Commentary

Functional connections between self-referential thought and chronic pain: a dysfunctional relationship

Obtaining insight into brain mechanisms of chronic pain has long remained a significant challenge. The majority of non-invasive brain imaging studies of chronic pain focus on allodynia and/or hyperalgesia during evoked pain. In contrast, brain mechanisms of resting pain remain poorly understood due to many difficulties associated with imaging steady state conditions. In an elegant study published in the current issue of PAIN, Loggia and colleagues employed a number of novel techniques to explore brain mechanisms of resting pain in patients with chronic low back pain (CLBP) [8].

Brain activation associated with baseline pain, change in pain provoked by performing a body maneuver (i.e., leg raising or pelvic tilt), and consequential lingering pain was assessed. However, instead of using Blood Oxygen Level Dependent fMRI (BOLD) to gain insight into neural activity, Loggia et al employed arterial spin labeling fMRI (ASL). In brief, ASL is a perfusion-based, non-invasive neuroimaging technique that provides quantification of regional cerebral blood flow (ml of blood/100 g of tissue/min) with a diffusible tracer (magnetically labeled arterial water) [1]. ASL is better suited than BOLD to image clinical pain [14]. BOLD data are not fully quantitative and are subject to confounds arising from low frequency signal drifts [15]. In contrast, ASL is fully quantitative, rendering it better suited to capture changes corresponding to steady cognitive states [2].

In their first study of this rich dataset of CLBP [16], Wasan and colleagues used ASL to assess snapshots of brain activation corresponding to pain in response to pain-inducing body maneuvers. They found that brain regions (somatosensory, insular, and prefrontal cortices) activated by experimental heat pain were also activated by body maneuvers [16].

In the current issue of PAIN, Loggia et al. [8] delineate a mechanistic relationship between resting state brain networks and clinical pain. Generally, ASL data are very noisy, such that substantial signal averaging over time is required to gain inferences about brain activation. It is surprising and impressive that signal-to-noise ratios in Loggia and colleagues’ perfusion data were sufficiently high to allow connectivity analyses to be performed. This allows ASL analyses to be extended from snapshots of a single window of time (~5 min) to explore multiple temporal components of the pain experience at a much higher temporal resolution (~4.6 s).

In fMRI studies, one of the most frequently examined temporal components is activation in resting networks such as the default mode network (DMN). The DMN is defined by oscillating activity within a group of distinct brain regions [medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/precuneus, inferior and lateral temporal cortex] and is associated with a self-referential mental state [13]. Since some of the earliest brain imaging studies of pain, changes have been detected in regions associated with the DMN. In 1994, Coghill et al. reported reduced PCC activity during noxious stimulation [6]. Recently, Balki et al. found that chronic pain patients exhibited altered deactivation in the mPFC, one node of the DMN, while performing a motor/visual task [3].

The neural mechanisms by which chronic pain interacts with default mode activity remain poorly understood. The current study by Loggia et al now provides considerable insight into this relationship. They show that, in relation to healthy controls, CLBP patients exhibited greater baseline (i.e., before bodily maneuvers) DMN connectivity with the pregenual ACC (pgACC), a key node in the cognitive modulation of pain. Interestingly, those patients who reported the least amount of baseline pain exhibited the strongest DMN-pgACC connectivity. These findings suggest that the pgACC may play a role in the modulation of resting clinical pain.

Pain patients also exhibited greater DMN-insula connectivity at rest when compared to healthy controls. When pain was increased after body movements, stronger connectivity was detected between brain regions corresponding with the DMN and the right mid-insula [8]. The insula is one of the core regions in processing the evaluation of innocuous and noxious sensory events [9,12]. The right insula is postulated to process self-awareness of bodily sensations [7]. Thus, the increased connectivity between the DMN and the insula could be related to a pain-primed mental state due to years of unpredictable and fluctuating pain.

Patients who reported high lingering pain following body movements also exhibited decreased connectivity between the DMN and mPFC and aspects of the pgACC. Importantly, the three patients that did not report an increase in pain after mechanical maneuvers also did not exhibit a reduction in connectivity between the DMN and mPFC. This is fitting, as the inability to govern ruminative thought processes is associated with deactivation of cognitive control regions such as the PFC and ACC [4].

Connectivity within the DMN before clinical maneuvers was positively associated with increased pain reports evoked by the maneuvers. That is, patients that were less able to disengage from self-referential processes were more prone to lingering pain. In contrast, a present-centered mental stance is associated with positive affect and decreased DMN connectivity [5].

Persistent clinical pain is not only influenced by injury or disease progression, but also by the interaction of years of relentless pain, depression, and cognitive impairments. This raises the following question: is the progression of chronic pain related to shifts in patients’ self-referential thought processes such that the object of default mode activity becomes pain itself? In a previous study using BOLD fMRI, connectivity strength between the DMN and the insula was associated with spontaneous clinical pain in fibromyalgia patients [11]. Interestingly, 4 weeks of acupuncture...
therapy was found to reduce fibromyalgia pain in a fashion corresponding with reduced functional connectivity between the DMN and the insula [10]. This further supports the possibility that DMN-insular connectivity strength is a critical determinant of chronic pain.

Loggia et al developed an experimental approach that encompasses the best of both worlds. They can obtain snapshots of steady state activity during pain using ASL while simultaneously exploiting the temporal richness that previously was only accessible through BOLD studies. These two approaches together allow for activation data to inform connectivity analyses and represent a critical advance for exploring the brain mechanisms of chronic pain.

Conflict of interest statement

The authors declare no conflicts of interest.

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References