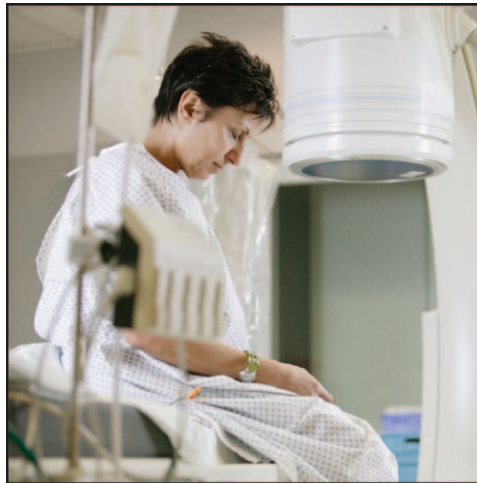


Comorbidities and the Complexities of Chronic Pain

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IRRESPECTIVE of their underlying mechanisms, many chronic pain syndromes share several comorbidities. These comorbidities include mood alterations (such as depression), anxiety, sleep disturbances, fatigue/lack of energy, neurocognitive changes, and other vague symptoms including generalized diffuse pain states. These comorbidities reduce the quality of life of the patient with chronic pain and by themselves cause the loss of working days and obstruct the living of a healthy social life. In this issue of *ANESTHESIOLOGY*, Tajerian *et al.*¹ report on a set of experiments in a mouse model of Complex Regional Pain Syndrome type 1 (CRPS1). The authors show that CRPS1-related pain coincides with increased anxiety and memory impairment. Importantly, brain histology and brain protein assays show that the CRPS animals display signs of plastic changes and reduced synapse formation and neurotropy, indicative of neural plasticity, in areas of the brain involved in emotion, anxiety, fear and mood (amygdala), and cognition/memory (hippocampus and perirhinal cortex). These are important observations as they show conclusively that comorbidities in complex chronic pain syndromes, in this case, a surrogate model of CRPS1, have a pathophysiological substrate in the brain that may be an important target for intervention.

It is known for decades that the occurrence of chronic pain and neuropsychiatric disease, most importantly depression, is highly comorbid.² Indeed, on average up to 50% of patients with some form of chronic pain display symptoms of anxiety and depression,³ whereas in some studies the number exceeds 75%.⁴ A recent Canadian study showed that chronic pain of any kind is associated with the development of major depression within 2 yr in 16.4% of patients.² Importantly, the prevalence of major depression increased with greater pain severity. These findings are in agreement with those in the study by Tajerian *et al.*, showing that the temporal relationship between chronic pain and neurocognitive dysfunction is such that anxiety and memory impairment are secondary to the induction of experimental CRPS1. Still, the reverse is similarly true. For



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example, individuals without pain but diagnosed with major depression are almost three times more likely to develop musculoskeletal pain within a 2-yr time span than nondepressed persons.² Also anxiety affects pain perception in the brain. These studies demonstrate important coherent neural pathways exemplifying the impact of anxiety and depression on pain and *vice versa*.

A key component in the precipitating property of depression during chronic pain results from observations that brain inflammation after peripheral nerve injury contributes to the development of depression-like behavior, with increased cytokine expression in specific brain areas.⁵ Importantly, antagonizing the neuroinflammatory response ameliorates the effects of neuropathic pain on depression.⁵ In line with these animal data, peripheral release of proinflammatory cytokines including tumor necrosis factor- α is observed in a subset of patients with CRPS1,⁶ and these cytokines may be an initial causative factor in the central defects in cognition and mood alteration in a way similar to that observed in postoperative states.⁷ Of interest is further that stress is known to contribute to the development of depression as well as chronic pain.⁸ For example, in animals, stress exacerbates both pain and depression-like behavior.⁵ In humans, a healthy stress response, through activation of the hypothalamo-pituitary-adrenal axis, will initiate a cascade of adaptive responses aimed at enhanced cognitive performance and modified cardiovascular and immune functions.⁸ Activation of the hypothalamo-pituitary-adrenal axis and the sensation of acute pain after tissue damage are two highly functional and protective responses that allow the individual to focus attention toward the tissue damage, if necessary take evasive action and seek help. In contrast, because of chronic stress and chronic pain the hypothalamo-pituitary-adrenal axis becomes dysfunctional resulting in either hyper- or hypocortisolemia.⁸ Both of which are thought to be associated with mood disturbance.

Tajerian *et al.*¹ observed reductions in the brain growth factor, brain-derived neurotrophic factor, and synaptic

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protein synaptophysin. These findings support a model in which neuroinflammation and stress, secondary to chronic pain, induce depression and anxiety. Both neuroinflammation and stress increase inflammatory cytokines, which in turn reduce brain growth factors including brain-derived neurotrophic factor and cause synaptic loss with a reduction of synaptic markers such as synaptophysin.^{9,10}

In their animal study, Tajerian *et al.*¹ observed CRPS-induced changes in the amygdala, perirhinal cortex, and hippocampus. These brain areas are part of the limbic system, which plays a crucial role in the control of our emotions and the emotional augmentation of clinical pain.^{11,12} Also in patients with chronic pain, alterations in the limbic system and especially the hippocampus have been observed. For example, Mutso *et al.*¹³ show that patients with CRPS1 or chronic back pain have significantly less hippocampal volume compared with healthy controls. In another subset of patients with chronic back pain, lower hippocampal volumes were related to higher cortisol levels and abnormal pain responses (hypersensitivity) in the anterior hippocampal formation.¹² According to the findings by Tajerian *et al.*,¹ these human studies suggest a causal link between chronic pain, stress, anxiety, and hippocampal function (a stress model of chronic pain and emotional disturbance).^{11–14}

It is our experience that anxiety and depression play a crucial role in the persistence of chronic pain and the loss of quality of life. Still, these often-vague symptoms are seldom adequately diagnosed and treated, as most physicians do not consider them part of the pain syndrome or just do not take them seriously. As correctly stated by Tajerian *et al.*,¹ their data support the use of specific therapeutic interventions that should ameliorate both pain and comorbid symptoms. However, in CRPS1, as in most chronic pain syndromes, commonly used symptomatic treatments (such as rehabilitation therapy, pharmacological agents [including opioids], sympathetic blockade, surgery, and psychological interventions) show variable and often limited efficacy and are often only directed at pain-related symptoms.^{1,5} Given the possible role of stress and neuroinflammation in the chronification of pain and the pathogenesis of associated comorbid symptoms, we contend that therapy should be aimed at treating these underlying and causal processes. Examples of such therapy include antitumor necrosis factor- α treatment in patients with rheumatoid arthritis chronic pain and ketamine treatment in patients with CRPS1 chronic pain.^{4,15} Antitumor necrosis factor- α therapy effectively reduces nociceptive brain activity in the thalamus, the somatosensory cortex, and the limbic system.¹³ Ketamine has antiinflammatory and potent antidepressant properties and engages endogenous analgesic pathways.¹⁶ Furthermore, recent studies show that it also reduces posttraumatic stress responses.¹⁷ Finally, Ploghaus *et al.*¹² made an interesting suggestion in relation to more acute painful procedures. They suggest behavioral therapy to disengage (incapacitate) the hippocampus in its role as emotional pain modulator and/or amplifier. By giving

accurate information on a painful procedure, pain is alleviated and anxiety reduced.

Chronic pain of any kind is debilitating with far reaching consequences on the patient's life. The study by Tajerian *et al.*¹ shows that chronic pain is associated with pathological changes in brain areas of the limbic system. As current therapy is insufficient, we argue that targeting the underlying central mechanisms of these pathological changes will not only reduce pain but also neuropsychiatric symptoms, including anxiety and depression.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Tajerian M, Leu D, Zou Y, Sahbaie P, Li W, Khan H, Hsu V, Kingery W, Huang TT, Becerra L, Clark JD: Brain neuroplastic changes accompany anxiety and memory deficits in a model of complex regional pain syndrome. *ANESTHESIOLOGY* 2014; 121:852–65
2. Currie SR, Wang J: More data on major depression as an antecedent risk factor for first onset of chronic back pain. *Psychol Med* 2005; 35:1275–82
3. Banks SM, Kerns RD: Explaining high rates of depression in chronic pain: A diathesis-stress framework. *Psychol Bull* 1996; 119:95–110
4. Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY, Dahan A: Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain* 2009; 145:304–11
5. Norman GJ, Karelina K, Zhang N, Walton JC, Morris JS, Devries AC: Stress and IL-1 β contribute to the development of depressive-like behavior following peripheral nerve injury. *Mol Psychiatry* 2010; 15:404–14
6. Borchers AT, Gershwin ME: Complex regional pain syndrome: A comprehensive and critical review. *Autoimmun Rev* 2014; 13:242–65
7. Terrando N, Monaco M, Foxwell BMJ, Feldmann M, Maze M: Tumor necrosis factor- α triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci USA* 2010; 107:20518–22
8. Blackburn-Munro G, Blackburn-Munro R: Pain in the brain: Are hormones to blame? *Trends Endocrinol Metab* 2003; 14:20–7
9. Anisman H, Hayley S: Inflammatory factors contribute to depression and its comorbid conditions. *Sci Signal* 2012; 5:pe45
10. Rao JS, Kellom M, Kim HW, Rapoport SI, Reese EA: Neuroinflammation and synaptic loss. *Neurochem Res* 2012; 37:903–10
11. Schweinhardt P, Kalk N, Wartolowska K, Chessell I, Wordworth P, Tracey I: Investigation into the neural correlates of emotional augmentation of clinical pain. *Neuroimage* 2008; 40:759–66
12. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I: Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci* 2001; 21:9896–903
13. Mutso AA, Radzicki D, Baliki MN, Huang L, Banisadr G, Centeno MV, Radulovic J, Martina M, Miller RJ, Apkarian AV:

- Abnormalities in hippocampal functioning with persistent pain. *J Neurosci* 2012; 32:5747–56
14. Vachon-Presseau E, Roy M, Martel MO, Caron E, Marin MF, Chen J, Albouy G, Plante I, Sullivan MJ, Lupien SJ, Rainville P: The stress model of chronic pain: Evidence from basal cortisol and hippocampal structure and function in humans. *Brain* 2013; 136(Pt 3):815–27
 15. Hess A, Axmann R, Rech J, Finzel S, Heindl C, Kreitz S, Sergeeva M, Saake M, Garcia M, Kollias G, Straub RH, Sporns O, Doerfler A, Brune K, Schett G: Blockade of TNF- α rapidly inhibits pain responses in the central nervous system. *Proc Natl Acad Sci U S A* 2011; 108:3731–6
 16. Niesters M, Khalili-Mahani N, Martini C, Aarts L, van Gerven J, van Buchem MA, Dahan A, Rombouts S: Effect of subanesthetic ketamine on intrinsic functional brain connectivity: A placebo-controlled functional magnetic resonance imaging study in healthy male volunteers. *ANESTHESIOLOGY* 2012; 117:868–77
 17. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, Kirkwood K, Aan Het Rot M, Lapidus KA, Wan LB, Iosifescu D, Charney DS: Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial. *JAMA Psychiatry* 2014; 71:681–8