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Disentangling Mood and Pain: A Commentary on Two Manuscripts

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Keywords

default mode network; DMN; mood; pain; resting state; biomarker; signature pattern; chronic pain; medial prefrontal cortex; mPFC; posterior cingulate cortex; PCC; fibromyalgia; chronic low back pain; fMRI; neuroimaging; anxiety; depression; positive affect; negative affect; functional connectivity

Mood, negative affect and pain are entangled in complex ways. Earlier investigations identified the need to improve mood in order for analgesic medications to be effective [4]. While mood is typically a more transient, flexible state compared with affect, both mood and affect represent an important component of chronic pain conditions including chronic low back pain [1] and fibromyalgia [12].

In this issue of PAIN, Letzen and Robinson [6] importantly extend our knowledge of mood's influence on resting state functional connectivity (i.e., correlated oscillatory activity among brain regions), as demonstrated previously in healthy volunteers [3], by investigating mood's effect in a chronic low back pain population. When mood was altered it changed functional connectivity between default mode network (DMN) hub seed regions (medial prefrontal cortex, mPFC and posterior cingulate cortex, PCC) with a *different* constellation of changes for patients as compared with healthy controls. Meanwhile, in another publication in this issue, López-Solà et al. [7] uncover the effects of negative affect on a neurological pain signature (NPS) for fibromyalgia.

As individual brain regions, the PCC plays a role in self-reflection and introspection, and the mPFC is related to determining value and cost of reward, among other correlated functions. As for the relationship between self-reflection / introspection, reward cost / value and pain, the subjective experience of pain is often synonymous with performing self-reflection to monitor and ideally reduce it. The induction of negative mood increases the acute pain response [16] and increases chronic back pain [14]. Individuals unable to practice effective mindfulness meditation had greater anxiety levels and greater PCC activity, possibly reflecting excess self-introspection [17]. Even in localized urological chronic pelvic pain, increased PCC functional connectivity is correlated with ratings of self-esteem, self-

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confidence and quality of relationships [8] underscoring the theme of intertwined neural correlates of introspection and affective states.

How do we resolve the potential confounds of mood and negative affect in our quest to understand how neural circuits are altered in chronic pain? Some options are: A) to identify separate, specific pain and mood signatures by including patients without comorbid depression or anxiety, and directly manipulating mood states; B) to give up on such research concluding, “It’s too complicated!”, C) to identify each neurologic signature “as is” and then measure correlated effects of negative affect, mood, pain and other covariates and comorbidities. Letzen and Robinson [6] provide clear evidence that mood status influences resting state activity in persons with chronic low back pain. Hopefully, this work will be expanded upon to determine how activity between and within other brain networks and regions are affected by mood, and further, whether these effects differ among persons who vary with regard to type of chronic pain, sex, race, etc. Additionally, even when transient mood effects are measured directly, there may be compounding effects of positive and negative affect.

Also in this issue of PAIN, López-Solà et al. [7] provide an elegant example of how to disentangle these complex confounds. The information provided by their research paves the way for future studies and encourages investigators to delve deeper into the new questions that arise from their paper. Interestingly in their paper, these authors pursued option “A” by validating a NPS in healthy volunteers, highly specific to pain but not affective states [15]. However, after applying their original NPS to the fibromyalgia population, the signature was no longer free from effects of affect, anxiety levels, medication status, and pain severity. They then rigorously tested correlations for each of these factors to determine that patients with higher symptom severity were also medicated for anxiety and depression, yet, in these patients the symptom severity outweighed the potential (mood-improving) effects of medication.

While mood influences many things (e.g., brain circuits, response to analgesic medications, acute pain response, and chronic pain experience) the question of “how?” is a fascinating one. López-Solà et al. [7], while also assessing neural response to pressure-induced pain and multisensory stimulation, reinforce classic knowledge that increased subjective pain ratings match increased pain-related brain activation in healthy controls [2] and in patients with fibromyalgia [11]. Considering that mood and affect are complexly integrated within this same system, where are the effects of mood-induced pain increases / decreases taking place? Mood might be casting a positive or negative effect first on the cognitive subjective experience (e.g., as one thinks about and selects a pain rating), then, in turn, reducing pain via top-down mechanisms. For example, induced changes in mood can recruit increased mPFC activity, which is correlated with changes in periaqueductal gray activity, thereby suggesting a brain circuit by which mood changes influence and reduce acute pain [5]. Negative mood might decrease ventral striatum activity, that in turn, increases pain by a lack of inhibition from reward circuits. Recently, Schwartz et al. identified in a study of rodents a specific galanin-based mechanism in the nucleus accumbens required for the continued presence of decreased motivation (i.e., negative mood) following relief from chronic pain [10]. As an interesting parallel from over 60 years ago, even after relief of pain, a proportion

of rheumatoid arthritis patients paradoxically displayed worsened mood and hopelessness [9], possibly reflecting an intractable maintenance of negative affect.

It is also interesting to wonder, why are the mood-induced changes in functional connectivity different in chronic pain as compared with healthy states? These differences might be due to potential compensatory mechanisms, baseline differences in self-referential thought processes, or dysfunctional mood shifting involving the mPFC. Possibly additional brain regions responding differently to mood in chronic pain might influence the mPFC and PCC. Structural brain alterations within these networks may exist as well, and if so, different mood-induced functional connectivity changes in chronic pain might parallel underlying structural pathophysiology.

At present, more questions than answers surround the intricate web of mood, affect and pain. A recent meta-analysis including a sub-analysis of mood effects on hyperalgesia was unfortunately limited by few citations reporting mood in their subjects [13]. Additional experiments are therefore needed 1) that directly test for mood alterations (e.g. by mood induction) (as exemplified by Letzen and Robinson [7]), and 2) that rigorously measure correlations of differences in present mood, negative affect, medication status, and pain severity (as exemplified by López-Solà et al. [6]). Together these efforts will move our understanding of mood, affect and pain in a positive direction.

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