paralleled with decreased BOLD responses in key pain processing regions, such as the thalamus, somatosensory cortex, and dorsolateral prefrontal cortex (DLPFC)[3,31,38,39] but with an enhanced BOLD response in the perigenual anterior cingulate cortex (ACC) and periaqueductal grey (PAG).[24,38] The PAG is directly involved in endogenous modulation of input to the spinal cord[4,13,28,41] and is a key node within the descending pain modulation network.[25,27,29] Of importance, the PAG is bidirectionally connected to cortical regions involved in processing pain, including the DLPFC, anterior cingulate and insula cortices, thalamus and precuneus.[10,23,41]

Despite the need to better understand the brain's contribution to CPM effects, doing so using task-based fMRI is difficult because dissociating the neural responses to the 2 experimental stimuli (as well as nonadditive modulatory processes) is not straightforward. An alternative imaging approach is resting-state fMRI (rs-fMRI), which allows for the evaluation of interindividual variation in pain modulation capability at rest. This approach provides insight into brain connectivity differences that might be associated with interindividual variation in CPM.[34,37] Harper et al. identified lower grey matter density in the PAG in patients with fibromyalgia compared with that in healthy controls.[17] They then assessed rs-fMRI connectivity of the PAG across groups and found that CPM was associated with higher connectivity with regions associated with pain inhibition, including the pregenual ACC and mid-insula, suggesting this functional integration facilitates pain modulation.

Harper et al.[17] examined PAG connectivity in a combined group of patients and controls. To further elucidate individual differences in pain modulatory processes, this article used the same seed-based approach, but in a sample of healthy controls. We predict that CPM will be associated with a higher connectivity between PAG and regions associated with pain processing and inhibition.

3.2.4. Functional magnetic resonance imaging acquisition

Brain images were acquired using a 3T Siemens (Siemens, Erlangen, Germany) TRIO magnetic resonance imaging (MRI) scanner with a 32-channel head coil. For the 10-minute resting-state scan, participants were instructed to keep their eyes closed. The protocol consisted of 30 interleaved 3.5-mm sagittal T2*-weighted gradient echo echo-planar imaging slices (TE = 28 ms, TR = 2000 ms, flip angle = 90°, 1-mm interslice gap; 128 × 128 matrix, field of view = 240 mm). Consequently, 300 volumes were acquired and then prepared as 4D NIFTI images. Structural images were then acquired within an 8-minute T1-weighted inversion recovery fast gradient echo-high resolution structural scan (176 volumes, TE = 2.9 ms, TR = 2000 ms, flip angle = 90°, voxel size =

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4.1. Conditioned pain modulation

Participants rated the pain intensity of the thermode to be 5.93 (SD = 1.49). The mean stimulus temperature across the sample to elicit a 6/10 rating was 45.7°C (SD = 1.56). When combined with a conditioning stimulus, the rating for the thermode decreased to 4.27 (SD = 2.0), indicating a significant reduction of 1.65 (SD = 1.38) in pain intensity ($t(33) = 6.97$, $P < 0.001$). Each individual's difference score was used as their CPM score with higher CPM scores representing more effective pain modulation (Fig. 1).

4.2. Resting-state connectivity & conditioned pain modulation

In total, there were 4 clusters of activation where PAG connectivity

that CPM was associated with heightened integration of the PAG and somatosensory cortices, premotor and motor cortices, and the DLPFC, all regions associated with the processing or modulation of pain.[4,5,7,12,27,29] These findings partially corroborate those of Harper et al., who identified a similar functional

improve the robustness of our conclusions.[42] Nevertheless, correspondence between our findings and these event-related designs suggests the possibility that the patterns of resting-state functional connectivity found to be associated with individual differences in pain modulation in our study may be directly involved in CPM.

This study provides insight into CPM as a measure of the efficiency of pain modulation circuitry. CPM has been used as a predictive assessment for postsurgical outcomes, analgesic efficiency, and the risk of developing neuropathic pain,[8,16,43,45] indicating clinical applicability. This suggests that our results, alongside other fMRI studies of CPM cited here, may function as brain-based biomarkers for vulnerability or resilience to pain. Future research should therefore investigate whether resting-state connectivity between PAG and cortical regions involved in the processing and modulation of nociceptive input is useful in predicting clinical outcomes.

Disclos res

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