

Can we exploit cognitive brain networks to treat chronic pain?



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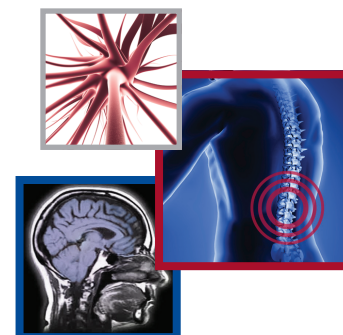
While research on the association between cognitive function and pain has been continuous for decades, it has surprisingly never been a major focus of pain neuroimaging research. Sometimes pain–cognition interactions in acute pain are intuitive: pain distracts away from a task, whereas focusing on a task can reduce pain. Presumably, these effects disappear when the task becomes too difficult or important to ignore, or when pain is too intense to be kept out of mind. In chronic pain, the interaction between pain and cognitive function is more complex. Growing evidence suggests that brain networks involved in executive functions are disrupted in chronic pain conditions. The abnormal activation of cognitive circuitry does not necessarily reflect an inability to perform difficult cognitive tasks. But it does implicate a functional brain alteration that has developed with the progression of chronic pain.

Chronic pain as cognitive network dysfunction

Here, we propose a model of chronic pain as a brain disorder related to cognitive

network dysfunction, which is useful in terms of understanding neurobiological mechanisms of chronic pain and for improving interventions. This model takes us away from more popular models that posit chronic pain is a brain disease involving sensory and emotional circuitry. The focus on cognitive network dysfunction potentially has broader implications for interventions at the level of the brain than do models focused on emotional and sensory dysfunction.

Sensory, perceptual and emotional components of pain are highly susceptible to cognitive effects. Cognition can override salience and emotional valuation of pain. This is exploited in some nonpharmacological approaches to treating pain, such as cognitive–behavioral therapy (CBT). CBT focuses on reworking a cognitive framework in which pain is perceived by restructuring negative thoughts and beliefs, improving coping skills and problem solving and increasing adaptive behaviors. While several trials have shown CBT has efficacy (usually compared with wait-list groups), CBT is by no means a perfect treatment and could likely be improved



KEYWORDS

- attention • cognition • conflict
- default mode network
- dorsolateral prefrontal cortex
- extrinsic mode network • fMRI
- gray matter • intervention task

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or redesigned. Reframing our understanding of pain as a cognitive disorder will help us develop interventions more precisely targeted at cognitive network dysfunction.

Cognitive-related structural & functional brain changes

Chronic pain is associated with structural and functional alterations in brain regions related to cognition. A common finding is reduced gray matter volume (GMV) in prefrontal cortices [1]. GMV reductions in chronic pain are often correlated with pain severity or duration, but links to cognitive function have not been tested extensively, although there is some evidence that impaired cognitive performance might be related to reduced prefrontal GMV of chronic pain patients [2]. Pain severity and duration might be closely linked to severity of cognitive dysfunction. GMV and other structural and functional brain differences in chronic pain patients are often interpreted in relation to nociceptive and emotional aspects of pain, rather than cognitive dimensions.

There is abundant evidence of cognitive dysfunction (in the range of 5–20% reduction in performance ability, depending on the type of task imposed) in chronic pain and also demonstrated in animal models [3]. Aside from the indirect effects on cognition, such as sleep impairment, anxiety, distractibility, chronic pain might in fact be a direct source of cognitive conflict. This could explain the enhanced activity of cognitive networks when pain and cognitive task are presented simultaneously [4], whereby acute phasic pain acts as a cognitive load, enhancing the magnitude of cognitive-related activity during task performance in a frontoparietal cortical network referred to as extrinsic mode network (EMN; previously referred to as task-positive network [TPN]) and even activating this cognitive network in the absence of a task. Activation of the EMN, which includes dorsolateral prefrontal cortex (DLPFC), mid cingulate and posterior parietal cortical regions, is associated with greater suppression of the default mode network (DMN), comprised of posterior cingulate, precuneus and medial prefrontal cortex. Together, the DMN and EMN make up the major cognitive networks.

A consistent finding across chronic pain conditions is that patients show less suppression of DMN during cognitive tasks [5–7], and recent evidence suggests that patients also have less

modulation of DMN by cognitive load [8]. This ‘hyperactivity’ of the DMN does not only occur when patients are performing a (challenging) cognitive task, but is also evident in the brain at rest or in the presence of minimal attentional load [9,10]. At the same time, increased neural recruitment of other brain regions (commonly in the EMN) is often observed in these patients and interpreted as compensation for deficient functioning of the DMN [5,6]. However, there is also evidence for altered DMN without any compensatory recruitment [8], suggesting that the attenuation of DMN suppression and modulation might not be directly linked to cognitive dysfunction in chronic pain patients.

If the altered DMN suppression during a cognitive task is not directly related to cognitive dysfunction, how should we interpret these findings? DMN, sometimes referred to as the brain’s baseline metabolic state, is active during rest and suppressed during focused behavior. The baseline for chronic pain patients might be different than pain-free people – they might have ongoing pain in many situations and indeed, ongoing pain intensity has in some patients been linked to altered DMN baseline state [11,12]. But while the activation level of the EMN appears to be related to cognitive demand, suppression level of the DMN does not [8,13]. Furthermore, at least in experimental settings, patients are typically capable of performing a cognitive task at the same level as healthy subjects [5,7–8] and they are able to activate the EMN appropriately. Given the difference in DMN activity, there must be some cost to the pain patient. What is that cost and how do we intervene?

In addition to an altered DMN at baseline, another possible mechanism contributing to cognitive dysfunction is an imbalance between major cognitive networks. There exists some evidence that optimal cognitive processing depends on a balance in activity between DMN and EMN [14], and that this balance is under the control of a cognitive mediator network, which includes parts of the DLPFC and insula [15]. Recent evidence suggests that DMN alterations in chronic pain patients might at least in part reflect the nonengagement of this cognitive mediator network [10], resulting in a disrupted ‘switch’ between DMN and EMN active states. It is also possible that the DMN alterations observed in chronic pain are related to negative coping with pain. DMN activity has in chronic pain patients been linked to catastrophizing and rumination

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about pain [8,16], and in healthy subjects to mind-wandering about pain [17]. It is difficult to know whether disrupted cognitive network function influences pain (coping), or whether pain disrupts cognitive network function, and most likely there is a cyclic interaction.

Interventions based on cognitive network targets

For the purpose of developing a feasible intervention, one region worth focusing on is the left DLPFC, which lies at the border of EMN and DMN (in fact part of it is in each network) and seems to play an important role in cognitive dysfunction in chronic pain. Its activity is relatively enhanced in chronic pain during a cognitive conflict task compared with controls [5,7], and interventions for chronic pain increase its GMV [5,18]. The left DLPFC is a target for repetitive transcranial magnetic stimulation treatment of major depression and has shown some efficacy for chronic pain [19]. The mechanisms remain unclear, but repetitive transcranial magnetic stimulation of left DLPFC might have an effect by modulating cognitive networks. Other ways that we can target the left DLPFC include CBT and mindfulness meditation training [20]. Relieving pain might work to temporarily allow cognitive systems to take over; that is, the best therapies might occur in pain-free states, when pain's influence – by whatever mechanism – on cognitive function is minimal.

There may be even more direct ways that we can target cognitive brain networks – rather than a single brain node within those networks – to alleviate chronic pain. An ideal cognitive-based intervention for chronic pain might focus on relaxation with autonomic feedback regulation,

and mastery of cognitive conflict resolution (e.g., with neurofeedback) tailored to the individual. We have only touched on a few specific ways that cognitive network dysfunction could be a focus for chronic pain research and intervention. A collaborative effort across research groups and patient populations focusing on brain mechanisms of chronic pain and recovery (i.e., using cross-sectional and prospective designs) would allow us to identify which relevant cognitive networks are altered in different chronic pain states and how these alterations relate to cognitive performance, with or without compensatory neural recruitment. We can concurrently investigate how cognitive network activity normalizes after intervention and predict treatment outcomes based on cognitive network activity, as well as how clinical outcomes are associated with specific recovery of brain function. While we have plenty to learn yet on this topic, understanding how to target cognitive network dysfunction in chronic pain will create opportunities to develop better interventions.

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References

- Bushnell MC, Ćeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat. Rev. Neurosci.* 14(7), 502–511 (2013).
- Luerding R, Weigand T, Bogdahn U, Schmidt-Wilcke T. Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: structural correlates of pain–cognition interaction. *Brain* 131(Pt 12), 3222–3231 (2008).
- Moriarty O, Finn DP. Cognition and pain. *Curr. Opin. Support. Palliat. Care* 8(2), 130–136 (2014).
- Seminowicz DA, Davis KD. Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task. *J. Neurophysiol.* 97(5), 3651–3659 (2007).
- Seminowicz DA, Wideman TH, Naso L *et al.* Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J. Neurosci.* 31(20), 7540–7550 (2011).
- Weissman-Fogel I, Moayed M, Tenenbaum HC, Goldberg MB, Freeman BV, Davis KD. Abnormal cortical activity in patients with temporomandibular disorder evoked by cognitive and emotional tasks. *Pain* 152(2), 384–396 (2011).
- Mathur VA, Khan SA, Keaser ML, Hubbard CS, Goyal M, Seminowicz DA. Altered cognition-related brain activity and interactions with acute pain in migraine. *Neuroimage. Clin.* 7, 347–358 (2015).
- Ćeko M, Gracely JL, Fitzcharles MA, Seminowicz DA, Schweinhardt P, Bushnell MC. Is a responsive default mode network required for successful working memory task performance? *J. Neurosci.* (2015) (In Press).
- Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J. Neurosci.* 28(6), 1398–1403 (2008).

- 10 Ceko M, Shir Y, Ouellet JA, Ware MA, Stone LS, Seminowicz DA. Partial recovery of abnormal insula and dorsolateral prefrontal connectivity to cognitive networks in chronic low back pain after treatment. *Hum. Brain Mapp.* 36(6), 2075–2092 (2015).
- 11 Loggia ML, Kim J, Gollub RL *et al.* Default mode network connectivity encodes clinical pain: an arterial spin labeling study. *Pain* 154(1), 24–33 (2013).
- 12 Napadow V, Lacount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis Rheum.* 62(8), 2545–2555 (2010).
- 13 Nagel IE, Preuschhof C, Li SC *et al.* Load modulation of bold response and connectivity predicts working memory performance in younger and older adults. *J. Cogn. Neurosci.* 23(8), 2030–2045 (2011).
- 14 Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Competition between functional brain networks mediates behavioral variability. *Neuroimage* 39(1), 527–537 (2008).
- 15 Spreng RN, Stevens WD, Chamberlain JP, Gilmore AW, Schacter DL. Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage* 53(1), 303–317 (2010).
- 16 Kucyi A, Moayed M, Weissman-Fogel I *et al.* Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. *J. Neurosci.* 34(11), 3969–3975 (2014).
- 17 Kucyi A, Davis KD. Dynamic functional connectivity of the default mode network tracks daydreaming. *Neuroimage* 100, 471–480 (2014).
- 18 Seminowicz DA, Shpaner M, Keaser ML *et al.* Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. *J. Pain* 14(12), 1573–1584 (2013).
- 19 Lefaucheur JP. Use of repetitive transcranial magnetic stimulation in pain relief. *Expert Rev. Neurother.* 8(5), 799–808 (2008).
- 20 Allen M, Dietz M, Blair KS *et al.* Cognitive-affective neural plasticity following active-controlled mindfulness intervention. *J. Neurosci.* 32(44), 15601–15610 (2012).