e-News Somatosens Rehab 2017, *14* (4)

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Official e-Journal of the Somatosensory Rehabilitation of Pain Network

www.neuropain.ch

Peer-reviewed open-access journal

GUESTEDITORIAL

Pain: the use and the pathology

To medical doctors To neuroscientists
To patients **To therapists**

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Pain is not evil

Pain is crucial to our survival

Pain is a mechanism that remained through evolution and therefore a byproduct of natural selection. It allows all the vertebrates to detect a harmful stimulus and protect themselves against dangers or diseases, which could undermine the integrity of the body. In order to feel pain, vertebrates have been equipped with pain sensors, or nociceptors, in appropriate places in the body. Our nervous system is as complex and well developed that we have all the adequate peripheral and central pain pathways, the neurotransmitters and the brain analyzers to process a painful stimulus and initiate the appropriate behavioral response. This is valid for acute pain as well as for long-lasting pain (excluding chronic pain): the first one leads the subject to remove its hand from the fire; the second encourages it to avoid touching a lesion and so to avoid an infection or the motility of an injured leg. Pain also acts as reinforcement in learning to avert potential physical damages: animals learn from their painful experiences. Indeed, the pain circuits recruits two brain regions involved in learning of salient information: the hippocampus and the amygdala.

Although, if the feeling and the processing of pain is crucial for survival, a constant pain is not interesting for evolution. So, as the nature is well made, we are endowed of internal control of pain. The descending circuits of pain take their origin in the brain and go towards the periphery, attenuating pain through endogenous opioid and neuromodulators (mostly the serotonin) delivery. In addition, noxious stimuli of a specific region can, by themselves, reduce the pain invading another region. In other words: pain inhibits pain. This idea anchors the theories of the Diffuse Noxious Inhibitory Control (Marchand, 2014) or the Gate Control Theory. You will find out more through the pages of this new edition of *e-News Somatosens Rehab*.

Anyway, Humans with a high sensitivity are better equipped to master the adaptive challenges. Within some tribes, the high sensitivity to pain is also proven during initiation rites. For example, the Iatmuls tribes in Papua-New-Guinea give the insider's body a crocodile look by mutilating the skin, cutting nicks in an extremely painful manner. Some of them, "the least resistant", die of a severe infection or because of the blood loss. The survivors are strong and fighted pain, can move from the childhood to the adult stage.

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All taken, the pain and the way we manage it increase our survival value. This could not be truer than in the case of patients with congenital insensitivity to pain, when a person cannot feel and has never felt pain. Most of the time, those patients die prematurely, because of heavy injuries or unnoticed illness which did not ring the alarm signal. In addition, this kind of global anesthesia modifies the relationship of those patients to their own body. They try to stimulate themselves, scratch themselves, scrape or bang their heads, expressing a lack of certainty about the limits of their bodies. A body that does not suffer can make us feel as strangers. Therefore, a life without pain is not desirable, because finally pain makes us feel alive. Moreover, it is under the prism of this quest for "feeling alive" that some people enjoy the pleasure of sadomasochist sexual practice: at the top of the pyramid of pleasure, above submission to pain and mastery of pain, **reigns above all the feeling of feeling and being alive**.

Pain is not evil, unless it conquers us

These words have been written by the English novelist George Eliot (1819-1880). They perfectly translate the fact that pain becomes evil when its first function (the protective effect) disappears for the benefit of a chronic pain. When it becomes chronic, meaning that it persists for months or for years, pain loses its sense of utility and becomes by itself a disease. More vicious with chronic pain is that even if the physical marks of an injury (a lesion or a cast) disappeared, the pain still invades the body and the spirit. "I don't have any lesion, so why am I suffering?". "You are not suffering as much as you are saying, as there is nothing wrong with your body!". In addition to the constant pain appear psychopathological manifestations and psycho-social troubles appear: "What is this body suffering that I cannot control?". Most of the time, chronic pain is mixed-up with depression: the patient is depressed because of the pain, and his/her pain is accentuated by the depression, all of this accompanied by a lack of understanding from the family and the health-care staff.

Chronic pain is induced either by a neuropathic lesion - **neuropathic pain** -, either by an excessive stimulation of the nociceptors - **inflammatory pain** -, or by a dysfunction of the internal controls of pain - **dysfunctional pain** -. Whatever the cause, chronic pain is a maladaptive response of the nervous system to damage. It results in spontaneous pain or in an exaggerated pain induced by a low-intensity noxious stimulus, or sometime by a simple tactile stimulus. In all cases, chronic pain is a consequence of a sensibilization of the sensitivity circuits and pain matrix, from the skin to the brain.

Above, we saw that pain reinforces for learning. Here, the notion of learning is also applicable as the chronic pain settles under the concept of neuronal plasticity. The neuronal synaptic plasticity underlines the cellular and molecular basis of learning and memory. It reflects the ability of a neuronal network to facilitate the transmission and the integration of an information by potentiating the nervous connections (long-term potentiation), or at the opposite, by a depression of the connections between neurons and circuits (long-term depression, the key of forgetting). We could say that the brain of patients suffering from chronic pain reinterprets a gentle tactile stimulation as a painful stimulus.

As an example, mechanical allodynia is one of the dramatic painful symptoms and ghostly pain remaining after a neuropathic injury. Imagine that while you are stroking your arm with a feather, it is an intense burning by a torch that you are feeling on your skin. This is what patients suffering

from allodynia feel when they put their clothes on, when they take a shower or simply when the bed sheet rubs their skin.

Currently, no pharmacological treatment is efficient enough to alleviate the pain. However, by using a sensitive re-education (by doing counter-stimulation), clinicians try to "re-arrange the connections" within the not-well configured brain circuits in patients suffering from allodynia. The idea is to initiate a new learning that this gentle stimulation on the skin territory innervated by the damaged nerve is not painful.

However, our understanding of pain circuits and how chronic pain sets-in still needs more investigations. Since the last decades, clinicians and researchers delve into the intricate details of pain mechanisms to find a way to treat this invisible but real pain, which affect 6.9 % of the population (Bouhassira et al., 2008). In fundamental research, our interest is to investigate the pain circuitry at circuits, cellular and molecular levels. By using animal models with invasive and challenging techniques, we can go deep in the brain to investigate the specific phenotype of neurons involved in a pain symptom (molecular biology[1]); we can look at the neuronal electrical activity and study how the neurons respond to a drug (by using electrophysiological recordings[2]); we can see the consequence of an activation or an inhibition of a specific population of neurons (through optogenetic activation/inhibition[3]) on the behavioral reaction to a painful or a tactile stimulus.

Clinicians and researchers work hand in hand to investigate and understand functions und dysfunctions of pain. So **could we dream of a life without pain** ? Certainly not, when it comes to its function as a necessary protection mechanisms that accompanies us through our development. But when it comes to pain that becomes a conqueror who invades our bodies we dare to dream of a life without it.

[1] Molecular biology corresponds to the study of the molecular basis of biological activity between molecules in a cell. It includes the study of interactions between DNA, RNA, and proteins and their biosynthesis.

[2] Electrophysiological recordings of neurons is a technique consisting to record the neuronal activity (electrophysiological activity) of a cell by inserting a micro-glass pipette containing a recording electrode around or into the neurons. By using this technique, we can gain the access to the electrophysiological and the morphological properties of neuronal circuits.

[3] Optogenetics is a biological technique involving the use of light to control neurons that have been genetically modified (by using virus) to express light-sensitive ion channels at the membrane. When expressed, the activation of those channels can modulate the excitability, and hence the activity of neurons.

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