Cognition and Pain

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Abstract

Purpose of review

Pain and cognition share common neural substrates and are known to interact reciprocally. This has implications for treatment and management of pain conditions; pain can negatively affect cognitive performance, while cognitively demanding tasks may reduce pain perception. This article will review recent research investigating the impact of pain on cognition and the cognitive modulation of pain.

Recent findings

Recent clinical and preclinical studies have provided new evidence for impairment of cognition in pain with a focus on the type of cognitive construct affected and the influence of factors such as age and pain localisation. Reduced connectivity between important brain structures has emerged as a possible underlying mechanism. Imaging studies have continued to identify neuroanatomical structures involved in different types of cognitive pain modulation, and attempts have been made to delineate the descending pathways by which pain relief is achieved. New and established methods to investigate cognitive modulation of pain in animal models have revealed insights into the molecular and neurochemical mechanisms involved.

Summary

Progress has been made in understanding the complex relationship between pain and cognitive function. However, both synthesis of current research findings and further novel research studies are required to maximise the therapeutic potential.

Keywords: Pain, analgesia, cognition, attention, descending pain inhibition

Introduction

Pain and cognition are inherently linked. Under normal circumstances, acute pain acts as a warning signal and protective mechanism to prevent harmful tissue damage. Therefore, it is associated with memory retrieval relating to previous painful experiences as well as adaptive learning and active decision making, collectively termed the cognitive-evaluative dimension of pain [1]. It is hypothesised that neural substrates involved in cognition and pain processing are linked, and that the two systems modulate one another reciprocally [2]. Increased pain would then impair cognitive function, and an increasing non pain-related cognitive load could reduce perceived pain. A better understanding of the interaction between pain and cognition is necessary to achieve two main therapeutic goals: (i) improved treatment strategies for chronic pain patients with pain-related cognitive dysfunction and (ii) the use of cognitive modulation as an analgesic approach. This article will review the most recent research on the effect of pain on cognition and the potential for pain reduction via cognitive modulation.

Effect of pain on cognitive function: clinical research

We previously reviewed the literature regarding the effect of pain on cognition, discussing preclinical and clinical evidence, potential mechanisms, and common confounds [2]. In clinical research, confounds included age, gender, motor impairment, co-morbid affective disorders, pain chronicity and analgesic use, as well as heterogeneity in psychometric assessments, sample demographics, and type of pain or pain disorder.

Landrø et al. [3**] recently investigated neurocognitive dysfunction in a multidisciplinary pain centre population. An advantage of their study over previous research was the grouping of patients based on the nature of their pain, thereby showing that generalised and neuropathic pain had a greater effect on cognition than localised pain. Using a comprehensive test battery, they found that 20% of chronic pain patients underperformed on tests measuring working

memory, verbal learning and memory, psychomotor speed and attention. Importantly, the tests distinguished between the different processes involved in sustained attention and attention switching, revealing a specific deficit in attentional control within the patient group. This finding is supported by previous research showing that experimental pain (cold pressor test) was associated with impaired attentional control in healthy participants [4]. A comprehensive study by Moore et al [5] also found that attention span, attention switching and divided attention were the aspects of attention most affected by experimental heat pain. Taken together, these results indicate that pain predominantly interferes with executive cognitive control. Landrø and colleagues [3**] speculated that poor attentional control might limit ability to direct attention away from pain and contribute to maintenance of clinical symptoms of chronic pain. However, conflicting results have also been reported. A study by Oosterman et al [6**] found that while chronic pain patients were impaired on tests of mental flexibility and sustained attention, the deficit in mental flexibility appeared to be explained by psychomotor slowing. Thus, the authors concluded that inhibitory/attentional control was unaffected in chronic pain but that there was a specific decline in ability to sustain attention. Veldhuijzen et al [7*] reached similar conclusions, as fibromyalgia patients had intact cognitive inhibition but decreased processing speeds compared with a matched control group. An important distinction between studies may be the use of experimental pain in healthy volunteers versus research involving chronic pain patient participants. Attention has been particularly well studied in the context of pain interference [8-15], and theoretical models exist to explain the relationship [16]. However, recent findings suggest a lack of consensus on the aspects of attention, if any, that are affected in chronic pain and on whether factors such as processing speed or type of pain experience (experimental vs. chronic) may be a determinant of attentional performance. In contrast, a recent systematic review and meta-analysis provides solid evidence for working-memory deficits in chronic pain [17**]. While acknowledging high experimental heterogeneity, the

authors concluded that chronic pain moderately affected working-memory performance in a consistent and significant manner. This type of pooled data analysis is among the most compelling evidence for the negative effect of chronic pain on cognition and represents a significant advancement of the field. A similar approach for different cognitive domains, as well as separate analysis of pooled results for specific pain conditions and pain types, may reveal a more precise pattern of impairment, allowing targeted investigation of the underlying mechanisms.

Effect of pain on cognitive function: the role of age

Age has been identified as an important factor in the relationship between pain and cognitive function. In rodent models, pain-related deficits in cognition have been shown to be age-specific [18], and clinical studies have shown mixed results regarding the impact of age on the relationship between pain and cognition. The most recent investigation of the effect of age on the pain-cognition interaction confirmed, using interaction analyses, that age moderates the relationship [19**]. Executive function and memory were inversely correlated with pain ratings in younger patients (19-40 years old); however, in older patients (50-80 years old) there was no relationship between pain ratings and memory, and a positive relationship between pain and executive function was observed. These results have important implications for sampling in future studies. Furthermore, the findings may be key to elucidating a mechanism for the effect of pain on executive function, as the authors hypothesise that the positive correlation in the older group may indicate “age-related reduced integrity of a shared neural substrate”. Interestingly, a neuroimaging study by Ceko et al [20*] found that structural alterations in fibromyalgia patients were also age-dependent, with older patients (51-60 years old) showing reduced grey-matter volume and white-matter integrity while younger (29-40 years old)

patients showed grey matter increases. Moreover, these authors found reduced connectivity between the insula and the dorsal anterior cingulate cortex (ACC; a region highly involved in cognitive processing), specifically in younger patients. These findings concur with another study showing abnormal patterns of grey-matter aging in chronic pain patients [21]. Future studies should aim to link these neuropsychological and neuroimaging results.

Effect of pain on cognitive function: animal models

Back-translation of human pain-related cognitive deficits to rodents provides additional support to the clinical literature and allows more detailed investigation of the mechanisms involved. Recent reviews have highlighted the contribution of rodent studies to investigation of the impact of pain on cognition [2, 22*]. The latest research shows that following nerve injury, rats display long-term (6 months post-injury) attentional deficits [23**], and impaired social-recognition memory [24**]. Notably, the social-recognition memory deficit was restored by treatment with duloxetine and gabapentin [24], which are used clinically to treat neuropathic pain. One of the most significant studies over the past 12-18 months was that of Leite-Almeida et al [25**], who found differential effects of pain on behaviour depending on nerve-injury lateralisation. Animals that underwent left spared-nerve injury (SNI) showed increased anxiety-like behaviours but intact cognitive function, while right-SNI animals did not display changes in anxiety-like behaviours but were impaired on cognitive tasks assessing spatial working memory, attentional set-shifting and impulsivity.

It has been shown previously that rats with chronic inflammatory pain adopt a “risk-prone” strategy in a gambling task, similar to chronic pain patients in analogous human tasks [26]. Using this paradigm, Pais-Vieira et al [27**] recorded neuronal activity in the orbitofrontal cortex (OFC) of rats performing the gambling task before and after induction of inflammatory

pain. Pain appeared to be associated with a reduction in the proportion of OFC cells that were able to encode reward. These results have implications for the study of pain and cognition as normal functioning in the OFC was found to be compromised by pain, and this region is known to be involved in processing choice/reward information and other executive-type functions. Two other studies by Cardoso-Cruz et al provide mechanistic insights into the effect of pain on cognition [28**,29**]. The first [28**] found that spatial working-memory performance was impaired in rats that had undergone SNI, and that this deficit was associated with electrophysiological changes in the fronto-hippocampal circuit. These changes included altered firing activity in the medial prefrontal cortex (mPFC) and an overall reduction in information flow in the circuit. The second [29**], in this case in a model of inflammatory pain, also found deficits in spatial working memory associated with a decrease in functional connectivity between mPFC and mediodorsal thalamus. As interactions within these circuits play a crucial role in learning, memory and cognition, these studies suggest a mechanism for pain-related cognitive impairment based on reduced connectivity between cognitive-associated brain regions. Future translational research should aim to determine if similar deficits in connectivity occur in chronic pain patients experiencing cognitive difficulties.

A clinical imaging study previously showed that increased functional connectivity between the nucleus accumbens and the PFC may be involved in the transition from acute to chronic pain [30*]. As such, it may also be interesting to investigate the possibility of an inverse relationship between chronic pain-related and cognition-related connectivity patterns. Deficits in connectivity are likely just one form of neuroplasticity that may underlie pain-related cognitive impairment and should also be considered alongside other theoretical models including the limited resource theory and the neuromediator theory (see Figure 1 and [2]).

[Insert Figure 1 here]

Cognitive modulation of pain: clinical research

Pain is a subjective experience [31] and its perception is highly dependent on context and on emotional (e.g. stress, anxiety, mood) and psychological (e.g. attention, expectation, beliefs, prior experience/conditioning, catastrophizing) factors. Placebo analgesia is one of the best-known and well-studied examples of cognitive modulation of pain, though simple cognitive interventions like distraction also have pain-relieving effects [32,33]. Increasingly, psychological techniques such as distraction, mindfulness and meditation are being recognised for their analgesic effects and adopted into multidisciplinary pain management programmes. Pain reduction is thought to be achieved via a top-down inhibitory process involving multiple brain regions [32,34-39] and multiple neurotransmitter systems including the endogenous opioid, cannabinoid and monoaminergic systems [33,40,41]. The most recent studies have further identified, using neuroimaging techniques, anatomical regions and connectivity patterns involved in cognitive modulation of pain. Recent studies have also aimed to investigate whether different types of cognitive modulation share common mechanisms. One study tested the combination of placebo and distraction on thermal pain perception and found additive reductions in pain [42**], suggesting that placebo is not an executive process dependent on attention and working memory, and that placebo and distraction therefore represent "separate routes" of pain modulation.

A recent study demonstrated the importance of context in expectation-mediated pain modulation [43**]. When a moderately noxious stimulus was presented following a cue predicting intense pain, the associated "relative relief" meant that the pain stimulus was described positively. Activity in the dorsal ACC and insula was reduced, while activity in the ventromedial PFC (vmPFC) increased compared with the control condition. Furthermore, there was an increase in the functional connectivity between the reward circuitry and the

periaqueductal grey (a component of the descending pain modulatory system) suggesting a type of reward-induced analgesia. Another study found that cue-conditioned modulation of pain depends on resting-state connectivity between the frontoparietal network and the rostral ACC/medial PFC [44**], providing a potential basis for individual variability in the effects of expectation on pain.

Zeidan et al [45*] recently reviewed the effects of mindfulness practice on pain and the neural substrates involved. Mindfulness appears to operate through a specific mechanism whereby higher centres in the PFC are deactivated. This was recently demonstrated by Gard et al. [46**] who found decreased activation of the lateral PFC during pain in mindfulness practitioners and concomitant increases in activation of the posterior insula/SII (somatosensory cortex II), while activity was increased in the rostral ACC in anticipation of pain. Another study by Lutz et al [47**] also found increased activity in the dorsal anterior insula and the anterior mid-cingulate in expert meditators during pain, while baseline activity in these regions, and in the amygdala, was significantly reduced. This differs from the top-down modulation observed in placebo and distraction. Conversely, cognitive behavioural therapy in fibromyalgia patients was found to be associated with reduced symptoms, increased activation of the ventrolateral PFC (vlPFC) and the OFC during pain processing, and increased connectivity between the vlPFC and the thalamus [48**]. The effects of cognitive modulation on nociceptive event-related potentials (ERPs) have also been investigated. Legrain et al [49**] found that performing a working-memory task was associated with a reduction in the cortical responses elicited by a nociceptive stimulus. This effect could be seen at the earliest stages of pain processing, suggesting that working memory may prevent the capture of attention by pain.

The effects of cognitive modulation on pain are complex and different cognitive interventions may elicit effects through different mechanisms. A challenge for this field of research is to develop a unifying theoretical model, such that complementary techniques may be used to maximise the therapeutic analgesic potential.

Cognitive modulation of pain: animal models

Similarly to investigation of the effect of pain on cognitive function, the study of cognitive modulation of pain would benefit greatly from development and validation of good animal models. There has, however, been little progress in this type of research. In October 2012, Nolan et al described placebo analgesia in an operant pain model in rats [50**]. Though not the first demonstration of a placebo response in rodents, the experiment employed an elegant conflict-reward paradigm which allowed for investigation of multiple pain dimensions rather than reflex nociceptive responses. The authors found similarities between their model and clinical placebo analgesia, in that there was large variability in responses, and the effect could be attenuated by administration of the opioid receptor antagonist naloxone. A recent study has also shown that the ACC is the key brain region involved in placebo analgesia in rats and that the effect is mediated by μ-opioid receptors in this region [51**]. We have previously described a rat model of distraction-induced analgesia whereby exposure to a non-aversive distractor (novel object) suppressed formalin-evoked nociceptive behaviour [33]. The reduced nociceptive behaviour was associated with alterations in monoaminergic transmission in the mPFC. Specifically, the serotonin metabolite, 5-HIAA, and the dopamine metabolite, DOPAC, were reduced in the mPFC of animals exposed to the novel object distractor. It is possible, therefore, that distraction-induced analgesia may be related to altered metabolism of monoamines within the mPFC. These animal models represent new strategies for further investigating the mechanisms underlying cognitive modulation of pain.

Animal models of stress/fear-induced analgesia are better established; in these paradigms, recall of an aversive experience (typically footshock) inhibits pain behaviour, and the neurochemical and molecular mechanisms involved have been investigated. The endocannabinoid system is known to play a key role in fear-conditioned analgesia (FCA); a recent study showed that the immediate early gene *zif268* is a molecular correlate of this endocannabinoid-mediated FCA, as footshock-conditioned rats had reduced nociceptive behaviour and an attenuation of formalin-evoked *zif268* expression in the dorsal horn of the spinal cord, an effect blocked by systemic administration of the cannabinoid receptor antagonist/inverse agonist AM251 [52*]. Another recent study has also shown that the mechanism by which the endocannabinoid system mediates FCA in rats may involve GABAergic and glutamatergic signalling in the basolateral amygdala, a key structure in the descending inhibitory pain pathway [53*]. These studies demonstrate that behavioural and pharmacological approaches in animal models can be used to dissect the molecular and neurochemical mechanisms involved in cognitive modulation of pain.

Conclusions

While this review has discussed the impact of pain on cognition and cognitive modulation of pain separately, these effects are intertwined and advances in both areas should help to broaden our understanding of the complex relationship between pain and cognition. Future research should adopt a collaborative, multidisciplinary approach, with translational studies key to elucidating the mechanisms underlying these effects. Understanding pain-cognition interactions will yield new therapeutic avenues for treatment of disabling chronic pain.

Key Points

- The mechanisms by which pain and cognition interact are poorly understood at present and research in this area will be of therapeutic benefit for patients suffering with chronic pain.

- Recent research investigating the effect of pain on cognitive function has provided new insights into the type of cognitive constructs affected and the influences of factors such as age and pain localisation, and studies investigating the underlying mechanisms suggest the involvement of changes in regional brain connectivity.

- Cognitive modulation of pain has potential as an analgesic approach and recent research has aimed to determine the brain regions and neuroanatomical pathways mediating this effect.

- Though recent research has advanced our understanding of the relationship between pain and cognition, further investigation is required to fully elucidate the mechanisms involved and enable the development of improved treatment strategies for pain.

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These authors found nerve injury was associated with impaired social-recognition memory in rats, and that this deficit could be prevented by treatment with duloxetine or gabapentin. This suggests that effective treatment of chronic pain may restore cognitive function.

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This study utilised a rat model of placebo analgesia to investigate brain regions and receptor signalling systems involved. The findings suggest that the rostral ACC is the key brain region involved and that the μ-opioid receptor mediates placebo analgesia in this region.

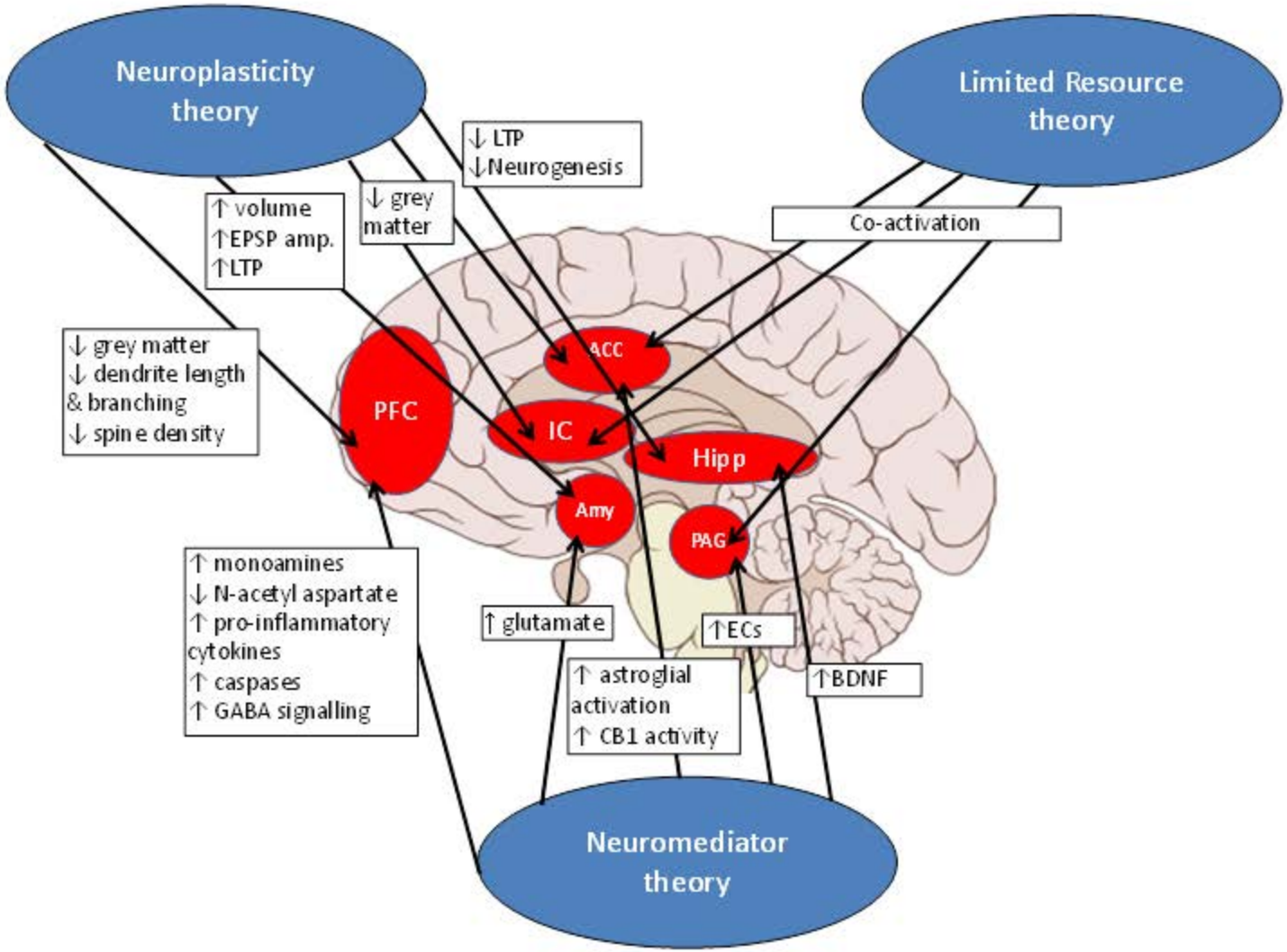
*52. Olango WM, Geranton SM, Roche M, Hunt SP, Finn DP. Novel molecular correlates of endocannabinoid-mediated fear-conditioned analgesia in rats. Eur J Pain. 2013. Epub 2013/07/23(doi: 10.1002/j.1532-2149.2013.00369).

The immediate early gene Zif268 was found to be an important molecular correlate of endocannabinoid-mediated fear-conditioned analgesia. This study advances our understanding of the descending pathway by which learned fear reduces pain.

*53. Rea K, Olango WM, Harhen B, Kerr DM, Galligan R, Fitzgerald S, et al. Evidence for a role of GABAergic and glutamatergic signalling in the basolateral amygdala in endocannabinoid-mediated fear-conditioned analgesia in rats. Pain. 2013;154(4):576-85.

Fear-conditioned analgesia was found to be mediated by cannabinoid CB_1 receptors in the basolateral amygdala, an effect modulated by GABAergic and glutamatergic antagonists. These findings provide insights into the neurochemical mechanisms involved in cognitive modulation of pain.

Figure 1. Potential mechanisms of pain-related cognitive impairment, a theoretical model. Pain-induced changes in resource utilisation, neuromediators and neuroplasticity may affect cognition through a network of brain regions. PFC: prefrontal cortex, IC: insular cortex, Hipp: hippocampus, Amy: amygdala, PAG: periaqueductal grey, ACC: anterior cingulate cortex, LTP: long-term potentiation, EPSP: excitatory post-synaptic potential, BDNF: brain-derived neurotrophic factor, ECs: endocannabinoids. (Figure re-produced with permission from Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. Progress in Neurobiology. 2011;93(3):385-404.


Neuroplasticity theory
Limited Resource theory
↓ LTP
↓Neurogenesis
↑ volume
↑EPSP amp.
↑LTP
↓ grey matter
Co-activation
↓ grey matter
↓ dendrite length & branching
↓ spine density
PFC
ACC
IC
Hipp
Amy
PAG
↑ monoamines
↓ N-acetyl aspartate
↑ pro-inflammatory cytokines
↑ caspases
↑ GABA signalling
↑ glutamate
↑ECs
↑ astroglial activation
↑ CB1 activity
↑BDNF
Neuromediator theory