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Interrelations between pain, stress and executive functioning

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Abstract

Aim: The purpose of this narrative review is to discuss the interrelations between pain, stress and executive functions.

Implications for practice: Self-regulation, through executive functioning, exerts control over cognition, emotion and behaviour. The reciprocal neural functional connectivity between the prefrontal cortex and the limbic system allows for the integration of cognitive and emotional neural pathways and then for higher-order psychological processes (reasoning, judgement etc.) to generate goal-directed adaptive behaviours and to regulate responses to psychosocial stressors and pain signals. Impairment in cognitive executive functioning may result in poor regulation of stress-, pain- and emotion-related processing of information. Conversely, adverse emotion, pain and stress impair executive functioning. The characteristic of the feedback and feedforward neural connections (quantity and quality) between the prefrontal cortex and the limbic system determine adaptive behaviour, stress response and pain experience.

Keywords

Chronic pain, psychosocial stressors, executive functioning, neural connections, stress response, pain experience

Introduction

Pain is a distressing physiological sensation in response to mechanical, chemical, thermal or electrical stimulation above the level of tolerable intensity; however, it can also arise spontaneously in dysregulated neural pathways of either the peripheral or the central nervous system (CNS). Chronic pain is a subjective experience that evokes emotional distress. Post-stress disorders, adverse life events and poor stress-coping capacity are some of the predisposing factors leading to both chronic pain and chronic psychosocial stress.[1] Certain chronic pain conditions are associated with central functional alterations in pain-processing neuronal circuits, but it is not known when this central functional dysregulation is the cause or the consequence of chronic pain.[2]

Stress is a state in which physical and emotional well-being are perceived to be, or actually are threatened or disrupted.[1,3] Psychosocial stress occurs when environmental or self-imposed demands exceed the emotional and/or cognitive capacity to cope. This may result in maladaptive behaviour, sleep disturbance and increased risk of certain physical or mental diseases.[4] Psychosocial stressors (Table 1) evoke complex dynamic reactions comprising perception and appraisal of the stressors followed by interactions between neural,

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Table 1. Some psychosocial stressors.[5,6]

• Poverty	• Chronic life stress
• Financial difficulties	• Subordination
• Loss of job	• Social marginalization/isolation
• Depravation	• Public speaking
• Martial conflict	• Paternal depression
• Divorce	• Challenging mental arithmetics
• Overall family distress	• Performing a difficult working memory task

endocrine and immune systems and are modulated by genetic susceptibility, environmental modifiers, age and gender.[1,7] As with chronic pain, psychosocial stress may be emotionally distressing.[8]

Executive functions refer to neurocognitive faculties including working memory, that is, the ability to update, integrate and retain information; cognitive flexibility, that is, the ability to shift between rules/modes of thought, inhibition of inappropriate responses and attentional control. All these can formulate higher-order cognitive processes such as reasoning, judgement and decision-making, regulation of emotional responses and control over cognition, self-gratification and pattern of behaviour. Together, these processes enable execution of goal-directed behaviours and regulation of responses to psychosocial stressors and to noxious stimuli.[9–15] Impairment of executive functioning increases the risk of poor stress regulation, depression, anxiety, aggression and addictive disorders. Responses to similar psychosocial stressors or to similar intensity of chronic pain vary significantly between persons, probably owing to differences in their executive functional capacities, self-regulation and self-control.[11,14,15]

Executive functions are generated in the prefrontal cortex which is functionally connected to the limbic system (amygdala, hippocampus, thalamus and hypothalamus) which is engaged in processing of emotion-related information and to brainstem regions which play roles in arousal, autonomic control, primitive emotional responses, such as aggression and rage, and in predatory and sexual behaviours.[11] The hippocampal–prefrontal cortex pathway is essential for executive functioning and for emotional regulation and is vulnerable to dysregulation by chronic stress and by chronic pain. The amygdala which plays an essential role in processing emotion-related information is regulated by hippocampal–prefrontal cortex neurocircuits.[16,17]

In short, these functional neural connections between the prefrontal cortex and the limbic system are essential for adaptive regulation of primitive, emotional and stress responses[11] and for emotions that influence cognitive mechanisms.[18] Stress response is thus the outcome of co-ordinated interactions between autonomic, neuroendocrine and psychological processes which require input from the limbic system and prefrontal cortex.[19]

Higher-order cognitive processes that are executive function driven can generate goal-directed behaviours that are mentally taxing rather than automatic or routine.[9,11] Reserves of mental energy operating the executive functions in the prefrontal cortex are limited. Repeated or continued exposure to psychosocial stressors, to pain or to involuntary negative emotions generated by subcortical brain regions may deplete these limited resources, leading to the impairment of the mechanisms of self-regulation and self-control, that is, to the ability to exert control over cognition, emotion and behaviour. Such impairment may lead to poor emotional control, judgement and decision-making, resulting in maladaptive behaviour.[9,11,12,20]

In this brief review of the literature, we consider the roles of executive functions in regulation of stress and pain responses and the factors that either foster risk or confer resistance to adverse stress-related outcomes.

Chronic pain

Pain is a subjective distressing experience that can be described in terms of quality, intensity and duration. Chronic pain is an abnormal sensation which occurs in the absence of any noxious stimulus or persists for more than 6 months after healing of an injury.[21] The generation of chronic pain is a complex adaptive process involving one or more dysregulated sensory neural pathways, dysregulated activity of certain neurotransmitters, synapses, receptors and cognitive, emotional and pain inhibitory neural circuits and the balance between degenerative and regenerative neural processes. This structural and functional neuroplasticity can result in increased neural sensitivity, leading to hyperalgesia and spontaneous pain. Chronic pain, chronic stress and executive functions share common central neural circuits, so the functional and structural neural alterations induced by chronic pain/stress also dysregulate executive functioning, resulting in impairment of higher-order cognitive performance. Risk factors for chronic pain include genetic predisposition, age, gender, use of certain drugs and previous chronic pain conditions.[22]

In subjects with chronic pain, the dysregulated pain mechanism may involve peripheral primary afferent nociceptors, neural circuits at the level of the dorsal horn of the spinal cord and the central pain matrix.[21]

Within the central pain matrix, cognitive interpretation of the pain based on previous experience, emotional evaluation of the severity of the pain and the intensity and duration of the noxious stimulus are integrated to create an experience of pain and to elicit a response. The experience of pain can be influenced inter alia by selective attention, by emotional state, by fatigue and by maladaptive stress responses.

The prefrontal cortex is primarily engaged in control of pain-related emotional responses generated in the limbic system, and it also determines the perception of magnitude and quality of pain. Nociceptive signals are moderated at the level of the spinal cord by descending modulatory neural pathways, which may either facilitate or inhibit their transmission.[21] Chronic stress and chronic pain share neural circuits that operate in the amygdala, the hippocampus and the prefrontal cortex[23]; and cortisol plays an essential role in the prefrontal cortex–dependent regulation of the hypothalamic–pituitary–adrenal (HPA) axis and in the processing of emotion-related information by the amygdala.[8]

It appears that on one hand, long-term exposure to psychosocial stressors brings about an increase in neuronal dendritic arborisation and axonal connections in the amygdala with the upregulation of activity of neuronal pathways for both nociception and stress; and on the other hand, a decrease in dendritic arborisation and axonal connections in the prefrontal cortex and the hippocampus with downregulation of activity of nociceptive and stress inhibitory pathways. These changes provide the mechanisms for both chronic pain sensation and for maladaptive stress responses.[16,21] Biological stress mediators of the HPA axis released in response to psychosocial stressors can decrease the threshold of nociception in response to mechanical stimuli, increase the release of algogenic mediators and activate glial cells in the spinal cord, resulting in exaggerated pain sensation.[21,23]

Neuroimaging studies show that in some subjects with long-term chronic pain conditions, there is diminution in the size of the amygdala, medial prefrontal cortex and hippocampus, with or without detectable alterations in their functional activity. The diminution in the size of these central structures is probably secondary to the chronic pain/stress.[23–25] On the contrary, these anatomical alterations, whatever their cause may be, may predispose to chronic pain and maladaptive stress responses.[25] Different chronic pain conditions are associated with distinctly different morphological/functional alterations,[26] and often chronic pain co-occurs with depression, anxiety or other emotional states.[26]

The experience of chronic pain is the result of complex interactions between nociceptive, emotional and cognitive neural pathways. Alone or in combination, emotional distress, maladaptive stress responses, fatigue, poor quality of sleep, negative thoughts, cognitive impairment and social dysfunction are factors predisposing to many chronic pain conditions.[27]

On one hand, these biopsychosocial stressors are a burden on the limited resources of mental energy available for executive functioning, making it difficult to meet self-regulatory pain-related demands.[27] On the other hand, the burden of pain itself exhausts the resources of mental energy for executive functioning, with reduction in capacity to deal with self-regulation in relation to social and psychosocial demands. Thus, it appears that deficient executive functioning with impaired capacity for self-control and self-regulation can play a role in the initiation and maintenance of chronic pain.[27] Executive functions with a strong demand for self-regulation and self-control can divert attention from pain, can control negative thoughts such as worry and rumination, can modify adverse emotional states and can promote healthy social interactions, all of which may reduce the suffering of pain.[27]

The biological mechanisms that drive psychosocial stress responses

In response to psychological threats (stressors), the central and peripheral nervous systems release biological stress mediators, which within seconds precipitate a stress response. CNS stress effectors include hypothalamic neuropeptides (hormones) such as arginine vasopressin, corticotropin-releasing hormone (CRH), the pro-opiomelanocortin-derived peptides, α-melanocyte-stimulating hormone and β-endorphin and also noradrenaline derived from the locus coeruleus in the brain stem and from the central autonomic nervous system.[3,28]

In the CNS, there are multiple interactions between the HPA axis and the sympathetic nervous system (SNS). CRH and noradrenaline are the predominant mediators of the integrated stress-response system.[22,28] Both CRH and noradrenergic neural circuits are stimulated by cholinergic and serotonergic neuronal systems and inhibited by γ-Aminobutyric acid (GABA) and opioid peptide neuronal circuits and by glucocorticoids.[3] Stress-induced central dysregulation of the HPA axis and the SNS may impair executive functioning, cognition and adaptive behaviour.[29]

Peripheral stress effectors include glucocorticoids regulated by the HPA axis and by noradrenaline and adrenalin which are regulated by the SNS.[28] Central and peripheral biological effectors of stress play important roles in controlling cognitive and emotional processes.[28]

The catecholamines noradrenaline and adrenalin, released by the sympathetic nervous component of the stress system in response to psychological stressors

Table 2. Some different strategies of coping with psychosocial stressors and chronic pain.[1,35,37,39,40]

Cognitive	Emotional/spiritual	Physical	Pharmacological
• Cognitive behavioural therapy • Psychotherapy • Mindfulness meditation • Hypnosis • Intellectual hobbies (chess/bridge) • Reading • Planning and time management • Problem-focused coping (conflict resolution) • Conscious disengagement	• Art therapy • Museum touring • Listening to music • Artistic hobbies (dancing, painting and photography) • Nature (walking and travelling) • Prayer • Religious studies • Social support	• Physical exercise • Yoga, tai chi, martial arts and archery • Breathing exercises • Massage • Sexual activity	• Antidepressants • Anxiolytics • Anticonvulsants • Mood stabilizers • Opioids • Cannabinoids

stimulate the β-adrenergic receptors of immune cells triggering intracellular signalling pathways which activate the transcription factors NF-$_k$B (nuclear factor–$_k$B) and activator protein 1 (AP-1). In turn, these transcription factors upregulate the expression of proinflammatory genes, resulting in the production and release of proinflammatory cytokines that promote inflammatory reactions.[28,30,31] Subsequently, stress-induced proinflammatory cytokines further stimulate the stress response, contributing to the development of both psychological and somatic disorders.[5,28,31]

Stress lead to an increase of CNS-derived neurotransmitters, such as acetylcholine, serotonin, histamine, glutamic acid and GABA, neuropeptides, such as adrenocorticotropic hormone, vasopressin, bradykinin, somatostatin, substance P, neuropeptide γ, calcitonin gene-related peptide and encephalin and neurotrophins, such as nerve growth factor, brain-derived neutrophic factor, neurotrophin 3 and neurotrophin 4.[32,33] It appears that psychosocial stressors can also upregulate the expression of cytokines in the prefrontal cortex and the hippocampus, which in turn play a role in the development of depression[34] and may impair executive functioning.[3,29,32]

Maladaptive response to chronic psychosocial stress or to chronic pain may include the onset of depression, anxiety and feelings of vulnerability, suffering and hostility, interfering with everyday activities such as eating, sleeping, working, social interactions and cognitive functions, thus significantly reducing quality of life.[35,36] The nature of the maladaptive response is determined by the type of the chronic stressor/pain and its severity and duration; by environmental, developmental, genetic and epigenetic factors and by the ability to mitigate or buffer the impact of the chronic stressor/pain via cognitive, emotional/spiritual, physical and pharmacological mechanisms[3,32,35–39] (Table 2).

The considerable personal variations in response to similar psychological stressors are also related to cognitive appraisal of the stressors which occurs in the prefrontal cortex.[41] Through neural connections from the prefrontal cortex to the limbic system (amygdala and hippocampus), cognitive/executive mechanisms influence the experience and expression of emotions.[5,38,42,43] The cognitively controlled emotions generated in the limbic system in turn influence the release of stress effectors of the SNS, and of the HPA axis.[41,43] Thus, specific psychological stressors may generate physiological and behavioural responses that differ between persons because of differences in cognitive appraisal and executive mechanisms.[41–43]

Stress, pain and executive functions

The biological mechanisms, whereby psychosocial stressors impair executive functioning processes in the prefrontal cortex are not well understood. However, it has been suggested that chronic exposure to psychosocial stress can dysregulate the neural pathways activated by dopamine, adrenaline and cortisol and can also downregulate glucocorticoid receptor sensitivity of the prefrontal cortex. All these probably contribute to defective executive functioning.[4,11,14] Chronic stress downregulates excitatory synaptic transmission with diminution of neural firing in the prefrontal cortex, and between the prefrontal cortex and other cerebral neural networks, with the impairment of executive functioning and of higher-order cognitive performance with consequent maladaptive behaviour.[44]

Furthermore, the release of CRH and noradrenaline in the brain in response to psychosocial stressors can modulate the function of central neural circuits that play roles in evaluation and processing of noxious and non-noxious sensory stimuli with the potential to exaggerate pain perception.[22] It appears that independently or concertedly, both psychosocial stressors and pain stimuli can modulate neuronal functional connectivity, stimulating stress/nociceptive activity in the limbic system and inhibiting antistress/antinociceptive activity in the prefrontal cortex and hippocampus, thus

exaggerating chronic pain and maladaptive stress responses.[22,45]

Chronic exposure to psychosocial stressors, constant worry and rumination are exhausting to resources of cognitive mental energy and may therefore lead to diminished executive functioning with prolongation of stress responses[11] and to chronicity of depression and anxiety inherent in the experience of pain.[15,34] Furthermore, as substantial resources of mental energy are expended in the regulation of responses to chronic stress and in modulation the experience of pain, only limited resources of executive control remain for core executive functions including working memory, attention control and cognitive flexibility, resulting in cognitive impairment.[12,13] Executive functioning under stress is therefore impaired and is different unstressed executive functioning. Therefore, the true efficacy of executive functioning should be evaluated under stressful conditions.[14]

Psychosocial stressors have an effect upon the cellular, molecular and genetic elements of neural signalling between the limbic structures and the prefrontal cortical regions, which determine cognitive executive functioning, emotional responses and adaptive/maladaptive behaviours. Variations in cerebral neural circuits, polymorphism of genes encoding neurotransmitters such as serotonin, dopamine, noradrenaline and glutamate and their receptors, neurodegenerative processes and gene interactions with environmental factors such as smoking, alcohol drinking, malnutrition and infection can modulate neurobiological responses including responses to psychosocial stressors and pain stimuli.[11,6] It appears that subjects with stress-related burnout syndrome have deficiencies in executive functioning with a reduction in the capacity of the prefrontal cortex to downregulate emotional stress and stress responses generated by the limbic system. This indicates that in predisposed subjects, the prefrontal cortex is vulnerable to stress-induced dysfunction.[46] Personality traits can also influence executive functioning. Neuroticism (worry, anger, frustration and anxiety) is strongly associated with poor stress regulation, while conscientiousness (self-discipline, impulse control, dutifulness and orderliness) is associated with better stress control.[11]

Cognitive control of emotion

'Emotions are balanced responses to external stimuli and/or to internal mental representations',[47] and can be regulated either cognitively and/or behaviourally. Emotions, including those brought about by chronic stress and by chronic pain, influence memories, perceptions, thoughts, judgements, decisions and actions.[18,47] Regulation of emotional responses refers to the initiation of new or the modification of ongoing emotional experiences and responses.[47]

Functional connectivity between the hippocampus and the prefrontal cortex is essential for executive functioning and emotional regulation and is vulnerable to functional dysregulation by stress. Hippocampal–prefrontal cortex circuits rely on dopaminergic–glutaminergic–GABAergic neuronal interactions which determine the balance between inhibition and excitation in the prefrontal cortex. Serotonergic, noradrenergic and cholinergic neuronal pathways also play an important role in the activity of the hippocampal–prefrontal cortex circuits. The amygdala plays an essential role in processing emotion-related information and is regulated by hippocampal–prefrontal cortex circuits.[16]

In general, executive control of emotional responses involves initial appraisal of their significance to current goals of the psychosocial stressor, reappraisal of the emotionally implicative stressors, and finally, the cognitive moderation of the automatic emotional response.[11,18] Deficient executive functioning enhances vulnerability to adverse emotional and pain experiences and stress responses, which in turn may further downregulate executive functioning,[11] impairing the processing of decisions[18]; and emotions have the capacity to dysregulate processing of information, thus influencing cognitive processes and goal-directed behaviours.

Cognitive behavioural therapy is a person-directed, structured short-term psychological technique which is effective in increasing the capacity to cope with stress by teaching how to self-identify and moderate maladaptive thoughts, emotions and behaviour. Understanding the nature of the dysregulation between thoughts, emotions and behaviour will enable someone experiencing chronic stress/pain to adopt alternative more normative thoughts, emotions and behaviour, lowering their levels of anxiety/depression.[35,48]

Cognitive behavioural therapy improves personal communication skills, coping capacity, sense of control over life events and an overall feeling of well-being.[49] This elevated positive effect has the capacity to increase resources of mental energy, further improving cognitive thought processes and social behaviour, thus mitigating the risk of depressive symptoms.[50] In addition to cognitive behavioural therapy, mindfulness/meditation is also effective in managing maladaptive emotions and maladaptive responses to persistent stress, for modulating experiences of chronic pain and for reducing symptoms of anxiety and depression.[49,40] This may result in adoption of novel cognitive thought processes and positive emotions, culminating in enhanced well-being.[51]

Conclusion

Balanced dynamic reciprocity between the prefrontal cortex and the limbic system is essential for adaptive stress responses and pain processing. Hyperactivity of

the limbic system in processing emotion-related information, deficient prefrontal cortex–related executive functioning or both may result in poor control of stress responses and poor regulation of pain experience.[11] Chronic psychosocial stress and chronic pain can dysregulate executive functioning. Conversely, impaired executive functioning increases the risk of chronic pain and maladaptive stress responses. Chronic pain increases the risk of compromised responses to psychosocial stressors.

There is a need for research into the identification of central neurocircuits involved in excitation, inhibition and disinhibition of pain/stress pathways and the mechanisms by which maladaptive stress responses promote pain chronicity. Finding answers to these issues may facilitate the development of target-specific pharmacotherapeutic agents with increased efficiency and fewer side effects.

Author contributions

LF and RAGK developed the study design. LF, RAGK and JL wrote the first draft of the manuscript, LF, RAGK, GF, TB, RC and JL critically revised the second and final draft. GF finalised the referencing.

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