, while still in contact with their mother via the maternal circulation (Fitzgerald, 1991). Electrical stimulation of the hindpaw was found to evoke occasional spikes in lumbar dorsal horn neurons from E17, but natural skin stimulation did not activate these neurons reliably until E19 and then only weakly. By E20, however, the majority of dorsal horn neurons had clearly defined receptive fields on the hindpaw, responding to both dynamic touch (brushing) and pinch of the skin, in some cases with bursts of $\leq$50 spikes from a single pinch with after-discharges that outlasted the stimulus by 10−15 s. Thus, rudimentary dorsal horn tactile and nociceptive circuits are functional prenatally and well placed to receive and process the massive sensory exposure that awaits them after birth (Fitzgerald, 1991).

The maturation of newborn nociceptive circuits in the dorsal horn. Electrophysiological recordings of dorsal horn cells in the intact newborn rat revealed dramatic changes over the neonatal period in their response to nociceptive and tactile cutaneous stimulation. In the first such developmental study, performed under urethane anaesthesia, I analysed responses evoked in 121 individual lumbar dorsal horn cells in rat pups aged 0−15 days (Fitzgerald, 1985), which was followed by later, detailed studies of developing dorsal horn activation patterns and receptive fields in different conditions and over longer time periods (Bremner & Fitzgerald, 2008; Fitzgerald & Jennings, 1999; Jennings & Fitzgerald, 1998; Koch & Fitzgerald, 2014; Koch et al., 2012; McKelvey et al., 2015; Ririe et al., 2008; Schwaller et al., 2016, 2017; Torsney & Fitzgerald, 2002).

Useful insights into the developmental physiology of cutaneous nociceptive processing in the dorsal horn are gained from analysis of receptive fields. A receptive field is defined as the sensory space that can elicit neuronal responses. In this case, it is the area of skin that, when stimulated, will evoke activity in a dorsal horn neuron. In reality, it is more than that. Mapping receptive fields informs us about how a dorsal horn neuron encodes the modality, intensity, duration and location of a stimulus on the body surface, in addition to the context or natural history. In adult *in vivo* electrophysiological studies, individual dorsal horn neurons display a range of cutaneous receptive field types and response characteristics, normally grouped into low-threshold (e.g. brush/touch) (LT), nociceptive-specific (e.g. mechanical pinch) (NS) or wide dynamic range (WDR) cells, which encode input from both low- and high-intensity modalities (see William & Coggeshall, 2003). Importantly, adult cutaneous receptive fields are not fixed but are subject to rapid changes in response to contextual factors, such as stimulus history, supraspinal connections and anaesthesia (Ahanonu et al., 2023; Dubner & Ruda, 1992; Sandkühler, 2009). Such flexibility is made possible by the presence of subliminal inputs surrounding a receptive field, which might or might not be recruited over minutes, depending on nearby events (Woolf & King, 1990), controlled by inhibitory circuits within the dorsal horn (Sivilotti & Woolf, 1994; Zeilhofer et al., 2012). Thus, dorsal horn nociceptive circuits do not simply carry out a moment-to-moment analysis of afferent noxious input, but instead represent a dynamic context-dependent process. The postnatal development of receptive field properties provides a picture of how these circuits develop at the level of the spinal cord (Fig. 1).

The key features of developing dorsal horn nociceptive circuits in the lumbar spinal cord were discovered using single-cell *in vivo* electrophysiology in a series of studies (Bremner & Fitzgerald, 2008; Fitzgerald & Jennings, 1999; Jennings & Fitzgerald, 1998; Koch & Fitzgerald, 2014; Koch et al., 2012; McKelvey et al., 2015; Ririe et al., 2008; Schwaller et al., 2016, 2017; Torsney & Fitzgerald, 2002), and these are summarized below.

First, the relative area of dorsal horn cell peripheral cutaneous receptive field decreases with age. At P3, the mean (±SEM) peripheral mechanoreceptive field occupies 50 ± 5.6% of the plantar hindpaw. This value drops to 36 ± 2.9% at P6, 20 ± 1.9% at P10 and 15 ± 1.6% at P21. The biggest change, therefore, occurs in the first postnatal week. Both low-threshold, dynamic brush and noxious pinch receptive field areas decrease in area with age; this is particularly evident in the WDR cells of the deep dorsal horn (see Fig. 1).

Second, the neonatal dorsal horn has relatively few NS or WDR neurons, with the majority responding to light mechanical static or dynamic stimulation only.

Third, low- or high-intensity stimulation of the receptive field of neonatal dorsal horn cells can result in long-lasting after-discharges (30–90 s) that are more pronounced than the initial evoked response. The duration and amplitude of these responses decrease with age. Repetitive electrical skin stimulation of the receptive fields of these cells also causes 'wind-up' (increasing number of spikes with each consecutive stimulus) and prolonged after-discharge.

Fourth, neonatal dorsal horn neurons respond predominantly to afferent input from myelinated A fibre afferents (both Aβ and Aδ), but with long and variable latencies of response; mean latencies decrease with postnatal age, from 33.1 ± 2.78 ms at P3 to 7.3 ± 0.3 ms at P21.

Fifth, robust responses to C fibre afferent cutaneous stimulation are not observed until the second postnatal week, and they remain rare for some weeks after this (Fitzgerald, 1988; Fitzgerald & Jennings, 1999; Jennings & Fitzgerald, 1996, 1998; Nakatsuka et al., 2000; Park et al., 1999).

These postnatal changes in response to peripheral cutaneous stimulation are attributable to alterations in synaptic inputs and circuit properties, rather than changes in intrinsic neuronal excitability. No significant differences in mean firing frequency, spike frequency adaptation, regularity of action potential discharge or rheobase current levels to defined current injections are found between P3 and P21 (Baccei & Fitzgerald, 2005). The excitability of the newborn dorsal horn is coupled with a high level of intrinsic spontaneous activity in developing superficial dorsal horn cells, including 'pacemaker' neurons, which might play a role in synchronizing neuronal network activity in the neonatal dorsal horn (Brewer & Baccei, 2020).

The slow emergence of C fibre-driven dorsal horn nociceptive circuits. The two major classes of peripheral nociceptive afferents are unmyelinated C fibres, many of which respond to noxious mechanical stimulation, heat and irritant chemicals and generate a sensation of slow, dull pain, and myelinated Aδ fibres, which generate rapid sharp mechanical pain. Their activity in adult human subjects can be distinguished by verbal descriptors (Beissner et al., 2010), which are correlated with distinct patterns of cortical activity (Fabrizi et al., 2013). Important questions surround the maturation of input of these two major classes of nociceptor in the developing dorsal horn.

Large, myelinated A fibre afferents enter the neonatal lumbar dorsal horn at E14, coinciding with hindlimb skin innervation. In contrast, C fibres are not detected in the dorsal horn until E18. Thus, A fibre inputs appear to have the advantage over dorsal horn cell targets in early development (Jackman & Fitzgerald, 2000). Perhaps as a result of this, there is a striking, transient projection of A fibres to the superficial laminae of the immature dorsal horn, which are the central target for C fibre nociceptor terminals in the adult. This phenomenon, originally observed using fibre-tracing methods (Beggs et al., 2002; Granmo et al., 2008), has recently been confirmed by mapping the exuberant A fibre terminals in the immature spinal dorsal horn in vesicular glutamate transporter 1(VGluT1) reporter mice and demonstrating their gradual withdrawal from superficial laminae by microglial engulfment (Xu et al., 2023)

Electrophysiological analysis shows that although C fibre terminals do make some synaptic connections in the superficial dorsal horn from birth, these are weak and sparse, and C fibre evoked activity is not transmitted to the deeper, WDR, presumptive projection neurons until the second postnatal week (Baccei et al., 2003; Fitzgerald, 1988; Fitzgerald & Jennings, 1999). Thus, dorsal horn neurons in the deeper laminae respond only to short-latency A fibre-mediated responses until P7–P8. This means that neonatal spinal nociceptive circuits are likely to be driven by nociceptive Aδ afferents rather than by C fibres, which has implications for the ability of the young spinal cord and brain to generate persistent slow pain. Lack of C fibre function also explains the weak or absent reflex behavioural responses to irritant chemicals until P10–P11 (Fitzgerald & Gibson, 1984; Jiang & Gebhart, 1998) and the accompanying lack of neurogenic oedema, a C fibre-mediated inflammatory reaction, which cannot be evoked before P11 despite exogenously

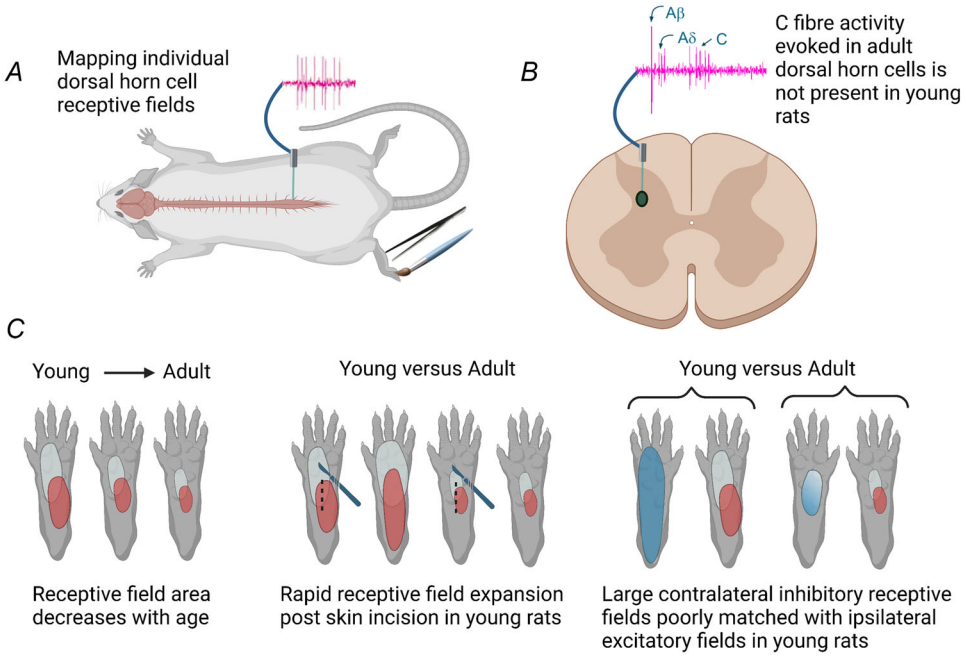

Figure 1. Dorsal horn cell sensory responses change with postnatal age
A, data were collected from electrophysiological recording of activity in single dorsal horn cells in the lumbar spinal cord of anaesthetized rats at different ages while mapping their receptive field areas to dynamic touch (brush) and noxious pinch stimulation of the hindpaw. *B*, electrical stimulation of the skin at different strengths evoked clear Aβ, Aδ and C fibre-evoked spikes in adult wide dynamic range neurons, at latencies determined by their conduction velocities. The late C fibre component was found to be weak or missing in young dorsal horn neurons. *C*, changing properties of dynamic touch (pale blue) and noxious pinch (red) receptive fields. Left, receptive field areas decreased with age. Middle, receptive fields expanded rapidly following skin incision in young but not old rats. Right, simultaneous mapping of ipsilateral excitatory and contralateral inhibitory receptive fields (dark blue) revealed mismatching and poor inhibitory tuning in young rats. See main text for details.

administered substance P producing extravasation at P3 (Fitzgerald & Gibson, 1984; Gonzales et al., 1991).

The effect of acute injury on newborn dorsal horn receptive fields. Despite the immaturity of neonatal dorsal horn receptive fields, they display clear contextual changes in relationship to tissue injury, which depend on the type of injury and neonatal age (Fig. 1). Local inflammation of the hindpaw, induced with carrageenan, rapidly increases spontaneous activity, the response to noxious stimuli and after-discharge from P3 onwards, consistent with behavioural hypersensitivity and, possibly, background pain (Torsney & Fitzgerald, 2002). However, inflammation-induced expansion of the receptive field size did not occur until P21. Interestingly, in the P21 carageenan group the distribution of receptive field size is remarkably similar to that at P3, suggesting that neonatal dorsal horn cells either lack or have poorly targeted inhibitory control (see next section).

In contrast, local skin incision, known to cause behavioural nociceptive hypersensitivity in young and adult rats (Walker et al., 2009), has a greater effect upon immature dorsal horn receptive fields. Continuous recordings of dorsal horn cell activity, performed before and after a standardized skin incision injury, showed that 1 h after incision, dynamic brush and noxious pinch receptive field area, spontaneous firing and evoked spike activity increased significantly in the 7-day-old animals, but not in the 28-day-old animals. Von Frey hair thresholds decreased at both ages (Ririe et al., 2008). This is consistent with *in vitro* data from spinal cord slices demonstrating selective increases in the frequency of glutamatergic miniature excitatory postsynaptic currents recorded 2−3 days after skin incision, whereas incision at P17 failed to affect excitatory or inhibitory synaptic function (Li et al., 2009).

The maturation of inhibition in dorsal horn nociceptive circuits. Inhibition in nociceptive networks is as important as excitation, and in the adult dorsal horn it is proposed that activity in inhibitory neurons sets individual pain thresholds (Hughes & Todd, 2020). Although ipsilateral, contralateral and distant inhibitory components of receptive fields can be observed in the rat dorsal horn from birth (Fitzgerald, 1985), the large excitatory cutaneous receptive fields and sensitivity to mechanical stimulation in the first weeks of life suggest a failure of inhibitory control in developing spinal sensory pathways at the network level. This was tested by mapping the spatial and modality organization of contralateral dorsal horn cell inhibitory receptive fields simultaneously with ipsilateral excitatory ones in decerebrate spinal adult and neonatal rats, to avoid any confounding effects of anaesthesia (Bremner & Fitzgerald, 2008). Application of a continuous noxious input from a small skin clamp on the plantar surface of the foot (ipsilateral) evokes prolonged firing in dorsal horn neurons, and selective inhibition of this activity was achieved by noxious stimulation of the other (contralateral) hindpaw, allowing contralateral inhibitory receptive fields to be mapped systematically at different ages (Fig. 1). This contralateral inhibition of dorsal horn cells is well established by P3, but inhibitory receptive fields were significantly larger at P3 than in the adult, and the intensity of inhibition across the receptive field was more evenly distributed and not matched to the contralateral excitatory fields in the neonate. Furthermore, contralateral inhibitory fields can be activated by both innocuous and noxious stimulation in the neonate, in contrast to the adult, in which noxious stimulation is normally required. These results demonstrate a 'mismatch' between excitatory and inhibitory receptive fields in young animals and a gradual postnatal spatial and modality 'tuning' of inhibition in the developing dorsal horn, which might contribute to the excitability of dorsal horn nociceptive circuits in young animals (Bremner & Fitzgerald, 2008) (Fig. 1).

Further evidence for poorly developed functional inhibition within the neonatal dorsal horn is the immaturity of glycinergic inhibition, which emerges only in the second week of life (Koch et al., 2012; and see Tasnim et al., 2024). Dorsal horn dynamic touch receptive fields and afferent-evoked excitation are initially facilitated by glycinergic activity attributable, at least in part, to glycinergic disinhibition of glutamic acid decarboxylase 67 expressing (GAD67) cells. Glycinergic inhibitory control emerges in the second postnatal week, coinciding with an expression switch from neonatal α_2 homomeric to predominantly mature α_1/β glycine receptors. The onset of glycinergic inhibition depends upon the maturation of C fibre inputs to the dorsal horn. Selective block of afferent C fibres in postnatal week 2 delays the maturation of both glycine receptor subunits and glycinergic inhibition, maintaining dorsal horn neurons in a neonatal state, in which tactile responses are facilitated, rather than inhibited, by glycinergic network activity. Thus, glycine might serve to facilitate tactile A fibre-mediated information and enhance activity-dependent synaptic strengthening in the immature dorsal horn. This period ceases in the second postnatal week with the maturation of C fibre spinal input, which triggers postsynaptic changes leading to glycinergic inhibition, and only then is balanced excitation and inhibition achieved in dorsal horn sensory circuits (Koch & Fitzgerald, 2013).

Studies of the postnatal development of inhibitory connections onto superficial dorsal horn neurons using whole-cell patch-clamp recordings made in spinal cord slices over a range of postnatal ages (P3, P10 and P21) show that amplitudes of evoked inhibitory

postsynaptic currents are significantly lower and more variable in younger animals, suggesting a lower fidelity of GABAergic signalling at early postnatal ages (Ingram et al., 2008). Furthermore, inhibitory synaptic input from dynorphin interneurons onto lamina I projecting neurons is weaker during the neonatal period, probably reflecting a lower number of GABAergic terminals and a reduced probability of GABA release compared with adults (Brewer et al., 2020).

Descending brainstem control of developing dorsal horn nociceptive circuits. The responses of dorsal horn neurons to peripheral noxious stimuli are dependent not only upon the afferent input to the spinal cord and local circuit modulation but also upon powerful descending control from supraspinal centres (Bannister & Dickenson, 2016; Gebhart, 2004). The importance of this control for spinal nociceptive function cannot be overemphasized, being the route by which all aspects of brain function, from attention to anticipation, emotion to expectation, can influence pain perception. Furthermore, the integration of bottom-up and top-down information across distributed pain circuits is required for the process of predictive coding, a computational theory describing how the brain perceives and acts, which has been widely adopted in sensory processing and motor control (Chen, 2023).

In adults, there is a well-established descending inhibitory pathway from the rostral ventral medial medulla (RVM) and the periaqueductal grey (PAG) to the dorsal horn. Electrical stimulation or morphine injection in the PAG and RVM reduces pain behaviours, an effect that depends upon descending pathways in the dorsolateral funiculus and also upon an excitatory connection between the PAG and the RVM (Bannister & Dickenson, 2016; Heinricher et al., 2009; Leith et al., 2010).

The RVM neurons project to the lumbar spinal dorsal horn in newborn rats, as demonstrated by retrograde labelling with intraspinal microinjection of microspheres (Schwaller et al., 2016); however, RVM descending control of spinal nociceptive networks serves very different functions in young and adult animals (Hathway et al., 2009) (Fig. 2). In the first 10 days of life, the RVM receives no ascending input from spinal circuits and thus functions independently of sensory input, exerting tonic descending excitation on dorsal horn cells (Schwaller et al., 2016), probably generated by spontaneous brainstem activity. Later in postnatal life, ascending nociceptive inputs reach the RVM, forming a functional spinal–bulbospinal feedback loop, but the dominance of excitatory descending control over spinal nociceptive processing continues for 4 postnatal weeks. After that time, top-down control over spinal nociceptive circuits switches from predominantly excitatory to

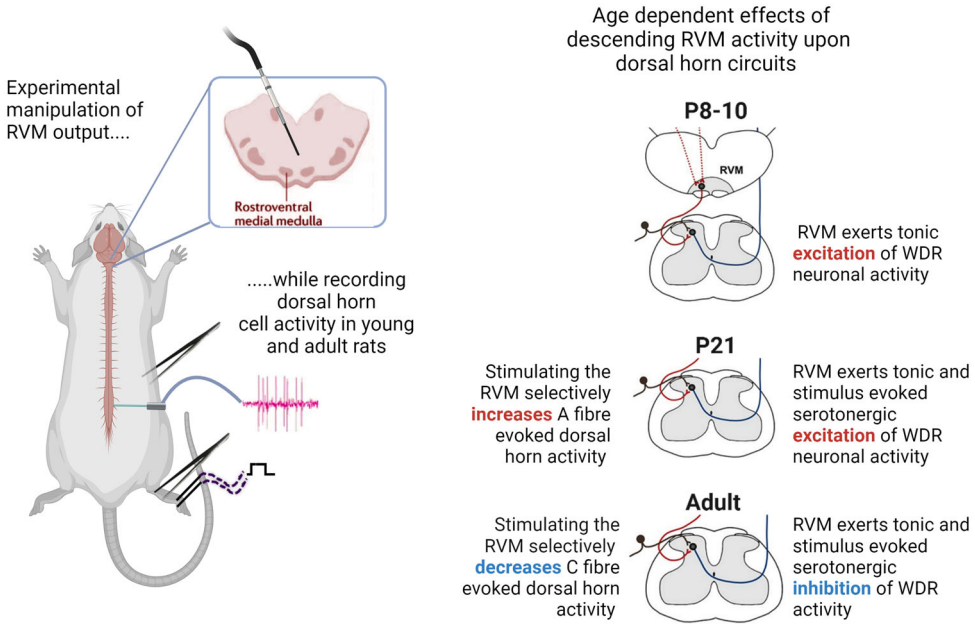

Figure 2. Descending control of dorsal horn activity from the rostroventral medulla changes from excitatory to inhibitory with postnatal age
Data were collected from electrophysiological recording of activity in single dorsal horn cells in the lumbar spinal cord of anaesthetized rats at different ages [postnatal day (P) 8–10, 21 and adult] while mapping their receptive field areas to dynamic touch (brush) and noxious pinch stimulation of the hindpaw. Rostroventral medulla (RVM) activity was experimentally silenced or activated pharmacologically or by electrical stimulation and the effect upon dorsal horn cell responses tested. See main text for details.

predominantly inhibitory, and descending inhibition gradually becomes more powerful until adulthood (Hathway et al., 2009). The serotonergic pathways undergo considerable reorganization, mediating the early life descending excitation; differential descending serotonergic control of spinal touch and pain processing emerges in late postnatal life, allowing flexible and context-dependent brain control of somatosensation (de Kort et al., 2022; Schwaller et al., 2017). The phenomenon of diffuse noxious inhibitory control also does not emerge until the third postnatal week in rat pups (Boucher et al., 1998).

Figure 2 summarizes the key changes in brainstem descending control over postnatal life, detailed below.

First, tonic descending control of dorsal horn neurons, tested using focal microinjection of lignocaine in the RVM, is excitatory in young animals. At P8 and P21, injection of lignocaine into the RVM reduces the mean WDR neuron noxious pinch-evoked firing and receptive field area, whereas in adult animals, RVM lignocaine injection increases them. Dynamic brush receptive fields are not affected (Schwaller et al., 2016).

Second, direct exogenous glutamatergic activation of RVM neurons does not add further modulation of spinal WDR neuron nociception at P10, but at P21 noxious pinch firing rate and receptive fields are significantly increased. In adults, they are both significantly decreased. This, together with the above results suggest that the descending excitation in very young animals is generated spontaneously by local brainstem activity. Later, from P21 onwards, descending controls are driven by inputs from elsewhere in the brain or from a peripheral feedback loop (Schwaller et al., 2016).

Third, direct electrical stimulation of RVM neurons in adults reveals that descending inhibition is targeted to neurons with a strong nociceptive C fibre input. In contrast, the neonatal RVM influence over dorsal horn neurons is not only excitatory but is targeted to A fibre (Aβ and Aδ)-evoked activity in dorsal horn neurons. Thus, the postnatal shift in RVM control of dorsal horn circuits is not only directional but also modality specific, from facilitation of A fibre input in the young animal to inhibition of nociceptive C input in the adult, with additional contextual factors (Koch & Fitzgerald, 2014).

Fourth, these effects are mediated, at least in part, by serotonergic fibres, which in adults exert tonic control over the dorsal horn, decreasing nociceptive activity and receptive field areas while increasing non-noxious tactile activity and receptive fields, via activation of spinal 5-HT_3 receptors. This differential serotonergic control in the adult emerges from a non-modality-selective system in young rats, where activation of descending serotonergic fibres exerts background 5-HT_3 receptor-mediated facilitation and increases both tactile and nociceptive dorsal horn receptive fields (Schwaller et al., 2017).

Fifth, the mechanism underlying this change in top-down control is likely to lie in the maturation of the cortex and of RVM and PAG circuitry. The maturation of brainstem opioidergic signalling is one important factor. Blockade of tonic opioidergic activity in the brain over a critical period from 3 to 4 weeks prevents the normal development of descending RVM inhibitory control of spinal nociceptive reflexes, whereas enhancing brain opioidergic activity with chronic morphine accelerates this development (Hathway et al., 2012).

The physiological development of nociceptive circuits in the immature somatosensory cortex

Somatosensory cortical development and the emergence of physiological sensory circuits. To generate pain, nociceptive information must be transmitted via ascending projection pathways to the cortex. The maturation of cortical nociceptive networks is essential if nociceptive information is to generate the experience of pain (Verriotis et al., 2016)

Information from dorsal horn nociceptive circuits reaches the brain via ascending spinal pathways terminating in subcortical regions in the medulla, PAG, parabrachial nucleus and thalamus (Todd, 2010). Spinothalamic tract neurons develop early; E18, P2 and P7 mice do not differ from adults in the number or distribution of spinothalamic tract neurons retrogradely labelled from the thalamus. Although these neurons increase significantly in diameter over the first postnatal week, morphological features required for functionality, such as arborizations, and boutons within the ventrobasal complex of the thalamus are present from before birth (Davidson et al., 2010). Neonatal Neurokinin-1 (NK-1)-expressing lamina I neurons in the lumbar dorsal horn also project to the parabrachial nucleus from at least P3 (Man et al., 2012). However, noxious pinch of the hindpaw evokes no Fos activation in either the RVM or the PAG at P4 or P8, indicating a lack of nociceptive input to these regions at these ages, until P12 (Schwaller et al., 2016). Functional mapping of nociceptive inputs to the thalamus and other supraspinal centres also suggests a slow postnatal maturation of these synaptic connections after the first postnatal week (Barr, 2011).

Peripheral and spinal cord sensory pathways and the central thalamocortical and corticothalamic pathways appear to begin developing separately and interact only at later stages. Thus, the early stages of thalamocortical development take place autonomously, with the information from the periphery 'plugging into' these immature circuits before beginning to transmit spontaneous and, later, somatosensory information. Thalamocortical projections form their first functional synaptic connections in the subplate region at E18 to

E19, extending into layers IV, V and VI of the developing somatosensory cortex in a topographically precise manner at birth. In early development, spontaneous activity synchronizes local- and wide-scale cortical networks. The earliest connections are established autonomously, but peripheral sensory activity shapes these circuits as soon as afferents reach the cortex. The early-generated, largely transient neurons of the subplate play a key role in integrating spontaneous and sensory-driven activity (Tolner et al., 2012). Transient patterns of correlated neuronal activity, including δ waves, γ- and spindle-burst oscillations, are mainly driven by the thalamus and triggered, in a topographic manner, by sensory feedback resulting from spontaneous movements (Khazipov & Milh, 2018). The refinement of topographical projections from the thalamus to the cortex arises through an activity-dependent process, in which thalamic axons compete for cortical targets; if this activity is altered during a critical period in early development, normal connectivity is disrupted (Molnár et al., 2020).

Much of our knowledge about the developmental physiology of the newborn somatosensory cortex relates to the whisker-dominated barrel fields, whose specialized anatomical organization and function and early development in rodents might mean that the events are not generalizable to the development of whole-body nociceptive circuits. Electrophysiological recording in the primary somatosensory cortex (S1) reveals the presence of cutaneous mechanical touch receptive fields on the hindlimb at P10 but that these are large in area and not topographically organized. By P15, a clear topographic organization begins to emerge coincident with a reduction in receptive field size, and by P20 these body maps are adult-like (Seelke et al., 2012). This is consistent with an earlier, single-cell study in 7-day-old and adult rat primary somatosensory cortex using cutaneous mechanical stimulation of the hindlimb. At 7 days old, S1 neurons had long latencies and low ability to follow repetitive cutaneous stimulation and large receptive fields, possibly owing to inadequate surround inhibition. In contrast to adult cells, the immature cells commonly responded cyclically, with alternating phases of increased and decreased firing rate for periods of $\leq$3 s after punctate stimulation (Armstrong-James, 1975).

In the first study to address nociceptive input to the developing S1 cortex, intracortical extracellular field potentials (local field potentials, LFPs) evoked by hindpaw electrical pulses sufficient to activate Aδ and C fibres were recorded in the rat somatosensory cortex at P7 under isoflurane anaesthesia (Chang et al., 2016b). By comparing S1 LFPs evoked by low-intensity A fibre skin afferent stimulation and high-intensity A + C fibre stimulation between P8 and P30, the developmental contribution of C fibres to the pattern of activation emerged. At younger ages, the changes in S1 oscillatory activity evoked by the two fibre groups were not significantly different, but by P30, C fibre stimulation evoked significantly larger γ, β and α energy increases compared with A fibre stimulation alone. Silencing TRPV1$^+$ C fibres with QX-314 significantly reduced the γ and β S1 oscillatory energy increases evoked by A + C fibres at P30 and P21, but not at younger ages. Thus, afferent C fibres differentially modulate S1 oscillatory activity only from the third postnatal week, well after the functional maturation of low-intensity tactile and A fibre inputs to the somatosensory cortex.

Studying the emergence of cortical nociceptive processing in awake, freely moving rat pups. Physiological studies of developing nociceptive circuits in the brain of intact animals will naturally be compromised by the presence of anaesthesia. Neural activity in developing S1 cortex is susceptible to anaesthesia (Shumkova et al., 2021), although less so in younger than adult animals (Chang et al., 2015). Unanaesthetized, head-fixed preparations offer stable recording options, but their use in developmental research is limited by physiological stress and loss of ethological relevance. Importantly, in awake pups the presence or absence of the mother has immediate effects upon infant brain activity, hence recording should be performed in as naturalistic conditions as possible (Sarro et al., 2014; Sullivan & Opendak, 2020).

In a novel approach, we have recorded developing nociceptive network activity in the hindlimb somatosensory cortex of freely moving rat pups (Chang et al., 2016a) using a telemetry system adapted for young animals (Chang et al., 2011). Continuous telemetric electrocorticogram (ECoG) recording from the hindlimb primary somatosensory cortex (S1) of awake, active rat pups in the presence of their mother allowed functional nociceptive processing in the developing brain to be mapped over the first 4 weeks of life. Network activity recorded from implanted electrodes in S1 was recorded in the form of LFPs generated by local populations of neurons in infant rats from P8 to P30. The underlying cortical oscillations, or rhythmic voltage deflections in various frequency bands caused by the synchronous synaptic activity of these neurons (Buzsáki et al., 2012), were also analysed. The results of this novel study in awake, active rat pups are summarized below and shown in Fig. 3.

First, bursting activity characteristic of the immature cortex (Colonnese et al., 2010; Minlebaev et al., 2011) was observed in hindlimb S1 at P8 and P11, but was no longer present at P14. Oscillatory energy increased steadily with age, but after P14, a distinctive beta (β) component peak at 20−30 Hz was replaced by a distinctive theta (θ) component at 6−7 Hz, perhaps reflecting longer-range interactions in the brain and the maturation

of basic mechanisms for learning and adaptation to the environment (Berger & Posner, 2023).

Second, differential coding of innocuous and noxious cutaneous mechanical stimuli in S1 was analysed from potentials evoked by dynamic brush and noxious mechanical pinch stimulation of the hindpaw. The response to tactile and noxious stimulation did not differ at P8 and P14, whereas at P21 and P30, S1 noxious-evoked potential amplitudes were significantly greater than those of tactile-evoked potentials. The data confirmed that event-related potentials could be evoked by brief noxious hindpaw skin stimulus, confirming the presence of spinothalamic connections, but the evoked activity was not distinguishable from innocuous tactile stimulation until the third postnatal week, indicating a delay in maturation of distinct nociceptive circuits.

Third, the effects of skin incision upon S1 background oscillatory activity were analysed to gain insight regarding whether network activity in the immature cortex changes to reflect a 'pain state' after a nociceptive skin injury known to cause behavioural nociceptive hypersensitivity (Walker et al., 2009). Activity was recorded in active, awake pups at 5, 30 and 60 min after hindpaw skin incision and compared with baseline (Fig. 3). Skin injury at P8 had no significant effect on the S1 oscillatory energy post-injury. Skin injury at P14 reduced oscillatory energy at 5 min postinjury and consisted of significant decrease in delta (δ), theta (θ), beta (β) and low gamma (γ) energy but essentially recovered by 30 min, with some remaining depression in the β and γ band. At P21 there was a marked change in the S1 ECoG response to skin injury compared with younger ages. The early, significant energy decrease in the θ band, observed at P14, remained but was now accompanied by a significant increase in the γ band that was not observed at younger ages. It was notable that the change in γ energy had switched from a significant decrease at P14 to an increase at P21. The increase in γ energy was short lived, however, and no longer present by 30 and 60 min. At P30 the increase in EcoG γ energy following skin injury was stronger and longer lasting than at P21 and was significant at 5 and 30 min postinjury. The early decrease in θ energy, observed at P14 and P21, was still present at 5 min but switched to a significant increase in θ energy at 30 and 60 min after skin incision. P30 was the first age at which the effects of skin injury lasted for the full hour of recording.

Thus, a defined skin injury that activates spinal nociceptive neurons, resulting in expansion of dorsal horn neuronal receptive field areas, spontaneous firing and evoked spike activity in young rats (Ririe et al., 2008), and nociceptive behaviour and hyperalgesia that lasts for days (Walker et al., 2009), does not significantly increase

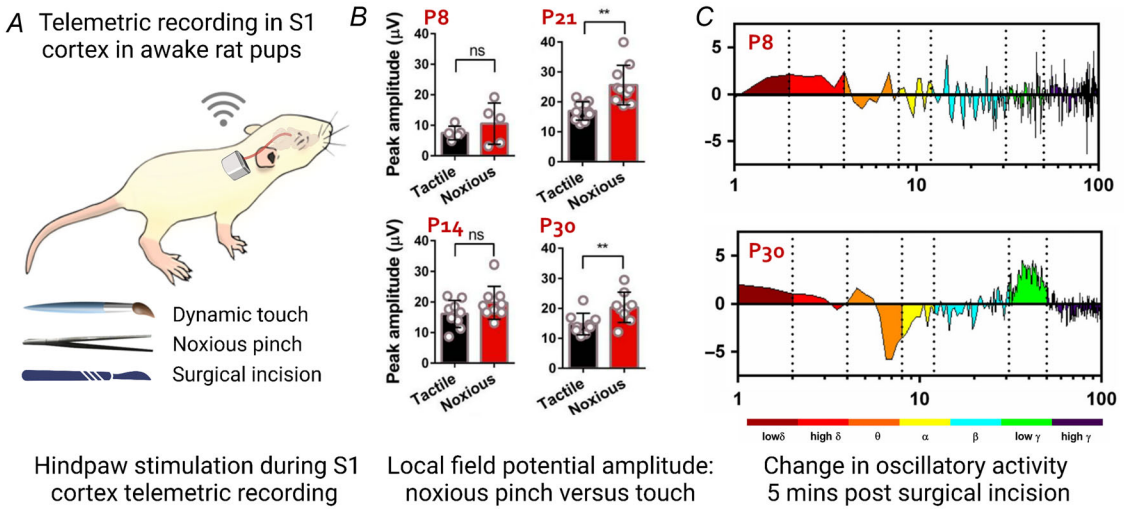

Figure 3. Recording nociceptive activity in the somatosensory cortex in the awake rat over postnatal development
A, somatosensory cortex (S)1 local field potentials (LFPs) were recorded telemetrically at different postnatal ages in awake, freely moving rat pups in the presence of their mother. The effects of cutaneous stimulation and the presence of a skin incision injury upon S1 LFPs were recorded. *B*, mean peak-to-peak amplitude of the potentials at each age. The LFPs evoked by tactile and noxious stimulation did not differ at postnatal day (P) 8 and P14, whereas at P21 and P30, S1 noxious-evoked potential amplitudes were significantly greater than those of tactile-evoked potentials. The S1 activity did not display a distinct difference between noxious and non-noxious stimulation before P21. *C*, analysis of the LFP oscillatory components 5 min after contralateral hindpaw skin incision: *y*-axis, frequency (in herz); *x*-axis, *P*-values (change relative to background). The spectral differences in LFP frequency bands are colour coded (low δ, 1–2 Hz; high δ, 2–4 Hz; θ, 4–8 Hz; α, 8–12 Hz; β, 12–30 Hz; low γ, 30–50 Hz; and high γ, 50–100 Hz). Positive values indicate that energy increased post-incision, whereas negative values indicate that energy decreased. See main text for details.

somatosensory ECoG energy until the third postnatal week (Fig. 3).

The importance of gamma (γ) activity. Cortical γ activity is highly associated with pain behaviour in adult rats and pain experience in humans, where it is strongly correlated with subjective pain intensity (Hu & Iannetti, 2019). Furthermore, subjective perception of ongoing, tonic heat pain is encoded selectively by γ oscillations in the human medial prefrontal cortex (mPFC), differing fundamentally from that of objective stimulus intensity and of brief pain stimuli (Heid et al., 2020; Schulz et al., 2015). The γ oscillations reflect neural activity strongly coupled with the fast spiking of interneurons in S1 (Yue et al., 2020), probably generated by supragranular inhibitory parvalbumin interneurons (David et al., 2023). The data above, shown in Fig. 3, suggest that specific nociceptive circuits and somatosensory cortical coding of an ongoing pain 'state' in awake rat pups is not apparent until after 3 weeks of age and is still maturing at 4 postnatal weeks (Chang et al., 2016a).

Developing connections between somatosensory and emotional cortical nociceptive circuits. In the adult, many ascending nociceptive pathways are directed towards the parabrachial nucleus and periaqueductal grey which send projections to the amygdala and medial prefrontal cortex (mPFC), brain regions that are proposed to subserve the important emotional or affective aspects of pain. Functional mapping of these connections in young rodents suggests that these pathways mature later than direct spinothalamic pathways (Verriotis et al., 2016). Thus, there is no nociceptive spinal input to either the parabrachial nucleus or the ventrolateral PAG before P12, at a time when the somatosensory cortex can clearly be activated by nociceptive input, suggesting a slower maturation of pathways responsible for signalling emotional components, relative to nociceptive or sensory components of pain (Chang et al., 2016a; Schwaller et al., 2016).

Mapping brain activation using manganese-enhanced MRI suggests that both limbic and sensory paths are functional by P12 (Sperry et al., 2017). The neural circuitry of the mPFC, an area of the brain that is key to assessing the threat of sensory stimuli and generating defensive responses, progressively develops more capacities as the animal matures. When rats are exposed to a threatening stimulus at P14, the mPFC is neither active nor responsive; it becomes responsive in processing aversive sensory stimulation at P26, but only regulates freezing in adolescence, at P38–P42 (Chan et al.,

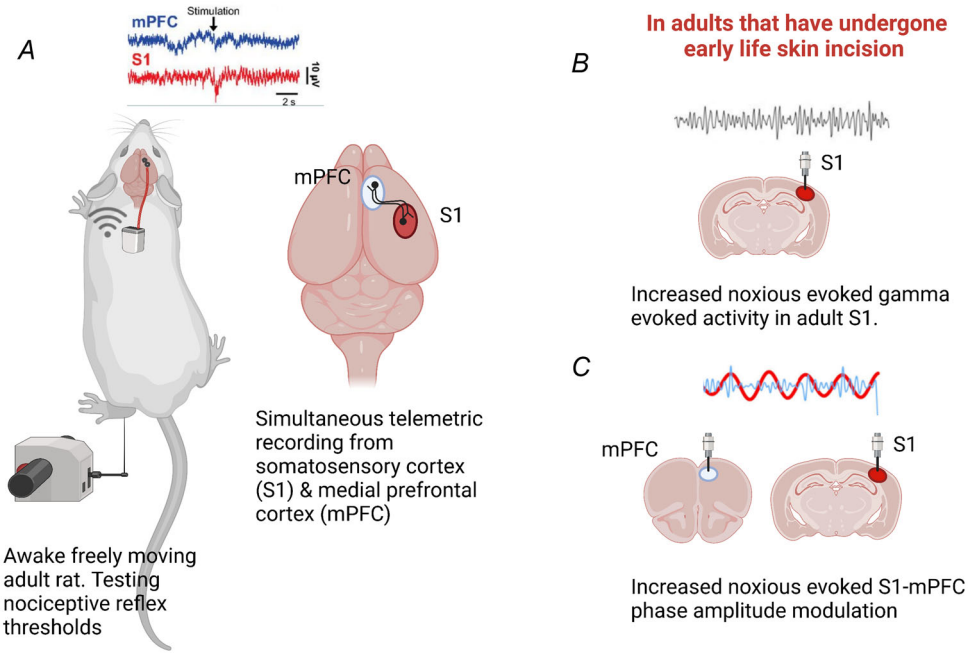

Figure 4. Early life skin incision alters adult nociceptive circuits in the somatosensory and medial prefrontal cortex
A, local field potential telemetric recording in the somatosensory cortex (S1) and medial prefrontal cortex (mPFC) simultaneously, in awake, freely moving rats. *B*, noxious stimulation evoked greater oscillatory γ power in rats with early life pain history compared with control animals. This suggests that they might feel greater pain. *C*, noxious stimulation evoked more prolonged phase amplitude modulation between S1 and mPFC γ power in rats with early life pain history compared with control animals. This suggests a greater connection between sensory and emotional aspects of pain. From Chang et al. (2022). See main text for details.

2011; Sullivan & Opendak, 2020). The amygdala is the central component of a functional brain system regulating fear and emotional behaviours. Distinct behaviours related to amygdala activation emerge at different time points during postnatal development and continue to mature over a prolonged period (Tallot et al., 2016). Both rodent and human research show that the presence/absence of the parent is crucial to the development of amygdala activation and fear learning (Sullivan & Opendak, 2020)

The development and vulnerability of connections between nociceptive sensory and emotional processing in the cortex might be a clue to susceptibility to chronic pain in adults. Early life injury in rodents is known to increase injury-induced pain hypersensitivity (Melchior et al., 2022; Schwaller & Fitzgerald, 2014; Walker, 2019), but only recently has the effect of early life injury on the long-term development of functional sensory and emotional nociceptive circuits in the brain been demonstrated from continuous LFP recording in awake adult rats (Chang et al., 2022). The S1 and mPFC LFPs evoked by mechanical hindpaw stimulation were recorded simultaneously with pain reflex behaviour following adult skin incision injury. Two main effects of early life injury were observed in adults. First, noxious stimulation-evoked S1 δ and γ energy and S1 LFP δ/γ frequency coupling were significantly increased in rats that experienced early life injury compared with control animals. Second, noxious stimulation increased S1–mPFC functional connectivity, which was significantly prolonged in rats exposed to early life injury, lasting 4 days compared with 1 day in control animals. Importantly, the increases in LFP energy and connectivity in rats exposed to early life injury were directly correlated with increased behavioural nociceptive hypersensitivity. Thus, by recording pain-related cortical activity and simultaneous pain behaviour in awake adult male rats previously exposed to early life injury, we showed that functional connectivity within and between the somatosensory cortex and the mPFC was increased in these rats and that these increases were correlated with their behavioural nociceptive hypersensitivity (Fig. 4).

Conclusion and future directions

Nociceptive circuits in the spinal cord, brainstem and cortex undergo dramatic physiological changes over postnatal life. The greatest changes can be grouped into three phases: the organization of nociceptive circuits in the dorsal horn of the spinal cord over the first weeks of life, when sensitivity is favoured over specificity, followed by the later maturation of descending brainstem control of nociception, which favours top-down amplification of spinal circuits over inhibition, and finally, the maturation of cortical nociceptive networks, which emerge over a later, prolonged period. These are overlapping and interdependent processes that are likely to reflect the requirement of the developing nervous system to maximize responses to external sensory input and thus enhance synaptogenesis and shape the formation of sensory circuits to match environmental needs, while also establishing selective pathways for the unique emotional and sensory experience of pain. Given that repeated noxious stimulation is not the norm in early life, it is likely that nociceptive circuits are shaped 'on the back' of dynamic tactile inputs, especially those from maternal care. In this context, it is not surprising that their maturation is especially susceptible to early life injury, which has long-lasting effects upon future pain behaviour and upon the function of adult cortical pain circuits.

This review has summarized data from the *in vivo* recording studies underpinning our knowledge of the maturation of neural pathways generating pain. However, improving technology using multiunit, whole-cortex recording in awake, freely moving infant animals, in the presence of their mother, will provide more integrated and ethologically relevant data on developing nociceptive circuits at all levels of the CNS. Future studies will inform us how individual patterns of sensory and emotional connectivity to pain emerge and what early life factors determine individual vulnerability to chronic pain.

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Additional information

Competing interests

None.

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Sole author.

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Supporting information

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