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Parabrachial Projections to PAG-RVM Axis May Promote Placebo Hypoalgesia and Nocebo Hyperalgesia

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Review of Crawford et al.

Pain is a hallmark of many ailments and represents an important signal of health and well being. Therefore, understanding how nociceptive signals are transmitted and the pathways that promote pain perception and modulation is fundamental to health care. Pain modulation can occur not only via pharmacological agents or other therapeutic interventions that alter nociceptive transmission through the nervous system, but also through cognitive and psychosocial factors like expectation (Kirsch et al., 2014). Arguably, the most studied forms of expectation-induced pain modulation are the placebo and nocebo effects: decreases and increases, respectively, in pain perception that occur based on an individual's expectation. Placebo hypoalgesia and nocebo hyperalgesia are often generated via conditioning, verbal suggestion, or social observation, and they involve brain–mind–body responses to the manipulation context (Colloca and Barsky, 2020).

Pioneering studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have elucidated parts of the cortical circuitry involved in placebo hypoalgesia and nocebo hyperalgesia (Fu et al., 2021). Previous PET studies have shown that placebo hypoalgesia resulting from positive expectations leads to the release of endogenous opioids in brain regions involved in descending pain modulation, including the orbitofrontal cortex, dorsolateral prefrontal cortex, rostral anterior cingulate cortex, and the periaqueductal gray (PAG; for review, see Bingel and Tracey, 2008). The opioid-rich PAG is particularly implicated in placebo hypoalgesia because of its role as a crucial integration point between forebrain regions and the rostroventral medulla (RVM), which receives nociceptive inputs from the spinal cord (Wager and Atlas, 2015). Furthermore, fMRI studies have reported placebo hypoalgesia-induced blood oxygenation level-dependent signal increases in the prefrontal cortex and decreases in nociception-responsive brain regions, including the thalamus, insula, and dorsal anterior cingulate cortex (Wager et al., 2004). In comparison, few imaging studies have elucidated regions specific to nocebo hyperalgesia, though some have suggested that the anterior cingulate cortex and the insula/parietal operculum may mediate expectation-induced increases in pain perception (Kong et al., 2008). Finally, there is some evidence that the cortical brain regions described above recruit brainstem nuclei, from which projections to the spinal cord either attenuate or facilitate pain responses to modulate placebo hypoalgesia and nocebo hyperalgesia, respectively. However, which brainstem nuclei are involved in such expectancy-based pain modulation remain poorly delineated.

To address this gap, Crawford et al. (2021) examined the brainstem circuitry involved in both placebo hypoalgesia and nocebo hyperalgesia using ultra-high field 7 T fMRI. Healthy participants were administered three inert "treatments": a placebo cream (described as a topical analgesic containing lidocaine); a nocebo cream (described as a topical hyperalgesic containing capsaicin); and Vaseline (a negative control). The study involved three sessions over 2 consecutive days. Each participant underwent a placebo and nocebo conditioning session on day 1, an identical reinforcement session on day 2 inside the MRI scanner, and a test session on day 2 while fMRI data were collected. During conditioning, participants were told that a "moderate pain" heat stimulus would be applied to three treatment sites; however, temperatures applied to the lidocaine and capsaicin spots were deceptively modified to generate associations of perceived pain relief and exacerbation, respectively. During the test session, participants received the same moderate pain stimulus across the three sites and provided pain ratings using a visual analog scale anchored by 0 ("no pain") and 100 ("worst pain imaginable"). Notably, although participants were told that lidocaine, capsaicin, and Vaseline treatments were used during the sessions, only

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Vaseline was used. Participants were labeled "responders" if their mean pain ratings during the lidocaine or capsaicin conditions were more than 2 SDs below or above those of the control (Vaseline) condition. Otherwise, participants were considered nonresponders. fMRI analyses involved comparisons between the percentage of signal changes within brainstem nuclei, correlation analyses between signal changes and individual responder abilities, and regional analyses to determine anatomic specificity within pain modulatory nuclei.

Crawford et al. (2021) demonstrated that, among placebo responders, perceived pain intensity was lower during the lidocaine versus control trials, and among nocebo responders, perceived pain intensity was higher during the capsaicin versus control trials. During the test session, fMRI revealed differential recruitment of brainstem regions during placebo and nocebo conditions. During placebo trials (lidocaine site stimulation), responders showed increased activation relative to control trials in the substantia nigra (SN), RVM, and ventrolateral PAG, and decreased activation in the locus coeruleus (LC) relative to control. Placebo nonresponders also showed increased activation relative to control trials in the ventrolateral PAG, but showed decreased activation in the RVM and SN, as well as in the subnucleus reticularis dorsalis and the ventral tegmental area (VTA). Across placebo responders and nonresponders, correlation analyses demonstrated that individual placebo responsiveness was positively associated with signal changes in the RVM and SN, and was negatively associated with signal changes in the parabrachial (PB) complex, LC, and lateral/dorsolateral PAG. During nocebo trials (capsaicin site stimulation), responders showed patterns opposite to those in placebo responders during placebo treatment: decreased activation in the SN, RVM, and ventrolateral PAG. Similar to placebo nonresponders, nocebo nonresponders showed increased activation in the lateral PAG but differed in the other regions with increased activation in the RVM, SN, VTA, and LC relative to control site stimulation. They also showed decreased activation in the PB. Correlation analyses for the nocebo trials involving responders and nonresponders revealed associations that differed from placebo trials: while individual nocebo responsiveness was also positively associated with signal changes in the SN, it was negatively associated with signal changes in the RVM. In addition, the negative correlations seen in placebo correlations remained with LC signal changes, but individual nocebo responsiveness showed positive correlations with the PB and PAG signal changes. Finally, regional analyses confirmed that, among PAG voxels associated with placebo and nocebo effects, the majority were in the contralateral lateral/dorsolateral (but not ventrolateral) columns. Associated RVM voxels were rostrally located in the middle/ventral aspects.

Results from the study by Crawford et al. (2021) reveal brainstem-level circuits that may work in tandem to facilitate placebo hypoalgesia and nocebo hyperalgesia. For example, the authors observed that changes in PB activation negatively correlated with placebo effectiveness but positively correlated with nocebo effectiveness. The PB forms part of the spinoparabrachial tract—a major ascending pain pathway—and transmits emotional-motivational aspects of pain experience to the brain. PB neurons respond to nociceptive stimuli (Raver et al., 2020), and activation of lateral PB is necessary and sufficient to produce aversive learning (Sato et al., 2015). Moreover, lesions in lateral PB block conditioned taste preference, conditioned taste avoidance, and conditioned capsaicin avoidance (Reilly and Trifunovic, 2000). Pain-related neuroplastic changes in the central amygdala (CeA) may encode associations between neutral stimuli (e.g., nocebo treatment) and aversive outcomes (e.g., pain exacerbation) during associative learning (Han et al., 2015). Importantly, PB-projecting CeA neurons provide dense inhibitory input to the lateral PB, and stimulating this pathway attenuates acute pain responses, suggesting that CeA–PB connections modulate perceived pain (Raver et al., 2020). Thus, the inverse associations between PB activation and placebo/nocebo responsiveness found by Crawford et al. (2021) may result from CeA-mediated inhibition/disinhibition, respectively, of threat-signaling PB neurons. Indeed, that PB activation was observed ipsilateral to nociceptive stimulation suggests descending pain modulation involvement.

PB projections to the PAG–RVM axis may also lead to pain relief or exacerbation based on expectations. For example, lateral PAG-projecting PB neurons are excitatory, and activating them produces robust analgesia (Chiang et al., 2020). However, Crawford et al. (2021) observed that stronger changes in the lateral/dorsolateral PAG signal were correlated with weaker placebo responses (and vice versa with nocebo). This is consistent with evidence that lateral/dorsolateral PAG activity relates to active coping needs (Keay and Bandler, 2001): greater placebo hypoalgesia should correspond to less demand for coping behavior. Conversely, RVM-projecting PB neurons are excitatory or inhibitory and net excitation of RVM ON cells (increase firing in response to nociception; associated with pain facilitation) and net inhibition of RVM OFF cells (decrease firing in response to nociception; associated with pain inhibition) are associated with acute pain responses. Importantly, inactivation of RVM-projecting PB neurons attenuates ON cell burst and OFF cell pause, which reduces paw withdrawal behavior magnitude. This suggests that excitatory and inhibitory PB inputs to the RVM are differentially recruited to promote pain relief or exacerbation (Chen et al., 2017). Crawford et al. (2021) reported that stronger RVM activation correlated with stronger placebo responses (and vice versa with nocebo), which agrees with the view that PB–RVM connections modulate perceived pain.

Finally, activity in dopaminergic and noradrenergic brain regions may track perceived pain relief/exacerbation associated with placebo/nocebo treatments. For example, nucleus accumbens dopamine D_2/D_3 activation correlates with placebo-related perceived pain relief (Scott et al., 2008). That Crawford et al. (2021) observed positive associations between SN signal changes and placebo and nocebo sensitivity is compatible with this "predictive coding" framework (Büchel et al., 2014). Specifically, SN activation may represent dissociable contributions from reward-responsive and punishment-responsive dopamine neurons (Matsumoto and Hikosaka, 2009), resulting in net activation that correlates with placebo and nocebo responses. Moreover, evidence of a nociception-responsive pathway between the PB and SN suggests a mechanism through which expectancy-based pain relief/exacerbation is communicated to dopamine neurons (Coizet et al., 2010). Interestingly, Crawford et al. (2021) also observed negative associations between LC signal changes and placebo and nocebo sensitivity. Noradrenergic LC neurons respond to novel, unpredicted stimulation across sensory modalities (Bouret and Sara, 2005). Therefore, reduced LC activation among participants with enhanced placebo/nocebo responsiveness may reflect concordance between predicted and perceived pain. Overall, results from the study by Crawford et al. (2021) elucidate brainstem-level

mechanisms, including the PB, PAG–RVM axis, and dopaminergic and noradrenergic regions, associated with expectancy-based pain modulation, and additional research is warranted to confirm how these regions interact to modulate pain.

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