NEUROSCIENCE of Consciousness

*Neuroscience of Consciousness*, 2023, **2023(1)**, 1–11

DOI: https://doi.org/10.1093/nc/niad002

**Research Article**

# Toward the unknown: consciousness and pain

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## Abstract

Studies of consciousness are hindered by the complexity of the brain, but it is possible to study the consciousness of a sensation, namely pain. Three systems are necessary to experience pain: the somatosensory system conveys information about an injury to the thalamus where an awareness of the injury but not the painfulness emerges. The thalamus distributes the information to the affective system, which modulates the intensity of the pain, and to the cognitive system that imparts attention to the pain. Imaging of patients in pain and those experiencing placebo and hypnosis-induced analgesia shows that two essential cortical circuits for pain and attention are located within the anterior cingulate cortex. The circuits are activated when a high-frequency input results in the development of a long-term potentiation (LTP) at synapses on the apical dendrites of pyramidal neurons. The LTP acts via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, and an anterior cingulate cortex–specific type-1 adenylate cyclase is necessary for both the LTP and the pain. The apical dendrites form an extensive network such that the input from serious injuries results in the emergence of a local field potential. Using mouse models, I propose experiments designed to test the hypothesis that the local field potential is necessary and sufficient for the consciousness of pain.

**Keywords:** consciosness; pain; anterior cingulate gyrus; long-term potentiation; local field potential; pyramidal neurons

### Highlights

The experience of pain requires:

- Interactions between somatosensory, affective, and cognitive systems.
- Two circuits, one for pain and another for attention, in the anterior cingulate cortex.
- Activation of each circuit by a high-frequency input from the site of an injury.
- Development of a long-term potentiation and a local field potential at pyramidal neuron synapses in each circuit.
- Experiments to determine the necessity for the LFP in the consciousness of pain.

## Introduction

Philosophers and theologians have pondered the nature of consciousness for centuries without much success largely because they did not understand the workings of the brain. Any theory that purports to explain consciousness must confront several problems, two of which were recognized by Chalmers (1995). The primary problem is to characterize the neuronal circuits within the brain whose activity is necessary for the emergence of consciousness. The second, and more difficult problem, is to explain how an immaterial consciousness can arise from the activity of a material brain. In addition, there is the binding problem, which is to understand how the various functions of the brain are integrated to form a single concept of the world in real time. Facing all three challenges appears to be impossible due to the overwhelming complexity of the human brain. However, it is possible by taking a reductionist approach to study the consciousness of a single sensation, namely pain. My basic premise is that what we experience as pain arises from the acquisition and processing of information about an injury and that this occurs via the activities of specific circuits in the nervous system and brain. To experience a sensation is to be aware of the sensation, and in this context, experience is synonymous with a consciousness of pain.

Pain is essential to life and is the dominant sensation because it commands the most attention. The neuronal pathways that convey information about pain are well understood, as are the cell and molecular mechanisms that are responsible for encoding this information as it is disseminated throughout the nervous system. What follows is a science-based proposal that uses what we know about pain to address the three problems mentioned earlier.

Pain is subjective: it is shaped by mood, belief, reward, and present and past circumstances. It is also dependent on attention. Consequently, to understand the experience of pain, I will first

**Received:** 29 July 2022; **Revised:** 12 December 2022; **Accepted:** 15 January 2023

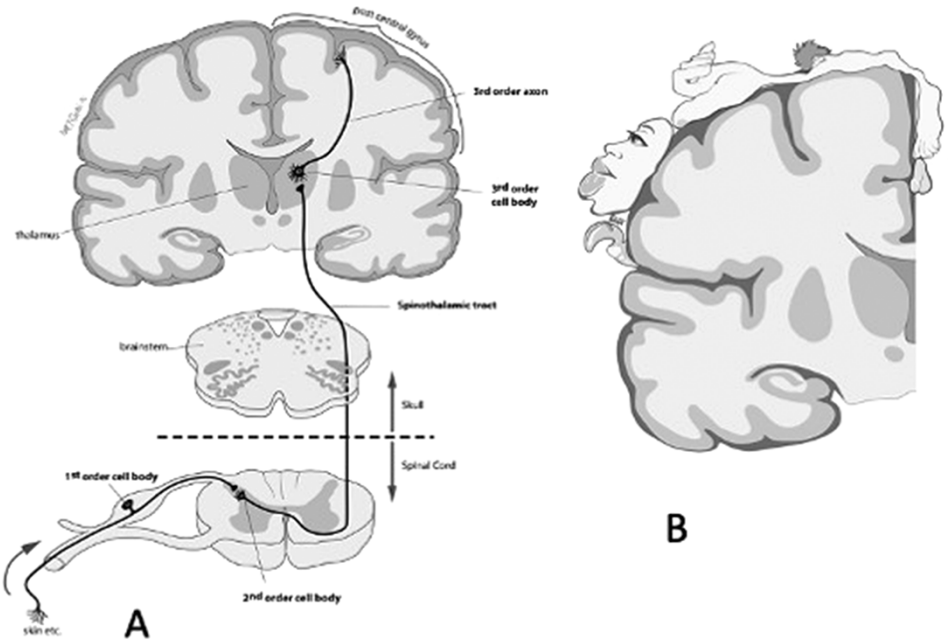


**Figure 1.** (A) The somatosensory system. A first-order C-type nociceptive neuron with a peripheral process that innervates the skin, a cell body in a dorsal root ganglion, and a central process that activates a second-order neuron in the spinal cord. The axon of the second-order neuron crosses to the opposite side and ascends within the spinothalamic tract to the thalamus, where it activates third-order neurons whose axons communicate with neurons in the sensory cortex in the postcentral gyrus. (B) Section through the left hemisphere showing the sensory homunculus in the postcentral gyrus. Activation of the neurons in the homunculus indicates the site of the injury

present evidence showing that all these attributes are due to the activity of three neuronal systems. I will then focus on the circuits that are both necessary and sufficient for pain and describe the key molecular events that link their activity to the consciousness of pain (Ambron and Sinav 2022).[1]

## Results and discussion

### The somatosensory system

First-order C-type nociceptive neurons prolong pain beyond the acute stage and are responsible for what eventually emerges as the experience of pain. The cell bodies of the first-order neurons reside in dorsal root ganglia, and their peripheral processes terminate in the skin and underlying tissues (Fig. 1A) (Dubin and Patapoutian 2010). Agents released from damaged cells after an injury bind to the receptors in the membrane of the terminals, resulting in the opening of ion channels and the generation of action potentials. The extent of the injury is encoded in the number and frequency of the action potentials that are elicited. The action potentials propagate along the peripheral and then the central processes of the first-order neurons to the dorsal region of the spinal cord where they synapse on the dendrites of second-order neurons (Fig. 1A). The transmission across this central synapse is tightly regulated, and it can be reduced or blocked by endogenous opioids.[2] The action potentials elicited in the second-order neurons propagate along their axons, ascending within the spinothalamic tract to synapse on third-order neurons in the thalamus. The third-order neurons process the information with three outcomes. First, the pain is perceived, indicating that there has been an injury and the severity of the injury is determined by the number and frequency of the action potentials. Second, action potentials from the third-order neurons activate circuits in the sensory cortex within the postcentral gyrus in each cerebral hemisphere. The sensory cortex contains a map of the body, and the location of the injury is determined by activating the neurons in the appropriate site on the map (Fig. 1B) (Penfield and Rasmussen 1950). Lastly, action potentials from the third-order neurons form thalamocortical tracts that transmit the information about the injury to other areas of the cerebrum (Hwang *et al.* 2017). In summary, the somatosensory system makes us aware of the injury, its severity, and its location in the body. The word "awareness" is significant. The thalamus was long considered to house the neuronal circuits responsible for the hurtful aspects of pain. This was questionable because studies of patients who received prefrontal lobotomies exhibited what is known as asymbolia, i.e. they were aware of an injury but did not care (Freeman and Watts 1948; Rubbins and Friedman 1948). More recent findings indicate that what emerges from circuits in the thalamus is a perception of an injury without the unpleasantness. Consequently, the experience of pain—the hurtfulness—must arise from the activity of circuits that receive information from the thalamus.

### The affective system

The experience of pain is subjective and is influenced by past experience, anticipation, belief, and attention, yet there is nothing the somatosensory system that can account for this subjectivity. Melzack and Casey (1968) published a theory stating that what we ultimately experience as painful depends on the activity of the neurons in several centers that comprise an affective system for pain. The function of this system is to modulate pain based on anticipation and aspects of mood. This idea was influential, especially with the advent of techniques, such as functional magnetic resonance imaging and Blood Oxygenation Level Dependent

[1] Some of these ideas were developed during the writing of the book R. T. Ambron and A. Sinav. "The Brain and Pain; Breakthroughs in Neuroscience". Columbia University Press. NY 2022.

[2] A traumatic event or severe injury will elicit the release of opioids onto the presynaptic terminal of the central synapse, resulting in stress-induced analgesia.

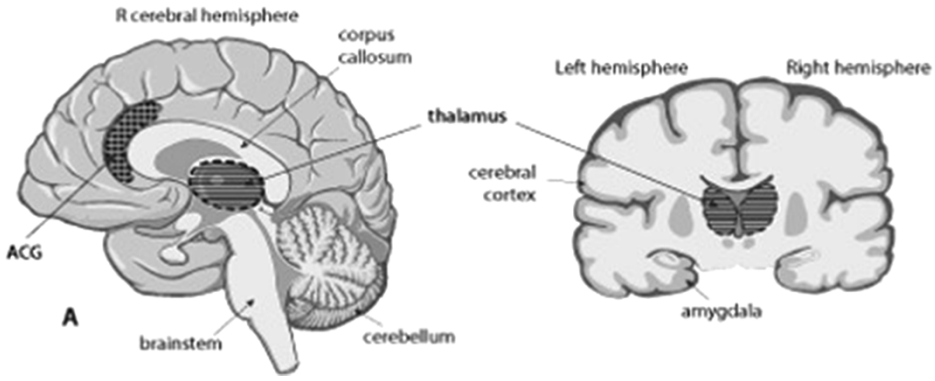


**Figure 2.** (A) A view of the inner (medial) surface of the right cerebral hemisphere showing the thalamus and the anterior cingulate gyrus (ACG), which is just above the anterior part of the corpus callosum. The anterior cingulate cortex (stippled area) is composed of the neurons that reside beneath the surface of the ACG. (B) Section through the cerebrum showing the right and left thalamus (striped) and the amygdala in each hemisphere

imaging, which provide images of the brain in pain. Images from volunteers responding to a painful stimulus consistently showed an increased activity in the thalamus and sensory cortex, as well as in the anterior cingulate cortex (ACC) in the affective system (Morton *et al.* 2016). The ACC is located above the corpus callosum on the medial surface of each cerebral hemisphere (Fig. 2A). The volunteers reported painfulness, unlike the awareness of the injury that emerges from the thalamus (Morton *et al.* 2016). The ACC obtains information via a medial thalamocortical tract that links the somatosensory and affective systems.

The ACC also contributes to the pain experienced in response to extreme grief (Eisenberger 2012). This psychological pain (aka psychalgia) arises from the activation of centers independent of the somatosensory system. fMRI scans show that psychological pain increases activity within the ACC (Wager *et al.* 2013). These findings indicate that the consciousness of both physical and psychological pain shares at least one underlying neurological mechanism and that the ACC is an important center in the consciousness of pain regardless of the source.

The information that reaches the ACC from the thalamus indicates the severity of the injury based on the number of action potentials. If there is no further processing of the information by circuits in the ACC, the pain is experienced as determined by the input. Often, however, the degree of painfulness is influenced by information from other affective centers that either increase or decrease the intensity of the pain. One of these is the amygdala that communicates with the ACC and stores memories of events that are especially traumatic (Fig. 2B) (Veinante *et al.* 2013). Neurons in the amygdala are active in subjects who are suffering and fearful, and fear can elicit anxiety, which exacerbates pain. However, an input from the amygdala does not necessarily result in fear. The ultimate experience of pain is a summation of several inputs, and those from another affective center, the nucleus accumbens (NA), can override those from the amygdala to overcome the fear of a particular event. Circuits in the NA contribute to the decision that bearing pain is acceptable because the reward is believed to be sufficiently important. For example, we might fear needles but decide to overcome the anticipated pain from an injection of an antibiotic because the outcome—elimination of infectious bacteria—is evaluated as being more important. The imposition of decision-making and belief as determinants of the reward system adds to the complexity of pain because the circuits responsible for making decisions and valuing beliefs are not part of the affective system but reside in centers within a higher-order system.

## The cognitive system

The centers in the cognitive system evaluate each sensation and decide which is most important. The decision is based on memories of similar events, expectations, potential outcomes, and beliefs. Thus, the experience of pain is further modulated by contributions from cortical circuits involved in these more complex processes. This is called "top-down" modulation, as opposed to the bottom-up modulation that involves the somatosensory input. Important is the connection between the thalamus and a center within the insula cortex (IC) that is involved in cognition and decision-making (Sawamoto *et al.* 2000). Neurons in the IC are subdivided into regions based on their connections to other cortical neurons and, importantly, to the ACC. The communications between the IC and ACC comprise a salience network in which each sensation is evaluated as to its significance (Lu *et al.* 2016). Pain in response to a lesion will command the most attention, and neurons in the IC seem to be particularly attuned to information about an injury. Neuroimaging studies show that IC neurons are activated by noxious stimuli via connections from the thalamus, and electrical stimulation of the IC evokes painful sensations, such as a pinprick or burning (Lu *et al.* 2016).

We have now added a new layer to our understanding of pain. The links between neurons in the thalamus and those in the ACC make us consciously aware of a given sensation, but it is the interactions between the ACC and IC that determines which particular sensation warrants immediate attention. We would expect that information about an injury would receive priority and result in enhanced attention, but this is not correct because under certain circumstances another stimulus can distract us from pain. This could be a caress, music, or anything else that diverts our attention. In contrast to its role in distraction, the IC is also activated when there is an anticipation of pain. Thus, the IC has a central role in determining whether or not pain will hurt.

Another component of the cognitive system resides within the prefrontal cortex (PFC).

The neurons in the PFC are highly interconnected with other cortical, subcortical, and brainstem sites. As such, the PFC is an essential part of a vast network that differentiates among conflicting thoughts and determines by predicting potential outcomes which one would be expected to achieve a given goal (Yuana and Raz 2014). Expectation is linked to reward and motivation that are important in assessing painfulness. Considering this, it is reasonable to believe that the hurtfulness of pain arises from the cumulative action of neurons in the thalamus, ACC, IC, and PFC.

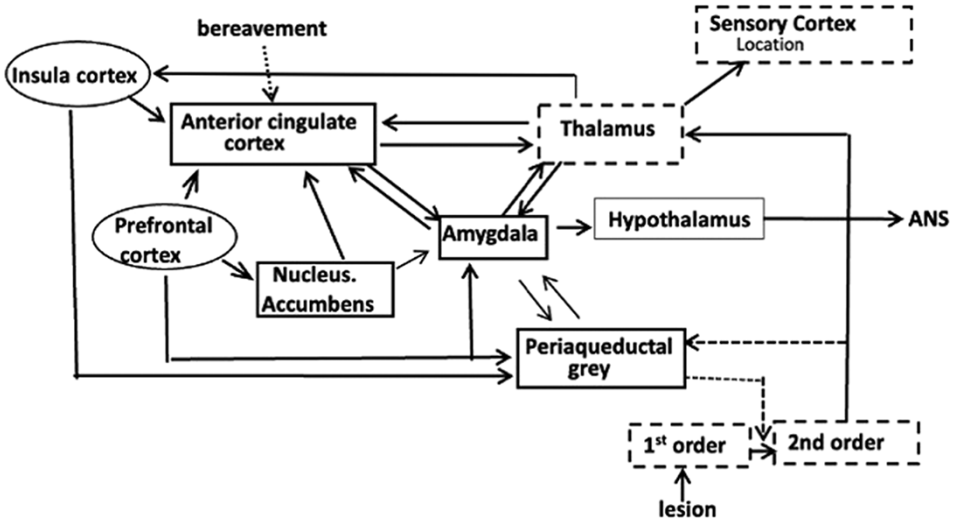


**Figure 3.** The integrated pain network comprising the connections between the components of the somatosensory system (dashed boxes), the affective system (solid boxes), and the cognitive system (ovals). ANS, autonomic nervous system

## The integrated pain network

Melzack (1990) extended the earlier idea with Casey by proposing that the modules in the affective system are linked together in a neuro-matrix for pain (Melzack 1990). This had a significant influence on contemporary ideas about pain, and Fig. 3 shows an updated version that incorporates recent results from real-time imaging supplemented by an analysis of thousands of images of thalamocortical connections (Beckmann *et al.* 2009). The network depicts the centers in the three systems that are responsible for the consciousness of pain. The thalamus is the hub that connects the somatosensory system to both the affective and cognitive systems and is the gateway for pain to both the ACC and IC. A thalamo-IC tract informs the insula cortical circuitry that there has been an injury and thereby recruits other information to the salience network. The connection between the IC and the periaqueductal gray (PAG) is important for the regulation of pain. The PAG is a group of neuronal cell bodies centered around the aqueduct of the ventricular system. Some of these neurons contain opioids, and their axons descend to the dorsal spinal cord where the release of the opioid regulates the transmission across the central synapse. After an extreme injury or traumatic event, the opioid can result in complete analgesia. The connection between the PFC and the NA is a major determinant of the value of a reward. Finally, the ACC receives information from multiple sources, including the IC for attention as well as those involved in bereavement. Circuits in the ACC are therefore likely to be essential components in how we become conscious of pain. The integrated pain network is dynamic because it responds rapidly as conditions change and shares information with other systems as the focus of attention shifts to best respond to external events. The network provides a working model depicting the interactions between the disparate neuronal centers that contribute to pain. The network is sure to be refined as we learn more about the functions of these centers and their connections with other areas of the cortex.

## Which circuits in the integrated pain network are both necessary and sufficient for the experience of pain?

Table 1 provides clues to answering this question by comparing the results of baseline images of pain with those obtained in response to various conditions and protocols. Images of patients suffering from either chronic lower back pain or fibromyalgia show increases in the activity of the IC, PFC, ACC, and amygdala but none in the centers in the somatosensory system (Staud 2011). That these centers are activated during prolonged pain indicates that they are essential.

**Table 1.** Changes in activity in the components of the pain matrix under the conditions specified. Open boxes indicate that the center was not monitored.

| | Injury | Chronic | Placebo | Hypnosis | Anticipation |
|---|---|---|---|---|---|
| PCG | Increase | None | Decrease | | Increase |
| Thalamus | Increase | None | Decrease | | |
| ACC | Increase | Increase | Decrease | Decrease | Increase |
| IC | Increase | Increase | Decrease | Increase | Increase |
| PFC | Increase | Increase | Increase | Decrease | |
| PAG | Increase[a] | | Increase | | |
| AMYGD | Increase[b] | Increase | Decrease | | |
| NUC ACC | | | Increase | | |

PCG, postcentral gyrus. [a]After extreme injury or stress.
[b]When fear is involved.

A different perspective is obtained from studies of the placebo effect in which patients believe that their pain will be relieved by a treatment that has no therapeutic effect. fMRI images of patients successfully treated with placebo revealed a decrease in the activity in the thalamus, somatosensory cortex, ACC, IC, amygdala, and spinal cord and an increase in the activity in the PFC, NA, and PAG (Ossipov 2012; Wager and Atlas 2015). Evidently, placebo-induced analgesia occurs due to the reward system acting via the PAG and the opioid pathway. This is confirmed by a study showing that the placebo effect is prevented by naloxone that blocks the opioid receptor (Ossipov 2012; Wager and Atlas 2015).

A very interesting response to pain was seen in patients who were treated by Franz Mesmer, a German physician who in the mid-1850s induced a state in which people were "mesmerized", i.e. hypnotized. Those in deep hypnosis focused attention on a particular object or sensation with a greatly diminished awareness of their surroundings. In spite of its potential use to mitigate pain, hypnosis was dismissed as a parlor trick but has seen a revival recently to treat pain and reduce anxiety. Unfortunately,

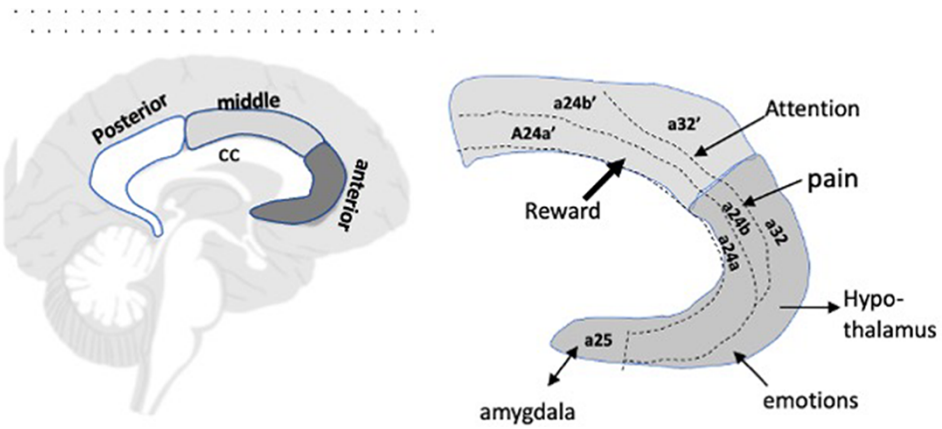


**Figure 4.** Divisions of the ACC. (A) The ACC, located above the corpus callosum (cc), is partitioned into posterior (white), middle (light gray), and new anterior (dark gray) regions. (B) Within the middle and new anterior divisions, Brodmann's area 24 has been divided into dorsal (b) and ventral (a) regions; these areas within the MCC are denoted with an apostrophe (′). The arrows point to areas that have been generally assigned to certain functions based on their inputs

only ~about 10% of the populace can enter a deep hypnotic trance. Brain images of subjects under deep hypnosis, like those believing in a placebo, had reduced activity in the ACC (Jiang *et al.* 2017). What was most intriguing happened when subjects under deep hypnosis were told to expect that a non-painful stimulus would be painful: the subjects reported feeling pain and imaging revealed increased activity in the ACC and the IC (Jiang *et al.* 2017). We know that painfulness is enhanced by anticipation, and studies show that the increase in pain correlates with an increased activity in the ACC (Table 1) (Lazaridou *et al.* 2018).

## The ACC is a primary center for pain

The results shown in Table 1 indicate that pain is associated with an increase in the activity of both the IC and ACC, which is reasonable since they are part of the salience network that determines which sensation will receive attention. However, it is the ACC that is essential for the consciousness of pain because its activity consistently correlates with the intensity of the pain. Thus, a higher activity is seen after an injury in patients experiencing chronic pain, extreme bereavement, or in response to stress or anxiety and a decrease in activity during hypnosis- and placebo-induced analgesia. Moreover, the activity in the ACC seems to be associated specifically with the hurtfulness of pain. Chronic pain patients whose cingulate cortex was surgically removed reported that the pain was present but was less bothersome (Foltz and White 1962). The removal did not prevent the patients from realizing that they were injured, and the separation of the painfulness from awareness was much like the response of the lobotomy patients.

Most persuasive, however, are the results obtained from a study that used real-time fMRI in a feedback protocol to teach a group of volunteers how to willfully increase and decrease the activity in the ACC (deCharms *et al.* 2005). Subjects who could successfully regulate the ACC activity were given a noxious, localized thermal stimulus. When asked to evaluate the pain, they reported that the painfulness increased when they deliberately increased the activity of the ACC and that the painfulness diminished when they reduced the activity in the ACC. The definitive experiment was then carried out on a small group of chronic pain patients who were trained to control the activity in the ACC. Unlike the subjects mentioned earlier, the patients were not given the noxious thermal stimulus but were asked to evaluate their ongoing pain. The results were the same: a significant decrease in the level of painfulness when they deliberately reduced the activity in the ACC. These results suggest that the control over the ACC was powerful enough to impact chronic clinical pain.

## The ACC has multiple circuits for nociception

The ACC contains circuits responsible for several aspects of the pain experience, but it is anatomically and functionally heterogeneous. Korbinian Brodmann stained sections through the cerebral hemispheres, and in a series of eight papers published from 1903 to 1908, he divided the cerebral cortex into 48 regions based on differences in the composition and organization of their neurons.[3] The ACC was subdivided into primary areas 24, 25, and 32, (Fig. 4). Subsequent studies showed that these areas could be further divided based on differences in function (Vogt *et al.* 2003). As a result, what was originally called the ACC now consists of new anterior cingulate cortex (nACC) and middle cingulate cortex (MCC) regions (Fig. 4). The addition of an MCC is a complication because many of the fMRI studies did not distinguish between the nACC and MCC. In general, the nACC assesses the emotional and motivational aspects of information received from internal sources, such as bereavement, and external sources, such as an injury. In contrast, the MCC contributes to cognitive control via connections to the PFC and contributes to the salience network that determines which sensation will be attended to, i.e. will reach consciousness. That both the nACC and MCC are functionally heterogeneous was confirmed by extensive tracing studies in which fiber tracts from cortical and subcortical regions divide to enter specific areas within the ACC (Beckmann *et al.* 2009). The connectivity profiles correspond to what was predicted by Melzack (1990) and to those depicted in the integrated pain network (Fig. 3). By combining these results with others, we can now assign specific functions to areas within both the nACC and MCC, and this requires a further parcellation of the cortical areas. Thus, the nACC, which occupies the frontal third of the cingulate cortex, contains a24a/b, a25, and a32, The MCC occupies the middle third of the cingulate cortex and contains areas a24a′/b', and a32′ (Fig. 4).

[3] Korbinian Brodmann (1868–1918) was a German neurologist who became famous for his publications on the cytoarchitectonic parcellation of the human cerebral cortex. He was a founder of the field of anatomical brain mapping, and Brodmann's areas have become particularly important recently due to fMRI and meta-analyses of their structural and functional relationships. As a measure of his importance, by 2018, his work was cited 170,000 times.

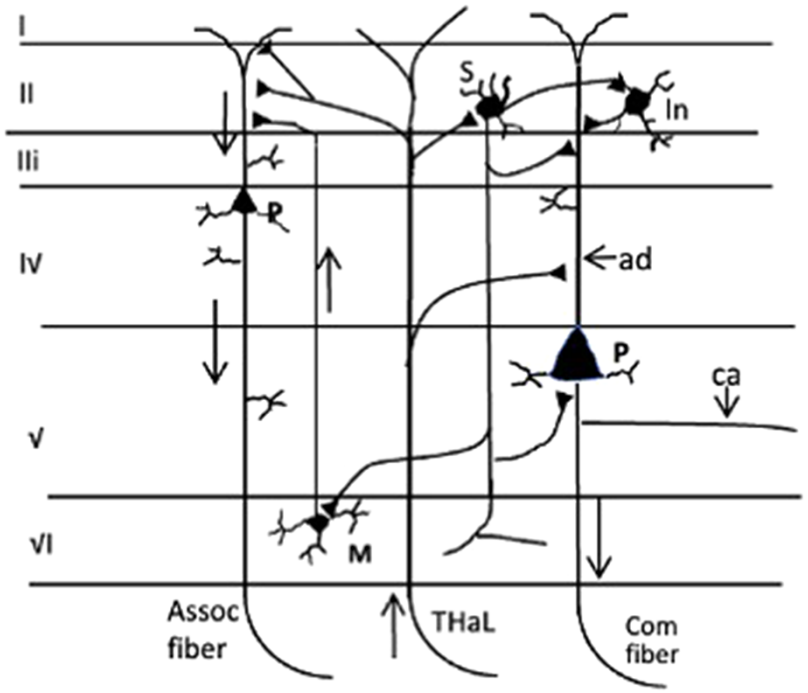


**Figure 5.** General intraneuronal circuits of the cerebral cortex. The cell bodies of the primary pyramidal neurons (P) are located in laminae IV. Each has a long apical dendrite that receives information from thalamocortical (THal) axons in laminae I–II, as well as inputs from other cortical regions. The main axon of the pyramidal neurons exits the cortex and can project to the cortex on the same side as an association (Assoc) fiber, cross through the corpus callosum to the opposite hemisphere as a commissural (com) fiber, or project to subcortical neurons in the thalamus. A shorter collateral axon (ca) courses to the adjacent cortex. Stellate cells (S) have long axons that project to deeper layers. Inhibitory Martinotti (M) axons project into lamina I where they synapse on the apical pyramidal dendrites. Other stellate cells have short axons that synapse on nearby pyramidal neurons (P)

## The functions of circuits in the ACC

Data indicate that inputs from the thalamus via a medial thalamocortical tract activate circuits for pain centered around a24a/b and a32 in the nACC (Fig. 4) (van Heukelum *et al.* 2020). There is some overlap with the contiguous regions in the MCC, which would explain why the original ACC was consistently detected in the imaging studies. However, the hurtfulness of pain does not emerge solely from the activity in this pain center but requires connections from the PFC and IC that activate the circuits in the center that is responsible for attention. Results place the area of focused attention in a24a'/b' within the MCC (Weissman *et al.* 2005). Thus, the area that receives pain information about an injury from the thalamus and other cortical centers is close to the area that focuses the attention on the pain. Other locations within the nACC and MCC receive inputs from the affective centers that regulate the extent of the pain.

Activation of circuits within the amygdala intensifies the onerous aspect of pain by increasing anxiety and eliciting fear. It is notable, therefore, that a25, and the rostral-most regions of a24a/b, and a32 within the nACC have strong reciprocal connections with the amygdala and the center for the expression of emotions, respectively (Fig. 4) (Beckmann *et al.* 2009; van Heukelum *et al.* 2020). Moreover, areas within a32 in the nACC communicate with the hypothalamus that can activate the autonomic nervous system to influence heart rate, blood pressure, and the facial expressions of pain.

The other primary determinants of the intensity of pain are the circuits responsible for reward. The area of activity associated with reward is located in the vicinity of a24a'/b' in the anterior region of the MCC (Fig. 4). Determining whether or not a reward is sufficiently valued to bear pain is complex because it involves beliefs, an evaluation of possible outcomes, and motivation. Activation patterns in these regions suggest that they have a role in decision-making and formulating predictions in terms of immediate gains and costs or in terms of information that will aid future decision-making (van Heukelum *et al.* 2020).

## Neuronal circuits within the ACC

Pyramidal neurons, stellate cells, and inhibitory neurons form the circuits within each cortical region (Eickhoff *et al.* 2017). The neurons are not randomly distributed but, as shown by Brodmann, can be assigned to one of the six laminae (Fig. 5). Pyramidal neurons are the primary communicators of the cortex, and they can be subdivided by size and location (Fig. 5). A typical large pyramidal neuron in lamina V has a long apical dendrite that extends toward the surface with extensive branches in laminae I–II. This large dendritic area receives the information from the thalamus and from other cortical areas. A single long axon from the pyramidal cell body exits the cortex into the white matter to communicate with distant cortical areas. Thus, the pyramidal neurons receive inputs from other cortical regions and are responsible for transmitting information via corticocortical pathways to other cortical regions. Interneurons and inhibitory neurons modulate the activity of the apical dendrites and regulate the output of the pyramidal neurons (Swanson and Maffei 2019). Most important is what occurs at the synapse between incoming axons and the apical dendrites in laminae I–II.

## Plasticity at pyramidal synapses

Transmission across the axodendritic synapses in laminae I–II is controlled via the development of a long-term potentiation (LTP).

LTP was first described in studies of learning and memory in *Aplysia* (Hawkins *et al.* 2006) and was subsequently found to occur in the hippocampus (Lømo *et al.* 2003). LTP sensitizes the synapse, making it is more responsive to incoming action potentials. The LTP is responsible for allodynia, whereby merely touching the injured area elicits few action potentials but causes intense pain. LTP has early and late phases, and it is the late phase that is required for the experience of pain. Understanding the molecular events responsible for the late phase is therefore important (Zhuo 2014).[4] The late phase begins when a barrage of action potentials generated by an injury propagate to the apical dendrites in laminae I–II. The action potentials cause the release of the excitatory neurotransmitter glutamate (Glu) from the presynaptic terminal. The Glu binds to AMPA receptors on the postsynaptic membrane, triggering an influx of Na+ and the generation of excitatory postsynaptic potentials (EPSPs) in the postsynaptic terminal. When the number of action potentials is sufficient to generate many EPSPs, NMDA receptors in the membrane of the postsynaptic terminal are activated. NMDA receptors are coupled to an ion channel with a preference for Ca++. The channel is normally closed by a tightly bound magnesium ion (Mg++), and when it opens in response to a high-frequency input, there is a major influx of Ca++ into the postsynaptic terminal (Blanke and Van Dongen, 2009).[5] The Ca++ combines with calmodulin to activate adenylyl cyclase-1 (AC-1). AC-1 is one of the 10 subtypes of adenylate cyclase and is the predominant type in the ACC (Shiers *et al.* 2022). Activated AC-1 synthesizes cyclic adenosine monophosphate (cAMP), which activates protein kinase A. The protein kinase A enters the nucleus (with other kinases) where it binds to the cAMP response element–binding protein (CREB). CREB is a transcription factor, and its activation leads to the synthesis of proteins that change the phenotype of the pyramidal neurons.

Phenotypic changes are long lasting, and the sensitization of the synapse due to LTP has a profound effect on the duration of pain. The role of AC-1 in the pyramidal neurons is important because inhibiting AC-1 in the ACC of mice both prevents the development of LTP and reduces the persistent pain in response to an injury without affecting acute pain (Liauw *et al.* 2005; Vadakkan *et al.* 2006; Liu *et al.* 2020; Zhou *et al.* 2021; Shiers *et al.* 2022). Thus, by manipulating AC-1 activity, we can obtain clues as to how pain emerges from the circuits in the ACC. The findings also support the idea that acute and persistent pain utilizes different pathways and circuits.

The LTP that develops at synapses in the ACC also has a dynamic effect because it enables one pathway to establish dominance over others. Suppose a pyramidal dendrite receives inputs from several neurons. If the frequency of incoming action potentials from one of these inputs produces LTP, that synapse and its connections will become dominant over those with fewer inputs. If two high-frequency inputs to the dendrite are received at the same time, it will further strengthen the pathway and the flow of information to its targets. The strengthening of one pathway over others is a form of neuronal plasticity in which the brain adapts to repeated events by reinforcing the pathway that best responds to the event. Pain is a priority, and the circuits involved will be dominant when responding to an injury. With chronic pain, these pathways could be so well established that they dominate all others and could even function autonomously.

## Consciousness and pain

The evidence presented earlier indicates that the experience of pain emerges in some way from activities in the centers for attention and pain within the ACC. An emergent property cannot arise from the activity of any single neuron but is due to the sum of the activities in an entire circuit. This is important because a circuit can be manipulated pharmacologically, electrically, and genetically. Presumably, what emerges from the activity of each circuit is some type of immaterial force, and I propose that by selectively interfering with the molecular events in the circuits for pain and attention, we will gain insights into the processes that are necessary for this force to emerge.

McFadden (2020) and Pockett (2012, 2017) independently proposed an electromagnetic (EM) field theory of consciousness that relies on the formation of local field potentials (LFPs). Their ideas are attractive because they can be objectively evaluated by using the circuits in the pain and attention centers as models. Studies of the hippocampus and other cortical regions have shown that an LFP is a consequence of the flow of ions during the generation of EPSPs in pyramidal neurons (Linden *et al.* 2010; Lømo *et al.* 2003; Buzsáki *et al.* 2016). As in the hippocampus, the pyramidal neurons in both the centers for pain and attention have a very long apical dendrite that branches extensively in laminae I–II (Fig. 6A). The branches intermingle with the dendritic terminals of adjacent pyramidal neurons to form a large field of postsynaptic terminals that are distant from their cell bodies in lamina V (Linden *et al* 2010; Pockett 2012, 2017; Buzsáki *et al.* 2016).

Based on the ideas of McFadden (2020) and Pockett (2012, 2017), I propose the following: high-frequency input from the thalamus and cortex causes the release of Glu from the presynaptic terminals in laminae I–II and the generation of EPSPs in the centers for pain and attention. The influx of Na+ into the very large number of postsynaptic terminals leaves a transient negative charge in the external fluid around the synapses. To balance this negativity, an equal number of positive ions exits the pyramidal cell bodies in lamina V, and the separation of charge generates an LFP (Fig. 6B) (Linden *et al.* 2010; Buzsáki *et al.* 2016). The LFP from an input to a single pyramidal dendrite is miniscule. However, the dendrites of many pyramidal neurons are aligned in laminae I–II, and when they fire in synchrony, as when pain is experienced, the result is the generation of a population EPSP and the accumulation of a very large number of negative charges in laminae I–II and positive charges in lamina V. A single large LFP is generated in the extracellular space that oscillates in synchrony with the activity at the synapses (Fig. 6) (Linden *et al.* 2010; Buzsáki *et al.* 2016).

The LFP is thought to be generated primarily by the ion fluxes due to the population EPSP and not from the rapid ion changes that result in action potentials (Linden *et al.* 2010; Buzsáki *et al.* 2016). The large LFP can be detected via an electrode placed in the extracellular space adjacent to the activated pyramidal neurons. From what we have learned, the LFP generated in response to an injury will be dominant relative to the LFPs in other cortical areas because it will be strengthened and maintained by the LTP.

The ideas proposed by Pockett (2012, 2017) and McFadden (2020) could not be tested in the whole brain. But by focusing on the two cortical centers in the ACC, we can now test two hypotheses: First that an injury generates an LFP that emerges from the activity of the pyramidal neurons in both the centers for pain and attention and second that the LFP is necessary for the experience of pain.

[4] The AMPA- and NMDA-dependent LTP is the predominant source of pyramidal synapse activity, but there is evidence that other electrophysiological changes also contribute, some of which are presynaptic. See the following for more information.

[5] The regulation of NMDA channels is unique in several respects, and they are essential for the expression of pain. For a review, see Blanke and Van Dongen, 2009.

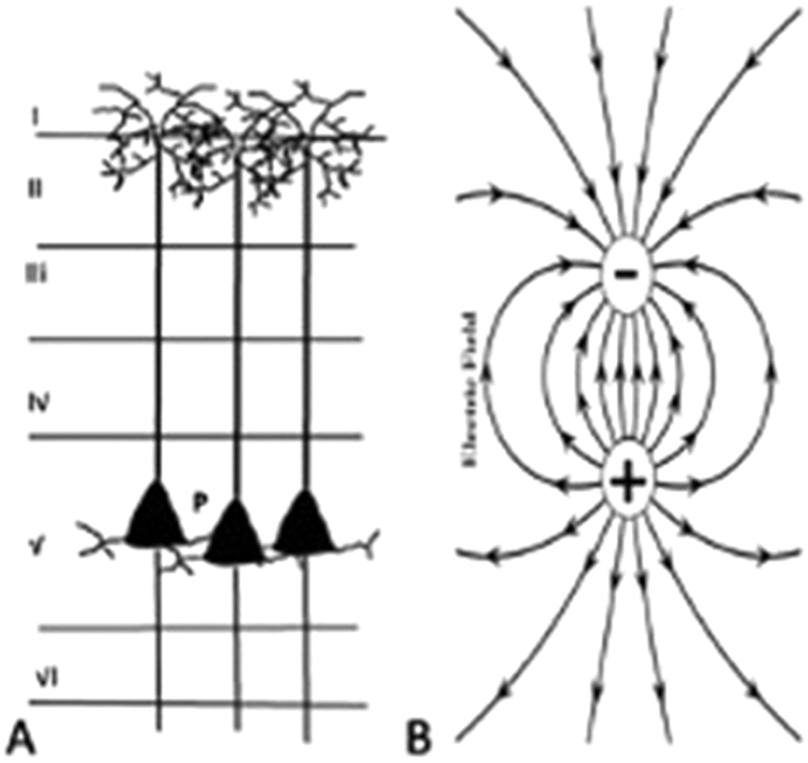


**Figure 6.** Formation of a local field potential. (A) The dendritic branches of many pyramidal neurons (P) form a large area of dendritic endings in laminae I–II. When activated by axons from nearby circuits for pain (not shown), the flow of positive ions into the terminals forms an area of negative charge in the adjacent external space. A compensatory flow of positive ions from the cell bodies in lamina V creates an area of positive charge in the external space. (B) The separation of charge creates a field potential that fluctuates with synaptic activity and extends from laminae I–II to lamina V

## The mouse ACC and the experience of pain

The experiments necessary to examine the relationship between neuronal activity and LFPs require procedures that, for ethical reasons, cannot be done in primates. Consequently, they will be carried out using mice as a surrogate. Mice are excellent models because areas in the mouse ACC can be precisely localized and because they share with humans many of the essential biochemical and electrophysiological processes that are necessary for the development of persistent pain. Among these, AC-1is especially important. AC-1 is the primary adenylate cyclase isoform in the ACC, and the development of LTP in the ACC in both mice and humans depends on Ca++ influx through NMDA channels and the activation of AC-1 (Liauw *et al.* 2005; Liu *et al.* 2020). Injecting NB001, an AC-1 inhibitor, directly into the mouse ACC effectively alleviated a chronic inflammatory pain but had no effect on anxiety or fear (Kang *et al.* 2016). The ACC contains centers for mood, and it receives inputs from the amygdala for fear. Consequently, the finding that these behaviors were not affected by NB001 implies that AC-1 activity in the ACC is specifically associated with pain. Additional evidence showing the importance of AC-1 for ongoing pain comes from the studies of a mouse where the gene that encodes the AC-1 protein was deleted. The absence of the AC-1 protein resulted in reduced neuropathic pain (Wei *et al.* 2002). Finally, chronic pain should require a persistent source of AC-1, and this is exactly what was found: studies of a mouse model of chronic inflammatory pain showed an increase in the levels of AC-1 protein in the ACC that lasted for 2 weeks (Liu *et al.* 2020).

## Locating the centers for pain and attention in mice

A consensus map of the ACC in mice showed that it could be divided into an nACC and an MCC, as in humans (van Heukelum *et al.* 2020). Although the functional areas in the human ACC are often overlapped, studies in the mice are more precise because the area being investigated can be defined by coordinates that relate the position of an external landmark (Bregma) on the skull with a map of the mouse brain (Paxinos and Franklin 2012). Coordinates identify precisely and unambiguously any location within the ACC and are used to guide the insertion of an electrode or probe into the target area. Using this approach, Koike *et al.* (2016) identified a center for attention in the rostral region of a24a in the mouse ACC. This study used a novel procedure called chemogenetics to express a protein in the a24a pyramidal neurons. The protein was engineered to block Glu-mediated synaptic activity. When the protein was activated, there was a suppression of attention in a standard behavioral test. We can use the coordinates they provided to evaluate the role of the LFP generated by the neurons for attention in a24a.

A center for pain in mice has been found in the rostral region of a24b. The assignment was based on the analysis of data from multiple sources, as well as a thorough study of the tracts from the thalamus to a24a and a24b (Koike *et al.* 2016; Fillinger *et al.* 2017; van Heukelum *et al.* 2020). A24b is located just below the center for attention, which is consistent with the findings in humans and primates that the two functions involve different cortical circuits. The location of the pain center is important because it is close to

the cortical circuits in mice that mediate anxiety and depression (Sellmeijer *et al.* 2018). Both are serious concomitants of chronic pain in humans, and much might be learned about how these areas interact by studying the circuits in mice.

## LFPs and the attention to pain

We can now test the first hypothesis: does the consciousness of pain require the formation of the LFPs that arise from the synchronized activity at pyramidal neuronal synapses? Actually, the basic experiments required to answer this question have already been done in the mouse ACC, just not in the context of consciousness, and they merely need to be repeated on the circuits in a24a and a24b. The protocols have been described in great detail and are only summarized here (Liauw *et al.* 2005; Vadakkan *et al.* 2006; Liu *et al.* 2020; Zhou *et al.* 2021).

The experiments should be carried out on both the center for attention, a24a, and on the center for pain, a24b, but will be described for the former. Published coordinates are used to insert a micropipette containing a fluorescent dye into a24a in the brain of an anesthetized mouse. The mouse is sacrificed, the brain is sliced into segments, and the segment that contains a24a is identified by the fluorescence. A microelectrode is inserted to deliver the stimulus protocol that elicits LTP at pyramidal neuronal synapses, and the presence of the LTP is verified via another electrode to record pyramidal neuronal activity. At the same time, the presence of the LFP is assessed via an electrode array inserted near laminae I–II. Detecting an LFP in a24a is expected based on previous results from the studies of the ACC and hippocampus.

The next step is to dissociate synaptic activity from the LFP by applying the AC-1 inhibitor to the slice. The AC-1 prevents the development of the LTP and should therefore block the appearance of the LFP. The crucial experiment is to block the formation of the LFP in a24a. Experiments have shown that the application of an exogenous force potential can either enhance or suppress an endogenous LFP generated by synaptic activity (Fröhlich 2014). This will first be tested in a24a in the brain slices. The LFP is generated as described earlier, and an electrode positioned in the external space adjacent to laminae I–II is then used to evoke an external field potential that is inversely matched to the strength and timing of the activity-generated LFP. The suppression of the LFP is verified by the external electrode.

An interesting experiment at this point would be to compare the properties of the LFP that emerges from the centers of attention and pain. An LFP oscillates with the activity of the pyramidal cell synaptic array and is therefore dependent on the characteristics of the LTP. The development of an LTP depends on both the frequency of the input and the subsequent activity of receptors, channels, and kinases. Differences among these will alter the properties of the LTP and the resulting LFP, and there is evidence that such differences exist among circuits in the cortex (Zhuo 2014). Finding differences in the frequency of these oscillations between the LFP from a24a and a24b would mean that each LFP contains information unique to the circuit from which it arises. If correct, then each LFP contains information in real time about the activity of the synapses in its circuit and, by extrapolation, the event that is responsible for its formation.

## LFPs and the attention to pain in freely moving mice

The experiments using the brain slices will provide the parameters necessary to create and cancel the LFP, but brain slices cannot be used to determine whether or not cancelling the LFP prevents the experience of pain. These experiments will be carried out in freely moving mice where the response to a painful stimulus can be measured (Kolb *et al.* 2018).[6] The parameters from the slices will be used to study mice that experience chronic allodynia due to a damaged nerve in the paw. The intensity of the pain or analgesia is assessed using a standard protocol. Two microelectrodes are inserted into the external space of laminae I–II in a24a. One is used to record the appearance of the LFP created in response to attending to pain, and the other is used to neutralize the LFP. After the animal has recovered from the surgery, the injured paw is briefly touched to elicit withdrawal of the limb, which should coincide with the appearance of the LFP. If what was predicted about the role of the LFP is correct, the withdrawal will not occur when the LFP has been countered by the neutralizing stimulus.

There is nothing remarkable or difficult in these protocols; they have not been used previously to study consciousness simply because there was no site in the brain to test. The experiments are doable, but the outcomes could differ in important ways. For example, the stimulus parameters that cancel the LFP might be variable. They would then have to be determined in each experiment in the freely moving mice, and more electrodes will be required. This complicates the procedure but does not prevent the experiments from going forward.

## LFPs, the binding problem, and consciousness

Finding a direct correlation between the LFP and the attention to pain would have far-reaching consequences. Recent studies have shown that the LFP generated by the synchronous firing of a localized array of neurons is not a mere epiphenomenon of synaptic activity but that it can feedback via ephaptic coupling to influence the activity of the circuit from which it arises, as well as the activity of circuits nearby (Anastassiou *et al.* 2011; Frohlich and McCormick 2013). Consequently, the LFP generated by the circuit for attention could organize or coordinate activity in the adjacent circuits for fear and anxiety. LFPs could also perturb activity in ways that are not yet understood, especially if the LFPs generated by different circuits are different. Moreover, an LFP can only emerge from circuits in which a great number of pyramidal synapses fire synchronously. This means that regions of the brain that do not have the laminar structure, such as the thalamus, cannot generate an LFP, nor can many of the circuits responsible for refined motor movements (Pockett 2012, 2017; McFadden 2020).

The binding (aka combination) problem recognizes that although our concept of the external world is mediated by sensations, the circuits responsible for each sensation are located in distinct centers dispersed throughout the brain. How then does in the information from these centers merge to create a unified, coherent version of the world? The generation of LFPs might provide an explanation. For example, the LFP that arises from the synchronous firing of the lamina V neurons in response to a lesion is a non-material manifestation of pain. Through ephaptic coupling, the LFP containing the pain information could spread to merge with the LFPs that contain information from other sensations to create a single unified force field that yields the dynamic conceptualization of the external world in real time. Although this is pure speculation, we should not overlook that the properties of the LFPs upend the idea that the flow of information throughout the brain is determined solely by action potentials coursing along neuronal networks.

[6] For example, see Kolb *et al.* (2018).

## Conclusion

Any theory to explain consciousness must offer hypotheses that can be tested experimentally, and this has proven difficult when attempting to understand universal consciousness. I have taken a reductionist approach and asked a much simpler question: how do we experience or become conscious of pain? I selected pain because we know a great deal about the neuronal circuits that are responsible for communicating information about pain. These are depicted in an integrated pain matrix (Fig. 3) that indicates how the sensation of pain arises from three systems, each of which consists of discrete centers that impart different aspects to the ultimate experience of pain. Tract tracing combined with fMRI of subjects in pain indicated that essential circuits for pain are located in the ACC. Additional evidence from electrophysiology and molecular biology linked pain to the development of an LTP in lamina V pyramidal neurons in a circuit for pain and another for attention in the ACC (Fig. 4). The LTP depends on the release of glutamate at the pyramidal synapses, which activates AMPA and NMDA receptors, as well as an isoform of adenylate cyclase. Due to the overlapping distribution of the pyramidal dendrites, input from an injury will result in a synchronous firing at the synapses, resulting in a population EPSP and the generation of an LFP in the external space. All this evidence supports the electromotive field theory originally proposed independently by Pockett (2012, 2017) and McFadden (2020). The story is not complete, and there is more to be learned about the biochemical events responsible for generating the LTP and the LFP as well as the role of inhibitory and interneurons in the circuits. Nevertheless, the evidence accrued so far indicates that the LFP is a non-material representation of pain in the space surrounding the lamina V pyramidal neurons in each circuit. I have therefore proposed that the LFP is necessary for the experience—the consciousness—of pain and discuss how this hypothesis can be rigorously tested in mice using techniques and protocols that are already available. Finding that the hypothesis is correct will not allow us to conclude that the LFP actually encodes a consciousness of pain, but it should at least provide insights that will move us a step closer to understanding the nature of consciousness.

## Conflict of interest statement

The author attests that there is no conflict of interest or financial reward from the publication of this manuscrpt and that all information is freely available.

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