


Commentary on “Working Memory Load-Dependent Cortical Mechanism of Distraction Analgesia in Healthy Individuals: An fNIRS Study” [Response to Letter]

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Dear editor

We sincerely appreciate the insightful and constructive comments on our recently published article entitled “Working Memory Load-Dependent Cortical Mechanism of Distraction Analgesia in Healthy Individuals: An fNIRS Study” in the *Journal of Pain Research*.¹ We are grateful that Jia et al recognized the novelty and academic value of our work, as well as the contribution of integrating behavioral data with functional near-infrared spectroscopy (fNIRS) neuroimaging data to explore the mechanism of distraction analgesia. Jia et al’s perspectives on methodological, interpretational, and translational issues have provided important guidance for improving our subsequent research and further investigating the cognitive modulation mechanism of pain. We agree with most of the viewpoints and are pleased to respond to Jia et al’s concerns in detail, while further elaborating on the study design, data interpretation ideas, and future research directions of our work.

Response to Methodological Considerations in fNIRS Analysis

First, we fully acknowledge Jia et al’s concern regarding the generalizability of our findings due to the homogeneity of the study sample. Our study included 35 healthy participants aged 21–26 years, with the gender factor balanced. Although a homogeneous sample helps control individual variability in data, it limits the generalizability of the research results. As explicitly stated in the Limitations section of our study, the restricted age range and healthy participant cohort may affect the extrapolation of the results. We concur with Jia et al that cognitive load, attentional control ability, and pain sensitivity vary significantly with age, gender, and chronic pain pathological states, and the mechanism of cognitive modulation of pain in clinical populations is likely different from that in healthy young adults. This limitation is indeed a core entry point for our subsequent research. Currently, we have listed expanding the diversity of research samples as a key research direction, planning to recruit elderly populations as well as chronic pain patients with different etiologies, disease durations, and ages for follow-up experiments. The aim is to verify the applicability of the current findings in heterogeneous populations and clarify the differences in pain-cognitive modulation mechanisms between healthy individuals and clinical patients.

Second, we thank Jia et al for their valuable suggestions on fNIRS data processing and analysis methods. The details of the preprocessing workflow are supplemented as follows: We applied spline interpolation to correct motion artifacts in the channels, with noise identified by setting a standard deviation (STD) threshold of 6 and an amplitude (AMP) threshold of 0.5. Motion artifacts typically manifest as pulsatile or abrupt jumps caused by relative movement between the scalp and the probe.² We applied a bandpass filter (0.01–0.2 Hz) to remove physiological noise, such as respiration, cardiac activity, and low-frequency signal drift. Subsequently, based on the modified Beer-Lambert law, we calculated changes in oxygenated hemoglobin (HbO), deoxygenated hemoglobin (HbR), and total hemoglobin (HbT) concentrations. Although short-channel regression or global signal correction was not adopted in this study, we minimized the

interference of systemic noise on the experimental results to the greatest extent through strict experimental control (eg, fixed sitting posture of subjects, standardized pain stimulation protocol). Regarding the correlation analysis method between cortical regions, this study used Pearson correlation analysis to initially explore the functional connectivity between cortical regions, which is a common and conservative analytical method in exploratory fNIRS studies focusing on local activation patterns. We fully recognize that analytical techniques such as partial correlation, coherence analysis, and Granger causality analysis can improve the specificity of cortical network analysis and eliminate confounding interference in inter-regional correlations. Currently, we have included these advanced analytical methods in our subsequent data reanalysis plan and will further publish more refined cortical connectivity analysis results in the future. Meanwhile, we will fully detail all preprocessing and analysis steps in our future research to ensure the reproducibility of fNIRS data analysis.

Response to Interpretational Issues Regarding the Directionality of Effects

We highly agree with the critical insights proposed by the reviewers on the directionality of the relationship between working memory (WM) load and pain perception. In the original study, based on attentional control theories, we interpreted the research results as higher WM load reducing individuals' pain perception. However, we fully recognize that there is a bidirectional interaction between pain and cognitive processing. Pain can impair the execution efficiency of WM, thereby changing the cortical activation pattern, and this change may in turn affect the pain processing process. We also discussed the impairment of pain on n-back cognitive performance in the results and discussion section of our original study.

Regarding the discussion of brain regions, due to the limited detection depth of fNIRS, it is difficult to accurately capture activity signals from deep brain regions such as the insula and subcortical structures. Therefore, the optode placement scheme of this study was designed to conduct relevant analyses around the primary sensorimotor cortex (SM1), secondary somatosensory cortex (S2), anterior prefrontal cortex (aPFC), dorsolateral prefrontal cortex (DLPFC), and premotor cortex (PMC). We fully agree with Jia et al's view that multimodal neuroimaging technology combining fNIRS with electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) can make up for the shortcomings of single fNIRS technology and more comprehensively reveal the cortical-subcortical dynamic regulatory mechanism behind distraction analgesia. Currently, we have launched a research project using fNIRS-EEG combination, aiming to further explore the synergistic mode of pain-related brain regions during pain and analgesia.

Response to Translational and Conceptual Implications

We sincerely thank Jia et al for their prudent and objective comments on the Translational and Conceptual Implications of our study. We also fully recognize that there are many risks and challenges in directly extrapolating the conclusions of acute experimental pain models in healthy individuals to clinical applications. Chronic pain patients generally have problems such as abnormal prefrontal-limbic system connectivity, impaired executive function, and emotional regulation disorders, which may weaken or even reverse the analgesic effect of cognitive load. In response to this, we will recruit finely classified subject groups, such as chronic pain patients with different disease durations, healthy individuals of different age groups, and chronic pain patients of different age groups. Meanwhile, we will optimize and refine the experimental paradigm and adopt a multi-gradient cognitive paradigm for experimental design.

Conclusion

In summary, we sincerely appreciate the valuable comments and suggestions put forward by Jia et al., which have greatly promoted the in-depth thinking and improvement of our research. We will take these comments as an important guide to further optimize the experimental design, improve data analysis methods, expand the research population, and clarify the causal relationship and translational value of pain-cognitive modulation. We firmly believe that continuous academic discussion and mutual learning will promote the development of the fields of pain neuroimaging and cognitive analgesia. In the future, we will also carry out more rigorous and in-depth research to contribute to the academic progress of this field.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this communication.

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