REFRESHMENT

Brain and pain: old assumptions and new science about chronic pain

George Ikkos & Parashar Pravin Ramanuj

George Ikkos is a consultant liaison psychiatrist at the Royal National Orthopaedic Hospital, Director of the Royal Society of Medicine's (RSM's) 'Psychiatry in Dialogue with Neuroscience Medicine and Society' programme and Chair of the Royal College of Psychiatrists' History of Psychiatry Special Interest Group, London, UK. He has served as an honorary Visiting Research Professor at London South Bank University, first President of the RSM's Pain Medicine Section and President of the RSM's Psychiatry Section.
Parashar Pravin Ramanuj is a consultant liaison psychiatrist and clinical lead of the London Spinal Cord Injury Centre at the Royal National Orthopaedic Hospital, London, UK. He is Clinical Director of Mental Health and Community Programmes at Imperial College Health Partners, London, and a Senior Research Fellow at RAND Europe. He is an Executive Committee Member of the Royal College of Psychiatrists' Faculty of Liaison Psychiatry, London, UK.
Correspondence George Ikkos. Email: prof@georgeikkos.com

First received 3 Aug 2019
Final revision 17 Nov 2019
Accepted 21 Nov 2019

SUMMARY

The authors summarise the evolving understanding of the neuropsychophysiology of chronic pain, including the relevance of adverse childhood experiences in facilitating it and similarities between the central physiology of chronic pain and opioid addiction. Emerging understanding highlights the importance of dopamine-expressing GABAergic neurons in the nucleus accumbens and suggests that D_1 expression is associated with a sense of pleasure and approach behaviour and D_2 with a sense of punishment and behavioural inhibition. Regulation of D_1 and D_2 expression may be mediated by nigrostriatal and medial frontal striatal pathways within the increasingly understood brain as a 'predictive' organ. The distinction between the predictive brain and personal 'expectations' and the importance of the latter for clinical outcomes are emphasised. The relevance of findings for possible future psychopharmacological treatment avenues is also presented.

DECLARATION OF INTEREST

None.

KEYWORDS

Neurophysiology; childhood experience; opiate disorders.

Old assumptions

The early modern philosopher René Descartes is much maligned by contemporary neuroscientists and psychiatrists for his advocacy of mind–body dualism. However, like many of his contemporary philosophers, Descartes was a 'natural philosopher' (i.e. 'scientist' in our idiom). For example, he was a keen student of sensation, including pain, as the well-known drawing in Fig. 1 illustrates (Descartes 1985 reprint).

Figure 1 is consistent with common sense and logic, which suggest that the experience of our body is generated by the impact of peripheral stimuli and their transmission through the peripheral and central nervous system to the sensory cortex. The relatively recent distinction of types of pain into neuropathic, nociceptive and mixed, whether in the presence or absence of cancer, is consistent with this formulation. Although this distinction maintains its clinical utility, recent evidence in relation to persistent pain, more often referred to as 'chronic pain', confirms the suspicion that common sense and logic may mislead when trying to understand this frequent and disabling clinical phenomenon (Balantyne 2018). Here we focus on central neuropsychophysiological aspects of chronic pain to illustrate the point and aid clinical understanding and practice.

New science

The suspicion that common sense and logic may mislead has been implicit in the International Association for the Study of Pain (IASP) definition of pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (cited in Sommer 2016). In other words, the sensation of pain, although signalling risk or actual damage, may occur either in the presence or absence of such risk or damage. Furthermore, sensation and emotions are central to the definition of pain, whereas threat or actual damage to tissue integrity is not.

Placebo/nocebo in chronic pain

The placebo (and nocebo) phenomena have long been observed and may be particularly relevant to the understanding of chronic pain (McQueen 2013a). Speculation and research into the relative influence of peripheral and central nervous system phenomena in the determination of pain have flourished. It has become apparent that placebo phenomena exercise their action through neuropsychophysiological mechanisms that also serve in secure attachment processes in mammals (McQueen 2013b). Similarly, we know now that adverse childhood experiences (ACEs) may disrupt the physiology that underlies the capacity to benefit from the soothing influence of the attachment figure. Such a comforting figure may be an actual physical person or, in psychoanalytic terms, an internalised figure. The disruption is mediated by adverse effects on the dynamics of the central endogenous opioid system (Balantyne 2018).

FIG 1 Descartes illustration of sensory transmission (Descartes 1985 reprint, p. 102).

Neuropsychophysiology of chronic pain

New understandings of the central neuropsychophysiology of chronic pain are summarised in reviews by plenary speakers at the IASP 17th World Congress (2018 Biennial Review of Pain, https://journals.lww.com/pain/toc/2018/09001). Central to chronic pain appears to be the nucleus accumbens and the inputs to it from the nigrostriatal and frontostriatal pathways (Fields 2018). The nucleus accumbens is populated by GABAergic neurons with dopamine-expressing dendrites. These dopamine-expressing dendrites are of two types: dopamine 1 (D_1) and dopamine 2 (D_2). D_1 is associated with pleasure and approach behaviour towards the eliciting stimulus and D_2 with punishment and inhibition of behaviour in the face of the stimulus. It is the balance between D_1 and D_2 activity that plays a crucial part in the experience of pleasure and pain and the expression of associated behaviours, including approach or avoidance. Interestingly, a recent systematic review has suggested that antipsychotics, especially olanzapine, may be effective against chronic pain. The superior efficacy of olanzapine may be due to its stronger D_2 blocking action compared with other antipsychotics (Jimenez 2018).

Opioids have diverse multisystem actions and effects, but their analgesic effect may be produced through stimulation of these D_1-expressing dendrites. Conversely, in opioid dependence syndrome a dynamic imbalance occurs whereby D_1 expression is associated with decreasing impact (hence the need for increasing doses to achieve the same effect) and, in contrast, there is increased impact of D_2 activity, hence the highly 'punishing' experience of opioid withdrawal. ACEs result in a range of adverse biological changes and health outcomes. One of these is a dynamic D_1/D_2 imbalance that is remarkably like that of opioid addiction. It is believed that ACEs lead to initial overactivity and later exhaustion of D_1 expression and increasing impact of D_2 activity (Balantyne 2018).

Although the impact of emotional factors on the experience of pain may be markedly determined by nigrostriatal pathways, the well-recognised impact of cognitive factors may be mediated by frontostriatal pathways (Fields 2018). Animal research suggests that medial prefrontal cortex stimulation of the nucleus accumbens is associated with increased threshold to pain and persistent approach behaviour towards what feels like an attractive target regardless of pain, for example continuing to walk towards a source of nutrition despite pain. Furthermore, it has been argued that stimulation of the nucleus accumbens by the infra-limbic prefrontal cortex is necessary to overcome the inhibition arising out of pain. Such phenomena seem to apply irrespective of whether the clinician is dealing with neuropathic, nociceptive, mixed or cancer pain.

No CNS pain centre

Contrary to naive assumptions, evidence has demonstrated that there are no sensory channels exclusive to pain (Sommer 2016). There is no pain centre in the brain (Bushnell 2013). Rather, the experience of pain is a complex dynamic phenomenon including ascending stimulation from the periphery, through the spinal cord and brain-stem, to diverging sensory and emotional areas in the brain (see Fig. 1 in Davis *et al* (2017)[a]). This is sometimes referred to as the 'pain neuromatrix'. Along the way, neurophysiological phenomena of peripheral and central sensitisation may occur (Sommer 2016). These increase sensitivity to pain. At the level of the brain-stem, particularly the periaqueductal grey, there is an overlap between pain, anxiety and mood substrates. This is because they are all crucial to securing safety: whether in the face of injury (pain), or threat (anxiety) (Kozlowska 2015) or separation from a secure base (mood) (McQueen 2013b). There are also descending modulating pathways from the emotional brain that may act either to increase or decrease pain (see Fig. 1 in Davis *et al* (2017)). Such descending modulating pathways are subject to cognitive control, although only partially so. We may say, by analogy, that sometimes the pain experience is like a lift that is stuck at a particularly high level; at other times, the lift is moving up and down out of control.

a. This figure is available open access at https://www.nature.com/articles/nrneurol.2017.122/figures/1.

Conclusions

Contemporary neuroscience suggests that our sense of our body 'may largely reflect limbic predictions about [its] expected state' (Barrett 2015). This perhaps helps explain recent research that has found that the best single predictor of persistence of pain following peripheral limb injury is intensity of anxiety when originally attending the accident and emergency department. Symptoms of post-traumatic stress at 4 months' follow-up also have an association with significant pain persistence (Rosenbloom 2016). It may also explain the finding by Cormier *et al* (2016) that the single best predictor of response to treatment through individualised pain management programmes was expectation of improvement – not the site, type, intensity, chronicity or other characteristic of the pain itself. Similarly, it may help explain the complex and sometimes counterintuitive way in which the reactions of others may help augment or soothe pain (Hurter 2014).

The emerging importance of expectation in bodily experience highlights the relevance of Fields' (2018) observation that, although brains 'predict' and persons 'expect', and both are important in chronic pain, the two should not be conflated. Perhaps Wilhelm Wundt, the 19th-century father of experimental psychology, captured something of the essence of this when he stated:

> 'Thought escapes our sensory perception: we can hear the word that expresses it, see the man who formulated it, analyse the brain that thought it, but the word, the man, and the brain are not the thought […] In the same way, the blood that flows in the brain, the chemical transformation of substances that occur in it, the heat and the electricity liberated there – none of these is the thought' [cited in Araujo 2016: p. 75].

References

Araujo SF (2016) *Wundt and the Philosophical Foundations of Psychology: A Reappraisal*. Springer.

Balantyne J (2018) The brain on opioids. *Pain*, **159**(suppl 1): S24–30.

Barrett LF, Simmons WK (2015) Interoceptive predictions in the brain. *Nature Reviews Neuroscience*, **16**: 419–29.

Bushnell MC, Čeko M, Low LA (2013) Cognitive and emotional control of pain. *Nature Reviews Neuroscience*, **14**: 502–11.

Cormier S, Lavigne GL, Choinière M, et al (2016) Expectations predict chronic pain treatment outcomes. *Pain*, **157**: 329–38.

Davis KD, Flor H, Greely HT, et al (2017) Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. *Nature Reviews Neurology*, **13**: 624–38.

Descartes R (1985 reprint) *The Philosophical Writings of Descartes: Vo1* (trans J Cottingham, R Stoothoff, D Murdoch). Cambridge University Press.

Fields H (2018) How expectations influence pain. *Pain*, **159**(suppl 1): S3–10.

Hurter S, Paloyelis Y, Williams ACdC, et al (2014) Partners' empathy increases pain ratings: effects of perceived empathy and attachment style on pain report and display. *Journal of Pain*, **15**: 934–44.

Jimenez X, Sundararajan T, Covington E (2018) A systematic review of atypical antipsychotics in chronic pain management: olanzapine demonstrates potential in central sensitization, fibromyalgia, and headache/migraine. *Clinical Journal of Pain*, **34**: 585–91.

Kozlowska K, Walker P, McLean L, et al (2015) Fear and the defense cascade: clinical implications and management. *Harvard Review of Psychiatry*, **23**: 263–87.

McQueen D, Cohen S, St John-Smith P, et al (2013a) Rethinking placebo in psychiatry: the range of placebo effects. *Advances in Psychiatric Treatment*, **19**: 162–70.

McQueen D, Cohen S, St John-Smith P, et al (2013b) Rethinking placebo in psychiatry: how and why placebo effects occur. *Advances in Psychiatric Treatment*, **19**: 171–80.

Rosenbloom BN, Katz J, Chin KYW, et al (2016) Predicting pain outcomes after traumatic musculoskeletal injury. *Pain*, **157**: 1733–43.

Sommer C, Zeilhofer HU, Apkarian AV (2016) Brain circuits for acute and chronic pain. In *Pain 2016: Refresher Courses. 16th World Congress on Pain* (eds CL Sommer, MS Wallace, SP Cohen, et al): 19–26. International Association for the Study of Pain.

BJPsych Advances (2020), vol. 26, 156–158 doi: 10.1192/bja.2019.77