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Editorial comment

Important new insight in pain and pain treatment induced changes in functional connectivity between the Pain Matrix and the Salience, Central Executive, and Sensorimotor networks

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Kolesar et al. [1] are to be congratulated on this article, which goes one step beyond their original article [2] in analyzing brain activity at rest in patients with Failed Back Surgery Syndrome (FBSS). Together, data from both articles help us to understand more about brain function in chronic pain but also what might set FBSS apart from other forms of chronic pain. The original article looked at alterations in the Default Mode Network (DMN) using functional magnetic resonance imaging (fMRI). Reading these and other pertinent articles is rather difficult for those of us not familiar with brain neuroanatomy, neurophysiology, and the burgeoning literature on fMRI and Positron Emission Tomography (PET) in pain but it is worthwhile to persist since this field, especially that focusing on brain activity at rest in chronic pain patients, is crucial to understand many of the clinical signs and symptoms common to those with various chronic pain syndromes.

1. The Default Mode Network (DMN) – *"the mind in neutral"*

The DMN is what the brain does at rest when there is no reason to focus on a specific task, mental or physical – "*the mind in neutral*" if you will. It is an activity pattern of connectivity between various functional brain centres and the patterns are similar in everyone. A lot of data has been accumulated on this activity either awake, sleeping, under anaesthesia, etc. and the data also show how acute pain, chronic pain, and mental and physical tasks affect this connectivity.

In the original article by Kornelsen et al. [2], they demonstrated that, in contrast to a matched pain-free population, the DMN was less actively connected to areas of the brain not involved specifically in sensory or affective processing but was more connected to brain areas commonly associated with pain processing and "outside of the commonly reported DMN" [2]. This is not a new finding and has been reported by others in a variety of chronic pain syndromes [3] but in the case of FBSS, the relationships seem stronger [1,2]. Kolesar et al. attribute this to higher levels of background spontaneous pain in this group although, unfortunately, no such data on spontaneous pain are available from the subjects in the study [1,2]. It may be that there are other correlates to explain this in FBSS and more research needs to be done.

The changes found here and in other pain studies on the DMN are intuitively obvious since one would expect that patients in chronic pain would pay attention to these symptoms and change the background brain activity that we all have when not focusing on a task or a sensation (feeling), mental or physical.

2. The DMN, the Salience Network (SN), the Central Executive Network (CEN), and the Sensorimotor Network (SeN) and the "Pain Matrix"

The next step, the subject of the present article [1], was to look at specific networks within the DMN, the Salience Network (SN), the Central Executive Network (CEN), and the Sensorimotor Network (SeN). The naming is apt; the SN is involved in detection of external stimuli, the CEN is involved in cognition, and the SeN in sensory and motor integration. As could be expected, these networks all showed more functional connectivity than the normal controls to areas of the brain associated with pain sensations and pain processing, the "pain matrix". There was also less functional connectivity to other areas of the brain not associated with the "pain matrix". Also not surprising when thinking about brain function, was an interconnection between the SN and the SeN implying that the brain was considering the importance of the pain information coming in from the periphery.

Why should this information and the accumulating information surrounding the DMN be important for chronic pain? Similar changes as in the first Kolesar et al. article [2] have been found in non-specific low back pain [4], fibromyalgia [5], diabetic neuropathy [6], migraine headache [7], as well as in acute experimental pain states in healthy volunteers [8].

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3. Effective pain management can reverse pain-induced changes in the DMN

But do the modifications of brain activity at rest represent plastic change that is permanent? This does not seem to be the case since treating chronic pain patients successfully with medications [9], with mindfulness [10] or various forms of Cognitive Behavioural Therapy (CBT) [11,12] can reduce or abolish these changes. One hopes that the authors' next study will be to follow up this patient cohort after spinal cord stimulation (SCS) since these subjects came from a clinic evaluating them for this treatment. One can postulate that if successful, SCS could revert the DMN to what is the normal baseline function.

4. fMRI documents how CBT, mindfulness, and ACT can reverse pain-induced changes in the DMN

The information on CBT and mindfulness are particularly important since they both are methods for taking the focus of thoughts from pain to other elements of the patients' internal and/or external environment that are more important. This change in focus alone often allows patients to return to a more normal life. *In mindfulness*, the focus is to other thoughts and sensations that allow a break from the focus on pain and it is intuitively obvious that activity in the DMN would be changed connectivity to other areas of the brain not included in the pain matrix. The same is true for CBT.

If one considers *Acceptance and Commitment Therapy (ACT)*, here the purpose is to reduce the meaning of pain as a signal that the body is being threatened and to think of the chronic pain signals as background noise that should not be a distraction from more important things in life.

Again, it is intuitively obvious that a change in focus away from pain would decrease the functional connectivity of the DMN to the pain matrix and instead, to the areas which are found by fMRI in subjects without chronic pain.

5. Grey matter changes with chronic pain can be restored by effective pain treatment

A further point here is that most chronic pain patients complain of difficulty in concentration, memory and various other mental activities. There is data on the loss of grey matter in the cortex of patients with various chronic pain states [13,14] that might be considered the cause of the cognitive difficulties. It has been shown that changing the connectivity in the DMN away from the pain matrix improves mental functioning early. There is an effect of the successful treatment for pain on grey matter volume, which increases in patients studied after hip prosthesis surgery [15] indicating that the changes are reversible and not the cause of the pain but an effect. Little data is available on cognitive difficulties, cognitive improvement and grey matter volume however.

Here, again, if the DMN is strongly connected to the pain matrix it is obvious that this activity would distract patients from focusing on other mental activities such as concentrating on a task, doing simple arithmetic or other activities that need a mental focus for optimum performance such as driving a car which is affected negatively by chronic pain [16]. When those activities are not the focus of the brain with the change in DMN, the brain cells needed for them would atrophy leading to a loss of grey matter. Increased use of these neglected brain areas should lead to an increase in cell mass but this is a slow process.

6. Conclusions

The study by Kolesar et al. [1] as well as related research allow us to have a little more information on the functions of the "black box", the brain, in those with chronic pain. One hopes that continued research may give us a "grey box" where the increased knowledge should help us to both find and understand new therapies for better treatment of this difficult patient population.

Conflict of interest

None declared.

References

[1] Kolesar TA, Bilevicius E, Kornelsen J. Salience, central executive and sensorimotor functional connectivity alterations in failed back surgery syndrome. Scand J Pain 2017;16:10–4.
[2] Kornelsen J, Sboto-Frankenstein U, McIver T, Gervai P, Wacnik P, Berrington N, Tomanek B. Default mode network functional connectivity altered in failed back surgery syndrome. J Pain 2013;14:483–9.
[3] Baliki MN, Monsour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. PLoS ONE 2014;9:1–13.
[4] Tagliazucchi E, Balenzuela P, Fraiman D, Chiavo DR. Brain resting state is disrupted in chronic back pain patients. Neurosci Lett 2010;485:26–31.
[5] Napadow V, Kim J, Clauw DJ, Harris RE. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. Arthritis Rheum 2012;64:2398–403.
[6] Cauda F, D'Agata F, Sacco K, Duca S, Cocito D. Altered resting state attentional networks in diabetic neuropathic pain. J Neurol Neurosurg Psychiatry 2010;81:806–11.
[7] Faragó P, Tuka B, Tóth E, Szabó N, Király A, Csete G, Szok D, Tajti J, Párdutz Á, Vécsei L, Kincses ZT. Interictal brain activity differs in migraine with and without aura: resting state fMRI study. J Headache Pain 2017;18:8.
[8] Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci USA 2006;103:13848–53.
[9] Seminowicz DA, Wideman TH, Naso L, Hatami-Koroushahi Z, Fallatah S, Ware MA, Jarzen P, Bushnell MC, Shir Y, Ouellet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. J Neurosci 2011;31:7540–50.
[10] Bilevcius E, Kolesar TA, Kornelson J. Altered neural activity associated with mindfullness during nociception: a systematic review of functional MRI. Brain Sci 2016;6 [epub].
[11] Shpaner M, Kelly C, Lieberman G, Perelman H, Davis M, Keefe FJ, Naylor MR. Unlearning chronic pain: a randomized controlled trial to investigate changes in intrinsic brain connectivity following cognitive behavioral therapy. Neuroimage Clin 2014;5:365–76.
[12] Kucyi A, Salomons TV, Davis KD. Cognitive behavioral training reverses the effect of pain exposure on brain network activity. Pain 2016;157:1895–904.
[13] Smallwood RF, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, Williams DA, Schmidt-Wilcke T, Farrell MJ, Eickhoff SB, Robin DA. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. J Pain 2013;14:663–75.
[14] Cauda F, Palermo S, Costa T, Torta R, Duca S, Vercelli U, Geminiani G, Torta DM. Gray matter alterations in chronic pain: a network-oriented meta-analytic approach. Neuroimage Clin 2014;4:676–86.
[15] Gwilym SE, Filippini N, Douaud G, Carr AJ, Tracey I. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. Arthritis Rheum 2010;62:2930–40.
[16] Nilsen HK, Landrø NI, Kaasa S, Jenssen GD, Fayers P, Borchgrevink PC. Driving functions in a video simulator in chronic non-malignant pain patients using and not using codeine. Eur J Pain 2011;15:409–15.