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Dear Editors,

We are delighted to submit our manuscript entitled **"Dynamic Functional Brain Reconfiguration During Sustained Pain"** for consideration as a Research Article in *eLife*.

Pain is a dynamic experience: When pain persists, the experience of pain keeps changing over time (Kucyi & Davis, 2015). This dynamic nature of pain is particularly important for understanding chronic pain, given that a spontaneous fluctuation of pain is one of the key features of chronic pain (Baliki, Geha, Fields, & Apkarian, 2010). Though recent papers have emphasized the importance of understanding the dynamic brain representations of pain (e.g., refs. (Kucyi & Davis, 2015; Ploner & Tiemann, 2021)), we still do not have detailed information on how multiple brain networks dynamically interact to construct and modulate pain. For example, previous studies were limited to examining summary metrics of dynamic connectivity, such as mean and standard deviation (Bosma, Cheng, et al., 2018; Bosma, Kim, et al., 2018; Cheng et al., 2018; Cottam, Iwabuchi, Drabek, Reckziegel, & Auer, 2018).

To address this problem, we examined the dynamic reconfiguration of whole-brain functional networks for different phases of experimental sustained pain from its initiation, peak, and to remission. We conducted two functional Magnetic Resonance Imaging (fMRI) experiments (n = 48 and 74) while participants were experiencing capsaicin-induced sustained orofacial pain. With a multi-layer network community detection method (Mucha, Richardson, Macon, Porter, & Onnela, 2010) combined with a predictive modeling approach (or machine learning-based brain mapping) (Kohoutova et al., 2020; Woo, Chang, Lindquist, & Wager, 2017), we characterized and quantified the changes in functional brain architecture during sustained pain.

Our study includes numerous technical innovations and theoretical implications:

<u>Technical innovations:</u>

a) This study offers the first <u>detailed characterization of the dynamic brain network representations</u> during sustained pain. Using capsaicin, we experimentally induced the full range of pain experience (from the initiation to complete remission) for a relatively long time (> 20 min). This experimental procedure allowed us to model different phases of pain (i.e., the early, middle, and late periods of pain). Despite the importance of understanding the "dynamic pain connectome" (Kucyi & Davis, 2015), few empirical studies directly examined the dynamic changes in the functional pain connectome. In this regard, our study can serve as a model paper, opening up a new avenue for investigating the dynamic pain connectome.

b) We conducted network analyses at the voxel level in individuals' native brain space to fully utilize fine-grained spatiotemporal information of fMRI data to model dynamic brain representations. Previous studies that employed the multi-layer community detection method (Bassett et al., 2011; Bassett, Yang, Wymbs, & Grafton, 2015; Braun et al., 2016; Braun et al., 2015; Finc et al., 2020) mostly relied on brain parcels (rather than voxels) and thus could not fully embrace the spatial resolution of the current fMRI techniques. We aimed to capture the most detailed voxel-level brain community structures and their dynamics, paving a way for precision mapping of dynamic brain representations of pain (Gordon et al., 2017).

c) To our knowledge, the current study is the first to use module allegiance as features for developing predictive models and test their generalizability across two independent datasets. Though many previous studies that employed the multi-layer community detection method have been published in high-profile journals (e.g., papers from the Danielle Bassett group (Bassett et al., 2015; Finc et al., 2020)), the robustness of the findings is uncertain because they usually reported results from a single dataset. We believe that our study provides a new testing framework to demonstrate the robustness and replicability of module allegiance-based findings by combining them with expertise from predictive modeling (Kohoutova et al., 2020; Lee et al., 2021; Woo et al., 2017).

Theoretical implications:

d) One of our main findings is the emergence of an extended somatomotor network during sustained pain, referred to as a "pain supersystem" in the manuscript. The concept, *pain supersystem*, was first introduced in our recent publication (Zheng et al., 2019). The previous publication, however, was based on trial-level data with phasic pain stimulation (around 10 secs), and thus we could not model fine-grained dynamic spatiotemporal representations in response to a single pain epoch. The current study is the first to provide a detailed characterization and visualization of how the pain supersystem is constructed and reconfigured within a single pain epoch from its initiation to remission.

e) We found that the pain supersystem was mainly driven by the increased connectivity between the orofacial areas of the somatomotor cortex and multiple subcortical (e.g., thalamus, basal ganglia) and frontoparietal (e.g., dorsolateral prefrontal cortex) regions. The emergence of the pain supersystem during sustained pain suggests that conscious experience of pain requires system-level integration between the somatomotor network and the other brain systems, particularly subcortical and frontoparietal regions. These findings are in line with the global workspace theory (Baars, 2002), highlighting the importance of top-down regulation and coping responses (Huang et al., 2019) in sustained pain.

f) We also found that the cerebellum played an important role in pain relief. Although pain neuroimaging studies have consistently reported cerebellar activations (Moulton, Schmahmann, Becerra, & Borsook, 2010), its functional roles in pain remain unclear and less investigated. Therefore, our study has a potential to promote new investigations that can lead us to new discoveries on cerebellar contributions to pain and pain relief and ultimately to the development of new therapeutic targets.

We certify that none of the results presented here have been published or are under consideration for publication elsewhere and that no authors have financial or other conflicts of interest. Only the coauthors (Jae-Joong Lee, Sungwoo Lee, Dong Hee Lee, and Choong-Wan Woo) have reviewed the manuscript. This research conformed to all the guidelines of the Institutional Review Board of the Sungkyunkwan University. All participants provided written informed consent.

We thank you for your consideration and look forward to hearing from you. If you have any questions or require any clarifications about this work, please do not hesitate to contact us.

Sincerely,

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