Journal Club
Commentary

OPEN

PAIN REPORTS®

Chronic pain: breaking free from stickiness

Shahrzad Firouzian[a,b,*], Natalie R. Osborne[a,b]

Abstract

By introducing the concept of "pain stickiness" underlying treatment-resistant pain, Borsook et al. take a neurobiological perspective to capture the factors that may contribute to the transition of pain from acute to chronic form. However, there is more to consider, including the interconnected influences of resilience, brain gray matter and connectivity, sex differences, and the role of the environment. There still remains the question of how to eliminate this stickiness.

Keywords: Chronic pain, Resilience, Treatment

Commentary on: Borsook D, Youssef AM, Simons L, Elman I, Eccleston C. When pain gets stuck: the evolution of pain chronification and treatment resistance. PAIN 2018;159:2421–36.

In a recent comprehensive review, Borsook et al.[3] conceptualize pain chronification by creating an image of a patient whose allostatic mechanisms cannot "un-stick" them from a chronic pain state. Allostasis represents the adaptive forces drawing the patient back towards homeostasis when responding to stressors. "Stickiness" keeps the patient in chronic pain despite efforts for pain resolution, that is, treatment-resistant pain. Like a car stuck spinning its wheels, the system's efforts to resolve the condition are unsuccessful. Therefore, we ask: which factors enhance the "stickiness" of pain, and how can patients "un-stick" from their chronic pain? To address these questions in this commentary, we will expand on the concept of resilience, highlight relevant brain imaging findings, emphasize the importance of sex differences, and end by broadening the environmental perspective as an influencing factor for chronic pain.

The authors use the term "resilience" to refer to a system's malleable ability to return to homeostasis, which in the context of pain may include cognitive, emotional, genetic, and epigenetic mechanisms. We extend this definition to expand on the role of cognitive-affective influences on pain intensity and unpleasantness. Although the authors discuss cognitive-affective influences on chronic pain in relation to negative factors, we propose including positive or "protective" cognitive-affective influences. From a psychological perspective, resilience includes a combination of positive personality characteristics,[7] which affects one's ability to "bounce back" when faced with adverse events in life.[8] In patients with arthritis, resilience can be negatively correlated with clinical pain scores, and positively related to within-default mode network connectivity.[8] Resilience can also be positively correlated with age, and negatively correlated with relative pain unpleasantness, anxiety, and depression.[7] In fact, resilience and anxiety interact to predict the negative correlation between resilience and relative pain unpleasantness, such that those with higher anxiety scores may show a greater change in unpleasantness with change in resilience than those with lower anxiety scores.[7] Therefore, a patient's psychological resilience could influence whether acute pain takes on an adaptive (resolution) or maladaptive (chronification) direction. This also suggests that therapies designed to promote and cultivate the positive personality characteristics associated with resilience could be an effective tool for preventing or reversing pain "stickiness."

Furthermore, we suggest an expanded discussion of the authors' perspective of gray matter influences on chronic pain. First, the authors describe gray matter abnormalities as reflections of dendritic morphology and alterations in the number of neurons. However, gray matter alterations can also reflect changes in cell size, alterations in glia, changes in axon architecture,[10] and even the effects of neuroinflammation.[5] Therefore, it is important to consider how chronic pain may impact every aspect of the brain's microstructural environment. Second is the issue of whether gray matter alterations reflect a cause or a consequence of on-going pain. For

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Division of Brain, Imaging and Behaviour-Systems Neuroscience, Krembil Brain Institute, Krembil Research Institute, Toronto Western Hospital, University Health Network, Toronto, ON, Canada, [b] Institute of Medical Science, University of Toronto, Toronto, ON, Canada

**Corresponding author. Address: Krembil Brain Institute, Krembil Research Institute, Toronto Western Hospital, 399 Bathurst St, Room MP12-308, Toronto, ON M5T 2S8, Canada. E-mail address: shahrzad.firouzian@uhnresearch.ca (S. Firouzian).*

PR9 4 (2019) e746

http://dx.doi.org/10.1097/PR9.0000000000000746

example, Rodriquez-Raecke et al.[12] saw gray matter reductions in hip osteoarthritis patients, which increased after total hip replacement. This reversibility in gray matter may indicate that the initial reduction was a consequence of the presence of chronic pain. Perhaps if gray matter abnormalities were causes, then monitoring any changes may allow for early detection and prevention of these abnormalities in hopes of preventing pain chronification; this may become possible with advancements in technology. Resolving the question of whether gray matter changes are the cause or consequence of chronic pain will require long-term, prospective imaging studies with large cohorts to track morphological changes in those individuals who go on to develop chronic pain. Baliki et al.[2] expand our understanding of the underlying brain mechanisms of pain chronification through one such longitudinal investigation of subacute back pain patients. They found that functional connectivity between the medial prefrontal cortex and nucleus accumbens accurately predicted the transition from acute to chronic pain. Although it is important to observe those already experiencing persistent chronic pain, following patients from before their arrival at this state further contributes to understanding the cause and consequence dilemma. Although this longitudinal study was not discussed in this review, we believe it to be an important step in elucidating the neurobiological mechanisms of pain chronification.

Most chronic pain conditions are more prevalent in women.[11] This quantitative sex difference in chronic pain prevalence may be caused by qualitative differences, that is, differences in the biological mechanisms underlying pain sensing and coping in men and women. Therefore, we propose that pain chronification may be better understood by considering qualitative factors that contribute to this marked sex difference. Borsook et al.[3] propose that the more dynamic pattern of female dendritic complexity may increase their risk of developing chronic pain; this is interesting and merits further discussion on sex differences specifically in chronic pain. Factors that make pain chronic and treatment resistant may be different in men and women—just as sensitivity to acute pain and some neurobiological mechanisms associated with analgesia and rodent models of chronic pain differ between sexes.[11] Conversely, examining the neurobiological mechanisms of pain processing and analgesia in individuals more likely to develop chronic pain (ie, women) could provide general clues to the causes of pain chronification. The relationship between sex hormones and pain is complex, but understanding this interaction could identify how hormones may be therapeutically manipulated to treat or prevent chronic pain. Symptoms of some chronic pain conditions vary across the menstrual cycle,[14] suggesting that the allostatic load may change for females on the timescale of a few days. A study of 73 individuals receiving hormonal therapy during the sex-reassignment process reported that approximately 30% of participants undergoing male to female transitions developed chronic pain, while more than 50% of participants transitioning from female to male who previously had chronic pain conditions experienced improvements in their pain symptoms.[1] A recent study by Martin et al.[9] presents a paradigm that induced conditioned pain hypersensitivity specifically in male mice and humans, which was linked with testosterone and stress. Qualitative sex differences in the underlying biology of pain perception, tolerance, and especially coping mechanisms are likely important contributors to allostasis. In addition, sex differences in resting state functional connectivity of brain areas that signal pain have been found in healthy adults. For example, Wang et al.[15] revealed that the subgenual anterior cingulate cortex in females had stronger functional connectivity than males with the descending pain modulation system, including the periaqueductal gray, raphe nucleus, medial thalamus, and anterior midcingulate cortex. The functional connectivity in males, however, was stronger than females with areas implicated in the salience network, such as the anterior insula and temporoparietal junction. Understanding how these shared pain-related brain circuits are differently impacted in chronic pain may reveal different trajectories in pain chronification.

Environmental influences on pain are briefly addressed by the authors, which we elaborate on and also extend to factors beyond the natural environment, such as day-to-day interactions with the external world. Damkot et al.,[4] for example, investigated the details of work environments that explained the variance between pain groups of different severities. This included weights lifted, type of floor surface, type of chair support, and much more; such factors differentiated workers with no pain, moderate pain, and severe pain. Furthermore, pain treatment can be impacted by the natural environment, as was the case for a 4-week rehabilitation programme for rheumatoid arthritis.[13] In this study, 24% of patients treated in a warm Mediterranean climate reduced or stopped using nonsteroidal anti-inflammatory drugs during the 4 weeks, while only 8% did so in the cold Norwegian climate. In another study, patients with hip osteoarthritis showed an association between relative weather humidity and severity of pain, and between barometric pressure and hip function.[6] Therefore natural environmental factors, (eg, weather or climate) may impact treatment efficacy, and not just a patient's maladaptive pain state.

The key question remains to be answered: how do patients overcome pain stickiness and finally achieve pain resolution? The authors suggest an integrated biobehavioural perspective to understanding chronic pain, and this can be adopted by directing patients to a hub for biobehavioural expertise, from health care providers who can offer pharmacological interventions to social workers who can assist in day-to-day interactions with others. It is important that patients and care providers understand the degree to which each factor contributing to pain chronicity can be modified therapeutically. We propose a new stratification of the authors' model that considers a patient's level of control over pain-chronifying factors. In this model, primary-level factors, like psychological resilience, are more easily manipulated, such as through cognitive behavioural therapy. Secondary-level factors, like brain mechanisms and the environment, may occasionally be controlled, for example through pharmacological or brain stimulation treatments, or ergonomic modifications of the environment. Finally, tertiary-level factors are fairly uncontrollable, as in the case of biological sex. Although some patients may experience pain with an inevitably "sticky" prognosis, applying this label to all patients may discourage them from seeking a comprehensive approach to their pain management. Since the clinician's perspective is also important, we encourage clinicians to consider this biobehavioural approach when deciding on a pain management plan for their patients.

Disclosures

The authors have no conflict of interest to declare.

Article history:
Received 25 January 2019
Received in revised form 4 March 2019
Accepted 8 March 2019

References

[1] Aloisi AM, Bachiocco V, Costantino A, et al. Cross-sex hormone administration changes pain in transsexual women and men. PAIN 2007;132(suppl 1):S60–67.
[2] Baliki MN, Petre B, Torbey S, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci 2012;15:1117–9.
[3] Borsook D, Youssef AM, Simons L, Elman I, Eccleston C. When pain gets stuck: the evolution of pain chronification and treatment resistance. PAIN 2018;159:2421–36.
[4] Damkot DK, Pope MH, Lord J, Frymoyer JW. The relationship between work history, work-environment and low-back-pain in men. Spine 1984; 9:395–9.
[5] Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. J Neuroimmune Pharm 2013;8:518–34.
[6] Dorleijn DMJ, Luijsterburg PAJ, Burdorf A, et al. Associations between weather conditions and clinical symptoms in patients with hip osteoarthritis: a 2-year cohort study. PAIN 2014;155:808–13.
[7] Hemington KS, Cheng JC, Bosma RL, Rogachov A, Kim JA, Davis KD. Beyond negative pain-related psychological factors: resilience is related to lower pain affect in healthy adults. J Pain 2017;18: 1117–28.
[8] Hemington KS, Rogachov A, Cheng JC, et al. Patients with chronic pain exhibit a complex relationship triad between pain, resilience, and within- and cross-network functional connectivity of the default mode network. PAIN 2018;159:1621–30.
[9] Martin LJ, Acland EL, Cho C, et al. Male-specific conditioned pain hypersensitivity in mice and humans. Curr Biol 2019;29:192–201.e4.
[10] May A. Chronic pain may change the structure of the brain. PAIN 2008; 137:7–15.
[11] Mogil JS. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. Nat Rev Neurosci 2012;13:859–66.
[12] Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. J Neurosci 2009;29:13746–50.
[13] Strumse YAS, Nordvag BY, Stanghelle JK, et al. The efficacy of rehabilitation for patients with rheumatoid arthritis: comparison between a 4-week rehabilitation programme in a warm and a cold climate. Scand J Rheumatol 2009;38:28–37.
[14] Vincent K, Tracey I. Hormones and their interaction with the pain experience. Rev Pain 2008;2:20–4.
[15] Wang G, Erpelding N, Davis KD. Sex differences in connectivity of the subgenual anterior cingulate cortex. PAIN 2014;155:755–63.