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Placebo Analgesia Enhances Descending Pain-Related Effective Connectivity: A Dynamic Causal Modeling Study of Endogenous Pain Modulation

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Abstract: The use of placebo to reduce pain is well documented; however, knowledge of the neural mechanisms underlying placebo analgesia remains incomplete. This study used functional magnetic resonance imaging data from 30 healthy individuals and dynamic causal modeling to investigate changes in effective connectivity associated with the placebo analgesic response. Before scanning, participants were conditioned to expect less thermal pain at 2 of 4 sites on their feet. Visual analog scale pain ratings revealed a significant but small difference between the baseline and placebo sites (mean difference = 6.63, t(29) = 3.91, $P \leq .001$, $d = .97$), confirming an analgesic effect. However, no significant differences in the magnitude of brain activation between conditions were observed via traditional random effects general linear modeling. Dynamic causal modeling was then used to investigate changes in effective connectivity during placebo analgesia. The results indicate that during placebo analgesia but not baseline condition, couplings between brain regions, including those involved in cognitive processes (eg, attention, expectation, evaluation), were significantly enhanced. Specifically, a significantly consistent decrease in the dorsolateral prefrontal cortex → periaqueductal gray coupling was found. These findings highlight the differences between pain processing and modulation at the network level. Moreover, our results suggest that small placebo effects may be better characterized via changes in the temporal dynamics among pain modulatory regions than only via changes in the magnitude of blood oxygenation level dependent activation. Further application of nuanced analytical approaches that are sensitive to temporal dynamics of pain-related processes such as dynamic causal modeling are necessary to better understand the neural mechanisms underlying pain processing in patient populations.

***Perspective:** Changes in effective connectivity among pain-related brain regions may be more sensitive detectors of the neural representation of small placebo effects than are changes in the magnitude of brain activation. Knowledge of these mechanisms highlights the importance of integrated neural networks in the understanding of pain modulation.*

***Key words:** Placebo, functional magnetic resonance imaging, effective connectivity, dynamic causal modeling, pain modulation.*

Chronic pain is a significant health concern, affecting over 100 million Americans and resulting in over $600 billion in lost income and health care costs.[9,19] However, long-term, powerful treatments for chronic pain remain elusive. One way to mitigate this problem is through the enhancement of currently available treatments. Placebo analgesia (PA) is an endogenous process that can effectively reduce an individual's pain.[31] Furthermore, PA is seen as an acceptable treatment by many patients who have learned that they

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have received a placebo.[7] However, PA is a complex and multifaceted phenomenon that is influenced by multiple psychological constructs and mediated by multidimensional neuronal systems.[20,24,26,29,37,39,40] Given this complexity, the neural mechanisms that underlie PA and the factors that predict an individual's placebo response are only partially understood. Early investigations of PA that used functional magnetic resonance imaging (fMRI) associated PA with the modulation of neural activity among pain-related brain regions. Nuanced analytical methods that investigate the temporal development of PAs are necessary to better understand the dynamic changes in brain regions involved in endogenous pain modulation.

PA has been linked to the pain modulatory processes of classic conditioning,[40] expectation,[41] anxiety,[27,30] and optimism.[20] This complexity is reflected in the results of neuroimaging studies of PA, which have shown effects at regional and network levels. Multiple studies have associated PA with reductions in blood oxygenation level dependent (BOLD) activity in pain-related brain areas such as the thalamus, somatosensory cortices, insula, and anterior cingulate cortex (ACC).[14,31,42] Increased activity in regions responsible for cognitive control and evaluative processes, such as the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, and rostral ACC, has also been observed in anticipation of and during PA.[14,31,42] Afferent inhibition and the activation of pathways involving the release of endogenous opioids noradrenaline and serotonin[4,6,29,33] have been implicated in these activation differences. In a structural equation model analysis of PA in patients with chronic pain, Craggs and colleagues[11] reported that compared with a baseline painful condition, the interregional relationships among pain-related brain regions were drastically altered during the experience of PA. However, the data in this study for the baseline painful and PA conditions were collected on separate visits. Thus, it remains unclear whether these same changes occur among healthy individuals and whether the BOLD response to rapidly presented thermal stimuli could distinguish pain and PA processes from a single scanning session.

fMRI studies of PA have used experimental paradigms in which the stimulation of baseline pain-related and PA sites was either temporally separated by several seconds or performed during separate scanning sessions,[11,41] preventing a more robust understanding of PA neural processes. The present study examined effective connectivity (EC) during PA using dynamic causal modeling (DCM). In critical distinction from past studies,[11,41] rapid succession of experimental conditions (baseline painful vs PA) allowed for a robust understanding of PA-related modulation. Based upon our previous work investigating the placebo analgesic response,[10,11,30] we hypothesized that 1) comparisons between BOLD activation during PA versus baseline pain would show decreased activation in regions commonly associated with pain experience (thalamus, insula, primary and secondary somatosensory cortices, ACC) and increased activation in regions associated with descending pain modulation (DLPFC and ACC) and 2) PA but not baseline stimuli would be associated with the modulation of descending pain-related, interregional connectivity parameters among regions such as the DLPFC and dorsal ACC (dACC).

Methods

The data used in the present study represent a portion of a larger study designed to investigate the mechanisms of PA. This study aimed to identify the temporal characteristics and psychological processes associated with brain networks involved in afferent pain processing and pain modulation. The study received approval from the University of Florida institutional review board, and all participants provided written informed consent.

During a screening visit, pain and placebo temperatures were identified for each participant. Participants then completed 3 fMRI scanning visits designed to establish baseline neural response to thermal quantitative sensory testing (QST), identify the neural correlates of PA (placebo imaging visit), and assess the durability of the placebo response over time. Participants completed an initial demographics questionnaire and during each visit completed 2 self-report questionnaires, the State-Trait Anxiety Inventory and the Pennebaker Inventory of Limbic Languidness, and provided electronic visual analog scale (VAS) ratings of their pain during QST. Only fMRI data and VAS ratings from participants' placebo imaging visit were analyzed in the present study, which used a within-participants design to assess differences in brain activation and EC during painful and placebo analgesic stimulation.

Participants

Contact was made with 367 individuals, who were recruited from the University of Florida campus area. A total of 126 individuals were initially screened, and 101 were enrolled. Of these participants, 52 completed the study. As the aims of the primary study proposed validation of results with a second sample of 30 participants, data from the first 30 participants (mean age = 22.27 years, standard deviation [SD] = 2.90 years) with complete behavioral and imaging data (excluding participants with excessive in-scanner motion) were used in the present study. Eleven participants were identified as Caucasian, 8 as Asian, 5 as Hispanic, 6 as African American, and 1 as Native Hawaiian or other Pacific Islander (1 identified as both African American and Hispanic). Exclusion criteria included 1) current participation in another research protocol that could interfere with or influence the present study (ie, other studies of pain); 2) use of prescription or nonprescription drugs that might affect pain processing that could not be stopped 7 days before testing (eg, nonsteroidal anti-inflammatory drugs, antihistamines, antidepressants, anticonvulsants, migraine medications, cough suppressants); 3) history of psychiatric, psychological, neurologic, or other disorders (eg, diabetes, thyroid disease, gastrointestinal/liver disease [other than irritable bowel syndrome], collagen