The periaqueductal gray and descending pain modulation: Why should we study them and what role do they play in chronic pain?

Running head: Periaqueductal gray connectivity in chronic pain

Kasey S Hemington$^{1,2,*}$ and Marie-Andrée Coulombe$^{1,*}$

*Co-first authors

1. Toronto Western Research Institute, University Health Network, Toronto, Canada; and 2. Institute of Medical Science, University of Toronto, Toronto, Canada.

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Corresponding Author:
Kasey Hemington
khemingt@uhnres.utoronto.ca
Toronto Western Hospital
Main Pavilion
14th Floor Room 14MP301
399 Bathurst St.
Toronto, Ontario
Canada M5T 2S8
(416) 603-5502

Abstract:

Here, we discuss the significance of a recent study by Yu et al. (Neuroimage: Clinical 6: 100-108, 2014). The authors examined functional connectivity of a key node of the descending pain modulation pathway, the periaqueductal gray (PAG), in chronic back pain patients. Altered PAG connectivity to pain-related regions was found; we place results within the context of recent literature and emphasize the importance of understanding the descending component of pain in pain research.

Keywords:
Periaqueductal gray; chronic low back pain; descending pain modulation; resting state fMRI
Pain is often described as an alarm system for the body; its role is to inform of actual or potential tissue damage. However, the perception of pain depends on the dynamic balance between nociceptive inputs and their modulation by the central nervous system. Specifically, inhibitory and facilitatory mechanisms finely tune excitability of the neurocircuitry involved in the overall pain experience. Even though pain is crucial for our survival, dysregulation in pain circuitry can give rise to chronic pain disorders, which affect millions of people globally and place a significant burden on healthcare systems.

The brain modulates pain perception via different mechanisms - one of these is the descending pain modulation system. The periaqueductal gray (PAG) is a key node of the descending pain modulation system. Located in the brainstem, it is involved in both ascending and descending pain modulation systems. It is known for its projections to the rostroventral medulla that in turn sends inhibitory/facilitatory projections to the dorsal horn of the spinal cord (Millan 2002). Some chronic pain disorders are associated with altered descending pain modulation, and therefore structural and functional brain plasticity are suspected.

These structural and functional alterations in chronic pain are not well described in the literature, providing motivation for a recent study by Yu et al. (Neuroimage: Clinical 6: 100-108, 2014). In this study, the authors examined how the PAG is connected to other brain areas in chronic low back pain (cLBP) patients. We examine this pivotal study here because: 1) The finding of altered PAG connectivity in combination with unique methodology (clinical pain exacerbation) is unprecedented, 2) The study of descending pain modulation specifically is a challenging, neglected piece of the pain puzzle, often unexplored by neuroimagers, and 3) Discussion of the future directions of this work and the impact of the findings on the field of pain research are needed.

Yu and colleagues (2014) performed functional connectivity (FC) analysis on resting state functional magnetic resonance imaging (fMRI) data to compare 18 healthy control (HC) subjects and 18 cLBP patients. Resting state fMRI measures fluctuations in the blood oxygenation level in the brain, thought to be representative of neuronal activity, while the subject is not performing any specific task. FC measures
the degree to which two brain regions have synchronous fluctuations in activity over time; regions with similar fluctuations are referred to as highly functionally connected. The HC subjects completed a single resting state scan while the cLBP patients completed two resting state scans; one before and one after performing 10 minutes of personalized clinical maneuvers (e.g. lumbar rotations, flexions) to exacerbate their low back pain (henceforth referred to as the ‘non-exacerbated’ (NE) and ‘exacerbated’ (E) states respectively).

The authors found the following: 1) Increased PAG-ventromedial prefrontal cortex (vmPFC) FC in both the NE and E states compared to HC subjects, 2) Pain intensity was negatively correlated with PAG-vmPFC FC and increased pInsula-PAG connectivity in the E state, compared to HC subjects, but decreased NE state pInsula-PAG connectivity over time (with length of illness) in cLBP was also seen, and 3) Illness duration was negatively correlated with PAG-left amygdala FC. A summary diagram is depicted in Figure 1, emphasizing prior literature and the group’s own prior work, in order to place the findings in wider context (Kong et al. 2010; Kong et al. 2013). Two critical observations can be made from the figure: 1) The direction of change in PAG FC in Yu et al. (2014) during the E state (acute pain, gray arrows on stripes) is in agreement with the direction of change in activation or FC during acute/experimental pain in prior literature (large gray arrows), and 2) The direction of change in PAG FC during the NE state (black arrows) always opposes the direction of change in acute pain both in the Yu et al. (2014) study and prior literature (all gray arrows). The authors discussed the latter observation as perplexing. In particular, patients with higher pain intensity in the E state actually tended to have lower PAG-vmPFC FC, despite higher FC in patients in general (NE state compared to HC subjects).

Knowledge of the role of the vmPFC in pain can shed light on this paradox. This region is known to be involved in emotion and the detection of negative outcomes (Baliki et al., 2006). The cLBP population studied by Yu et al. (2014) is known for high catastrophizing and emotional distress, which are ‘negative outcomes’ and possibly the reason for the increased vmPFC-PAG FC (NE state; Roussel et al. 2013). The literature also shows changes in vmPFC activity related to attention to pain, including deactivation: upon
acute painful stimulus application, while directing attention towards pain, and during expectation of a
salient painful stimulus (Baliki et al. 2006; Kucyi et al. 2013; Millan 2002). In Yu et al. (2014), the
negative correlation with pain intensity, found only in the E state, may be related to greater attention to
the novel stimulus, exacerbated pain in subjects who reported more pain. Therefore, we suggest that the
seemingly opposing vmPFC FC findings of Yu et al. are not inconsistent; decreased FC during increased
pain intensity is expected during acute/salient pain based on prior literature, while chronic changes may
be related to emotional factors and have different underlying mechanisms. This conclusion highlights an
important concept often neglected by pain neuroimagers and by neuroscientists in general; a single brain
region can be involved in many functions and its altered connectivity can be multicausal.

Similarly, the pInsula and amygdala have numerous pain-related roles. The sensory-discriminative
component of pain (e.g. intensity, location) is represented by the pInsula, and increased connectivity in
the E state, when a novel stimulus is present, may reflect this component (Brooks and Tracey 2005).
However, decreased NE state pInsula-PAG FC over time in cLBP is also seen in Yu et al. and may
indicate a connectivity disruption as back pain becomes chronic. Moreover, PAG-amygdala FC was
negatively correlated with illness duration. Weaker connectivity over time may reflect the amygdala’s
role in the negative emotions commonly experienced with pain (Neugebauer et al. 2004). Accordingly,
we propose that in chronic painful stimulation, PAG connectivity (to the amygdala, pInsula, and vmPFC)
may drift to a different set point over time due to neuronal plasticity, while maintaining an acute response
similar to healthy populations (see Figure 1). As little is known of the evolution of FC over long periods
of time, this divergent response phenomenon offers a new direction for pain researchers (Calhoun et al.
2014).

The unique focus on the PAG in chronic pain by Yu et al. (2014) highlights the potential for the study of
descending pain modulation to improve the caliber of pain research. Typically in MRI studies, brainstem
regions such as the PAG are not paid sufficient attention, often due to potential confounding effects of
cerebrospinal fluid or blood flow adjacent to the small target regions of the brainstem. However, the study
of descending pain systems is an important component in the bigger picture of pain experience, as long as interpretation is performed carefully. For example, in the study of Yu and colleagues, the authors conclude: ‘These findings are in line with the impairments of the descending pain modulation reported in patients with cLBP’. However, no work to date has found a direct relationship between structural or functional alterations of the PAG or the rostroventral medulla and impairments or decreased efficiency of descending pain modulation system in chronic pain populations. The authors are therefore, more precisely, first to demonstrate functional change in a key region involved in descending pain modulation in cLBP. These changes offer a first step in delineating the neurocircuitry involved in the overall pain experience of these patients. Moreover, there is no behavioural evidence in cLBP pointing to descending pain modulation dysfunction (e.g. diffuse noxious inhibitory control (DNIC) evaluation, which measures the potential for pain reduction in one body area during response to a noxious stimulus in another body area) (Roussel et al. 2013). A shift in cLBP research is inevitable, as these new incongruities beg the question ‘What are the behavioural correlates of altered PAG FC in cLBP?’

Without behavioural evidence of pain modulation dysfunction in a given population, many experimenters assume no contribution of the descending pain system and fail to study it. The positive findings of Yu et al. (2014) in cLBP suggest this is dangerous, presumptive reasoning, calling not only for the inclusion of the descending pain system in imaging studies but also thorough collection of corresponding behavioural and psychological measures. As suggested above, it is possible that emotional/cognitive, and saliency/pain factors contribute differently to changes in brain connectivity in chronic pain, therefore behavioural measures are required. Collecting data on anxiety, depression, and emotional affect, as well as psychophysical data (e.g. pain and sensory thresholds, central sensitization and DNIC evaluation) will become a renewed priority for neuroimagers studying pain pathology. Within-group heterogeneity (e.g. emotional/cognitive, psychophysical) in chronic pain populations is a prominent issue and another reason for detailed behavioural measurements. In the cLBP population in Yu et al. (2014) for example, within-group heterogeneity is likely. In addition to a lack of evidence for descending pain modulation
dysfunction in cLBP, the involvement of central pain mechanisms (using, for example, hyperalgesia outside of painful regions as a behavioural marker) is inconclusive (for review: Roussel et al. 2013). Thus, it is plausible that central sensitization occurs in some patients but not others, and subgrouping would provide a more accurate group representation in both cLBP and other chronic pain populations. Finally, behavioural data (psychophysical and psychological components) should be consistently collected in neuroimaging work and would help to separate possible contributions of multiple functions within a single brain region.

The research group of Yu et al. (2014) has recently taken the lead in an experimentation method that will change the way in which pain is understood: The group employs clinical maneuvers to examine the neural correlates of endogenous pain in patients. This methodology mirrors a given chronic pain condition more closely than typically employed experimental painful stimuli (e.g. thermal pain). One reason for its prior underutilization is ethical concern; one must ensure patients are aware of all implications and risks of the procedures. However, if ethical issues are appropriately addressed and the maneuvers are performed under the supervision of a clinician, the advantages are clear. As aforementioned, chronic pain patients are set apart from HC subjects not just by their pain but by emotional and cognitive factors, for example. The use of clinical maneuvers somewhat mitigates the issue of isolating the pain component from other factors by comparing patients before and after pain exacerbation. Moreover, this method can be used to explore psychological factors that might be amplified in exacerbated pain states. Experiments involving clinical maneuvers also assist the researcher to distinguish between clinical and experimental pain. For example, this method will allow for the modeling of pain neurocircuitry that more accurately reflects clinically relevant pain. Future research endeavors should compare both acute painful stimulation (e.g. thermal pain) and chronic pain exacerbation. In addition, a persistent pain applied in HC subjects would assist in controlling for the nature of the clinical manipulation in patients.

Finally, the descending pain modulation system is complex and includes many anatomically and functionally distinct regions. The study of Yu and colleagues emphasizes the importance of understanding
distinctive roles of subregions of the PAG. The authors carefully selected a seed region in the ventrolateral PAG, which is known to be involved in opioid-mediated analgesia (a mechanism for descending pain modulation). Animal experiments also provide evidence that this subregion is active in persistent pain models, regardless of its modulatory effects on pain (Keay and Bandler 2001). Therefore, this subregion may also have specific affinity for chronic pain states in humans, and is an excellent choice considering the cLBP population. The study of Yu and colleagues is the first to address the connectivity of this subregion in chronic pain, which is an excellent target for future study in other pain populations.

However, while opioid analgesia is the most widely known pain modulation mechanism, it is not the only one. The PAG is suggested to be divided into subregions (ventrolateral, lateral, dorsolateral, for review: Keay and Bandler 2001). Each subregion is involved in distinct functions (autonomic nervous system, sexual behavior, anxiety, pain and analgesia) and contains a different collection of receptors. The dorsolateral subregion of the PAG, for example, is known to be involved in non-opioid mediated analgesia (Keay and Bandler 2001). The study of distinct descending pain system regions, in combination with appropriate behavioural measures, offers a promising new direction in the understanding of the chronic pain disorders. As Tracey & Brooks (2005) write in review of pain neuroimaging “Imaging studies of the brainstem structures involved in descending control of pain are just beginning”.

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Figure 1: Summary of PAG Functional Connectivity (FC) in Chronic Low Back Pain (cLBP) in relation to prior fMRI literature (resting state or task-based). Grey arrows indicate findings in acute pain manipulations (experimental stimulus or clinical maneuver). Black arrows indicate findings in chronic back pain (non-exacerbated). References: a) Kong et al., 2013, b) Kong et al., 2010a, c) Brooks and Tracey, 2005, d) Kucyi et al., 2013.
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References:


Prior fMRI Literature

Amygdala

(+) during painful stimulation (healthy control)\(^{b,c}\)
\[\text{↗ correlation: pain rating and increase in FC (cLBP)}\(^{b}\)\]

Posterior Insula

(+/-) during painful stimulation (healthy control)\(^{b,c}\)
\[\text{↗ correlation: pain rating and increase in FC (cLBP)}\(^{a}\)\]

vmPFC

(-) during painful stimulation (healthy control)\(^{b}\)
\[\text{↘ correlation: FC and exacerbation pain intensity}\]

(+/-) with attention directed toward pain (healthy control)\(^{d}\)

Current Study: PAG

Amygdala

↘ correlation: FC and length of illness

Posterior Insula

(+/-) FC during exacerbated pain
\[\text{↘ correlation: FC and length of illness}\]

vmPFC

(+/-) FC in cLBP

PAG

\[\text{acute pain: stimulus or clinical maneuver}\]
\[\text{chronic back pain (non-exacerbated)}\]