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Topical review

A neurobiologist's attempt to understand persistent pain

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HIGHLIGHTS

- To explain persistent pain we must integrate biologic, mental and behavioural levels.
- Pain may be understood as a result of an interpretation of the health of the body.
- Many small challenges may together bring pain networks in a state of hypervigilance.
- The meaning of the pain to the patient is crucial if the goal is to reduce suffering.

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ABSTRACT

This topical review starts with a warning that despite an impressive wealth of neuroscientific data, a reductionist approach can never fully explain persistent pain. One reason is the complexity of clinical pain (in contrast to experimentally induced pain). Another reason is that the "pain system" shows degeneracy, which means that an outcome can have several causes. Problems also arise from lack of conceptual clarity regarding words like nociceptors, pain, and perception. It is, for example, argued that "homeoceptor" would be a more meaningful term than nociceptor.

Pain experience most likely depends on synchronized, oscillatory activity in a distributed neural network regardless of whether the pain is caused by tissue injury, deafferentation, or hypnosis. In experimental pain, the insula, the second somatosensory area, and the anterior cingulate gyrus are consistently activated. These regions are not pain-specific, however, and are now regarded by most authors as parts of the so-called salience network, which detects all kinds of salient events (pain being highly salient). The networks related to persistent pain seem to differ from the those identified experimentally, and show a more individually varied pattern of activations. One crucial difference seems to be activation of regions implicated in emotional and body-information processing in persistent pain.

Basic properties of the "pain system" may help to explain why it so often goes awry, leading to persistent pain. Thus, the system must be highly sensitive not to miss important homeostatic threats, it cannot be very specific, and it must be highly plastic to quickly learn important associations. Indeed, learning and memory processes play an important role in persistent pain. Thus, behaviour with the goal of avoiding pain provocation is quickly learned and may persist despite healing of the original insult. Experimental and clinical evidence suggest that the hippocampal formation and neurogenesis (formation of new neurons) in the dentate gyrus are involved in the development and maintenance of persistent pain.

There is evidence that persistent pain in many instances may be understood as the result of an interpretation of the organism's state of health. Any abnormal pattern of sensory information as well as lack of expected correspondence between motor commands and sensory feedback may be interpreted as bodily threats and evoke pain. This may, for example, be an important mechanism in many cases of neuropathic pain. Accordingly, many patients with persistent pain show evidence of a distorted body image.

Another approach to understanding why the "pain system" so often goes awry comes from knowledge of the dynamic and nonlinear behaviour of neuronal networks. In real life the emergence of persistent pain probably depends on the simultaneous occurrence of numerous challenges, and just one extra (however small) might put the network into a an inflexible state with heightened sensitivity to normally innocuous inputs.

Finally, the importance of seeking the meaning the patient attributes to his/her pain is emphasized. Only then can we understand why a particular person suffers so much more than another with very similar pathology, and subsequently be able to help the person to alter the meaning of the situation.

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Contents

1. Introduction

1.1. Complex problems require an integrated approach

1.1.1. The failure of reductionism

"The brain is not merely complex – it is fantastically complex. There are too many degrees of freedom to allow any practical constraint on the possibilities for our understanding." This statement by the British neuropsychologist Weiskrantz [1, p. 10] comes to mind when trying to explain persistent pain by reference to neural structures and processes. The complexity of the brain and the multitude of factors determining human mental life and behaviour strongly suggest that persistent pain cannot be understood by a reductionist approach alone [2–4]. As expressed by Keele in 1957 [5, p. 188]: "Perpetuated pain is... always complex pain, containing many components built into a pain edifice the exploration of which presents the clinician with a very different problem from the physiologist's analysis of experimental pain." This complexity may explain why – despite an exponential rise in publications – the translation of experimental pain research to clinical applications has been disappointingly slow [6,7]. The clinician cannot permit himself the luxury of focusing solely on one aspect, such as peripheral mechanisms, dorsal horn plasticity, or cognitive-emotional factors. In such a situation, it might be advisable to adopt a "bird's eye view" rather than addressing single factors in detail. This Topical Review is an attempt at such an approach.

1.1.2. Degeneracy and reductionism

A further reason why the reductionist approach fails is that complex biologic systems exhibit *degeneracy* – that is, an outcome does not have a unique basis, and similar patterns of activity can be produced by different mechanisms [8–10]. For example, several kinds of ion channels can render nociceptors hyperexcitable, and if one is blocked others take over [10]. Furthermore, neural networks typically exhibit degeneracy – that is, more than one neuronal system can produce the same response [11,12]. For example, pain with the same location and of the same character may be associated with different cortical activation patterns [13]. It is indeed striking how pain therapies aiming at eliminating one apparently crucial component in the "pain edifice" (e.g. cordotomy, dorsal rhizotomy, nerve section, blocking specific ion channels) so often give only temporary relief [10,14–16]. That persistent pain is associated with hyperexcitability (sensitization) in parts of the CNS begs the question of what causes the hyperexcitability and why it occurs in one person but not in another.

2. Pain and nociceptors – a conceptual note

2.1. What pain is and what it is not

Unfortunately, the "pain" literature is often conceptually unclear due to a lack of an explicit distinction between pain as a sensation (experience) on the one hand and its causes and underlying mechanisms on the other. Pain is a sensation, and in common with other sensations (e.g. itching) it has a bodily location. Nevertheless, pain is obviously not a *thing* that can be physically localized, in contrast to neurons and their activities (pain is not in the brain), inflammation, a herniated disc, and so forth. Neither is pain a perception: an object or event exists regardless of whether it is perceived or not, whereas a pain (e.g. in the knee) exists only as it is felt [17]. A perception may be falsified (I thought my pain was caused by a torn meniscus, but it turned out to be something else), while a sensation cannot. *Whether* pain is felt and the intensity of suffering, however, depend critically on how the person perceives the situation. In other words, we must distinguish between the experience of pain and the meaning that the person gives to it. It obviously does not make sense to say that "my knee hurts but I do not feel it", but the person's beliefs about the cause of pain may be right or wrong. It is an example of conceptual confusion when the doctor questions the patient's report of pain because he does not find a plausible cause by his examination. The pain is exactly as the person describes it (if we exclude persons that for some reason lie); the cause of pain, however, may be located somewhere else or not be what the person believes. As pointed out by Bennett and Hacker [17, p. 123]: "So-called referred pains (e.g. sciatica, referred toothache) are not pains which the subject *mistakenly* thinks are where he points or assuages, but rather pains that are felt in places other than the locus of the injury, infection, etc. . . . So, the *location of the cause of a pain* must be distinguished from the location of the pain itself."

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