Journal Club

Editor's Note: These short reviews of recent *JNeurosci* articles, written exclusively by students or postdoctoral fellows, summarize the important findings of the paper and provide additional insight and commentary. If the authors of the highlighted article have written a response to the Journal Club, the response can be found by viewing the Journal Club at www.jneurosci.org. For more information on the format, review process, and purpose of Journal Club articles, please see http://jneurosci.org/content/jneurosci-journal-club.

Intracortical Localization of a Promising Pain Biomarker

Christopher Joseph Black
School of Engineering, Brown University, Providence, Rhode Island 02912
Review of Yue et al.

Pain is a highly subjective experience that arises from the integration of emotional, cognitive, and sensory processes. Therefore, the painfulness of a given stimulus can be perceived differently across individuals. Although a patient's verbalization of pain is necessary for clinical diagnoses, individual subjectivity can obscure the underlying cause of pain. For this reason, neuroimaging methods, such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG), have been used to identify objective pain "biomarkers" that can decouple the subjective reports from the neural mechanisms that drive pain (Tracey et al., 2019).

Gamma-band oscillations (GBOs) in the 30–100 Hz range recorded epidurally over human primary somatosensory cortex (S1) are a potentially promising pain biomarker. The magnitude of GBOs recorded over S1 is correlated with perceived pain in humans given noxious stimulation (Gross et al., 2007; Zhang et al., 2012; Heid et al., 2020). In addition, electrocorticography (ECoG) recordings over rodent S1 have shown that GBO power correlates with hyperalgesia in models of chronic pain (Wang et al., 2016). Although these results suggest that epidurally recorded GBOs reflect the processing of noxious stimuli in S1, the exact intracortical source of these GBOs is highly debated. Importantly, reports using human EEG have localized nociception-related GBOs to primary motor cortex (M1) during acute pain (Schulz et al., 2012), and to prefrontal cortex in patients with chronic pain (Zhou et al., 2018). These results suggest that GBOs reflect changes in motor output and cognitive function that are pertinent for behavioral adaptations to pain, such as stimulus avoidance. Whether epidurally recorded GBOs can be used as an objective pain biomarker critically depends on identifying the cortical regions from which these oscillations emerge.

Recently, Yue et al. (2020) addressed this issue by performing chronic multilevel electrophysiology in awake, behaving rodents. The authors simultaneously recorded epidural potentials over sensorimotor areas with ECoG, and recorded spiking activity and local field potentials (LFPs) in superficial layers (II–IV) and deep layers (V/VI) of bilateral M1 and S1 with intracortical microelectrodes while rats received a noxious laser stimulus to the forepaw. On trials where rats displayed a nocifensive paw withdrawal response, laser-evoked GBOs increased in magnitude throughout layers in both contralateral and ipsilateral M1 and S1, with the strongest effect occurring in the superficial layers of contralateral S1.

To determine how these laser-evoked intracortical GBOs corresponded to epidurally recorded GBOs, Yue et al. (2020) performed a cross-correlation analysis between the instantaneous amplitude of GBOs in the ECoG recordings and the LFP recordings from intracortical sites. They found a significant correlation between the ECoG signals and the LFP signals recorded from the superficial layers of contralateral S1, but not the LFP signals recorded from other intracortical regions. Importantly, intracortically recorded GBOs in superficial, contralateral S1 preceded the ECoG GBOs by >5 ms, suggesting that this region of S1 is the primary intracortical source of nociception-related epidurally recorded GBOs. This cross-correlation analysis was further supported by results that compared the phases of oscillatory activity in S1 and ECoG recordings. Using a measure of phase synchronization, the authors showed that GBOs recorded in superficial, contralateral S1 exhibited significant phase consistency with epidurally recorded GBOs.

The authors then examined intracortical spiking activity to identify what neuronal subtypes contributed to the nociception-related GBOs. By sorting individual spikes based on peak-to-trough duration, they were able to identify putative pyramidal-cell spikes and fast-spiking interneuron spikes across all microelectrode recording sites. Importantly, putative interneurons in superficial, contralateral S1 were significantly activated by noxious stimulation, and their firing rates were phase locked with the epidurally recorded GBOs.

The recording methods implemented by Yue et al. (2020) allowed direct investigation of the intracortical circuits driving epidurally recorded GBOs during acute pain processing. Their analyses suggest

Received June 12, 2020; revised Oct. 24, 2020; accepted Oct. 29, 2020.
The author declares no competing financial interests.
This work was supported by National Institutes of Health NINDS BRAIN Initiative under grant 1R01NS108414-01. I would like to thank Dr. David A. Borton for support on this project and Dr. Jacqueline Hynes and Dr. Hyeyoung Shin for insightful comments on this manuscript.
Correspondence should be addressed to Christopher Joseph Black at christopher_black@brown.edu.
https://doi.org/10.1523/JNEUROSCI.1520-20.2020

not only that epidurally recorded oscillations reflect activity localized to contralateral S1 and not M1, but also that they are correlated with the activity of putative fast-spiking interneurons residing in the superficial layers of S1.

The results presented by Yue et al. (2020) provide a rationale for using epidurally recorded GBOs to objectively identify pain, but several questions remain. First, what objective features can be extrapolated from epidurally recorded GBOs? The finding that epidurally recorded GBOs originate from S1, which is thought to be responsible for processing the intensity, location, modality, and the presence of innocuous and noxious stimuli (Eto et al., 2011; Vierck et al., 2013; Jin et al., 2018), suggests that one might be able to derive sensory features of painful stimuli from epidurally recorded GBOs. Consistent with this, noxious stimulus intensity has been found to correlate with GBO magnitude recorded over S1 in human MEG (Gross et al., 2007).

Combining measures of GBOs with measures of additional oscillatory or evoked signals might increase the specificity and sensitivity of an objective pain measure (Tracey et al., 2019). One possible measure is theta–gamma coupling, which has been proposed to organize and relay various features of sensory information by activating neuronal ensembles in specific patterns (Lisman and Jensen, 2013). Notably, theta–gamma cross-frequency coupling in S1 occurs in both acute (Wang et al., 2011) and chronic (Wang et al., 2016) models of pain. It is possible that features of noxious stimuli such as intensity or type (e.g., thermal or mechanical) are represented in different phase-locked cycles in a theta–gamma complex. Combining epidurally recorded GBOs with other potential biomarkers would provide greater dimensionality when decoding objective information about pain from EEG or MEG recordings.

The result from Yue et al. (2020) showing that superficial fast-spiking S1 interneuron activity is correlated with epidurally recorded GBOs is in line with canonical mechanisms of sensory perception. Specifically, synchronization of fast-spiking parvalbumin-expressing (PV) interneurons at gamma oscillations regulate cortical information flow by eliciting temporal precision of spiking in excitatory pyramidal cells through inhibition (Hasenstaub et al., 2005). Therefore, gamma oscillations could produce high-fidelity, neocortical transmission of nociceptive information, such as pain intensity, by increasing the spike-timing precision of excitatory pyramidal cells through fast-spiking PV synchrony. In line with this theory, Tan et al. (2019) found that the entrainment of gamma oscillations in S1 using photostimulation of fast-spiking PV interneurons has been shown to enhance nociceptive behaviors in mice in both acute and inflammatory models of pain. But gamma entrainment in fast-spiking layer II/III PV interneurons in mouse barrel cortex have also been found to facilitate tactile detection (Siegle et al., 2014). This raises another question: are epidurally recorded GBOs specifically tied to nociception, or are they a neural mechanism associated with general information processing in S1?

Although several studies have tied gamma oscillations to different types of sensory processes in S1, such as tactile detection and nociception, it is possible that distinct sensory percepts are encoded within certain GBO features. For example, human EEG recordings over somatosensory cortex show that noxious stimuli elicit GBOs at ~80 Hz, while innocuous stimuli elicit GBOs at ~70 Hz (Michail et al., 2016). These results indicate that GBO frequency is tuned in a stimulus-dependent manner. Interestingly, sensory information entering S1 is sorted into separate cortical layers. Anatomical tracing has shown that noxious information arrives at the superficial layers of S1, while innocuous information arrives predominantly at the middle layers of S1 (Vierck et al., 2013). These different cortical layers also have distinct microcircuit connectivity that can give rise to different neural dynamics. For example, regular-spiking somatostatin-positive (SOM) interneurons in layer IV of S1, which modulate fast cortical oscillations (Lee et al., 2018), strongly inhibit PV interneurons, while SOM interneurons in layers II/III do not (Xu et al., 2013). Therefore, noxious and innocuous stimuli could differentially regulate fast-spiking interneuron activity to produce GBOs at different frequencies through the activation of regular-spiking inhibitory interneurons in different cortical layers. Testing this theory would require further dissection of the interneuron circuitry in S1. In this regard, one limitation of the study by Yue et al. (2020) is that extracellular electrophysiology has poor cell specificity and can only be used to identify neurons by their spike waveform (Nowak et al., 2003). While the fast-spiking phenotype in S1 is unique to PV interneurons (Puig et al., 2008; Rudy et al., 2011), the regular-spiking phenotype is expressed by a range of interneuron subtypes. Therefore, cell-specific techniques, such as optogenetics and calcium imaging, are needed alongside epidural recordings to determine the contribution of regular-spiking interneurons, such as SOM cells, in modulating GBOs.

Perhaps the most pertinent question not addressed by Yue et al. (2020) is how reliable are epidurally recorded GBOs as a biomarker for chronic (as opposed to acute) pain? As previously mentioned, superficial S1 PV interneurons have been linked to cortical GBOs in rodent chronic inflammatory pain models (Tan et al., 2019), so it is possible that epidurally recorded GBOs can serve as a reliable biomarker that reflect the same intracortical mechanisms for both acute and chronic pain. However, neural recordings in rodent S1 show that models of chronic neuropathic pain are correlated with reduced fast-spiking PV interneuron activity (Cichon et al., 2017) and increased 4–8 Hz LFP oscillations (Leblanc et al., 2014). Furthermore, the transition from acute to chronic pain initiates global changes in brain dynamics and connectivity (Kuner and Flor, 2016), so similar epidural signals may reflect vastly different cellular mechanisms. These global changes are also not conserved across pain pathologies; human fMRI has shown that brain activation of patients varies between conditions of neuralgia, chronic back pain, and osteoarthritis (Apkarian et al., 2011). The heterogeneity of brain activity underlying different subtypes of chronic pain suggests that epidural GBOs are not a universal biomarker for chronic pain, but may serve instead as a biomarker for subtypes of chronic pain that exhibit fast-spiking interneuron dynamics similar to those described in acute pain processing.

By identifying an intracortical, cellular source of epidurally recorded GBOs, the results presented by Yue et al. (2020) support the potential use of GBOs as an objective biomarker for acute pain. However, additional investigation into analytical methods to extract sensory features from oscillatory activity, the underlying interneuron circuit dynamics, and the link between acute and chronic pain processing will be necessary to expand the utility and our understanding of nociception-related, epidurally recorded GBOs.

References

Apkarian AV, Hashmi JA, Baliki MN (2011) Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain 152:S49–S64.

Cichon J, Blanck TJJ, Gan W-B, Yang G (2017) Activation of cortical somatostatin interneurons

prevents the development of neuropathic pain. Nat Neurosci 20:1122–1132.

Eto K, Wake H, Watanabe M, Ishibashi H, Noda M, Yanagawa Y, Nabekura J (2011) Inter-regional contribution of enhanced activity of the primary somatosensory cortex to the anterior cingulate cortex accelerates chronic pain behavior. J Neurosci 31:7631–7636.

Gross J, Schnitzler A, Timmermann L, Ploner M (2007) Gamma oscillations in human primary somatosensory cortex reflect pain perception. PLoS Biol 5:e133.

Hasenstaub A, Shu Y, Haider B, Kraushaar U, Duque A, McCormick DA (2005) Inhibitory postsynaptic potentials carry synchronized frequency information in active cortical networks. Neuron 47:423–435.

Heid C, Mouraux A, Treede RD, Schuh-Hofer S, Rupp A, Baumgärtner U (2020) Early gamma-oscillations as correlate of localized nociceptive processing in primary sensorimotor cortex. J Neurophysiol 123:1711–1726.

Jin QQ, Wu GQ, Peng WW, Xia XL, Hu L, Iannetti GD (2018) Somatotopic representation of second pain in the primary somatosensory cortex of humans and rodents. J Neurosci 38:5538–5550.

Kuner R, Flor H (2016) Structural plasticity and reorganisation in chronic pain. Nat Rev Neurosci 18:20–30.

Leblanc BW, Lii TR, Silverman AE, Alleyne RT, Saab CY (2014) Cortical theta is increased while thalamocortical coherence is decreased in rat models of acute and chronic pain. Pain 155:773–782.

Lee B, Shin D, Gross SP, Cho K-H (2018) Combined positive and negative feedback allows modulation of neuronal oscillation frequency during sensory processing. Cell Rep 25:1548–1560.e3.

Lisman JE, Jensen O (2013) The θ-γ neural code. Neuron 77:1002–1016.

Michail G, Dresel C, Witkovský V, Stankewitz A, Schulz E (2016) Neuronal oscillations in various frequency bands differ between pain and touch. Front Hum Neurosci 10:182.

Nowak LG, Azouz R, Sanchez-Vives MV, Gray CM, McCormick DA (2003) Electrophysiological classes of cat primary visual cortical neurons in vivo as revealed by quantitative analyses. J Neurophysiol 89:1541–1566.

Puig MV, Ushimaru M, Kawaguchi Y (2008) Two distinct activity patterns of fast-spiking interneurons during neocortical UP states. Proc Natl Acad Sci U S A 105:8428–8433.

Rudy B, Fishell G, Lee S, Hjerling-Leffler J (2011) Three groups of interneurons account for nearly 100% of neocortical GABAergic neurons. Dev Neurobiol 71:45–61.

Schulz E, Tiemann L, Witkovsky V, Schmidt P, Ploner M (2012) γ Oscillations are involved in the sensorimotor transformation of pain. J Neurophysiol 108:1025–1031.

Siegle JH, Pritchett DL, Moore CI (2014) Gamma-range synchronization of fast-spiking interneurons can enhance detection of tactile stimuli. Nat Neurosci 17:1371–1379.

Tan LL, Oswald MJ, Heinl C, Retana Romero OA, Kaushalya SK, Monyer H, Kuner R (2019) Gamma oscillations in somatosensory cortex recruit prefrontal and descending serotonergic pathways in aversion and nociception. Nat Commun 10:983.

Tracey I, Woolf CJ, Andrews NA (2019) Composite pain biomarker signatures for objective assessment and effective treatment. Neuron 101:783–800.

Vierck CJ, Whitsel BL, Favorov OV, Brown AW, Tommerdahl M (2013) Role of primary somatosensory cortex in the coding of pain. Pain 154:334–344.

Wang J, Li D, Li X, Liu F-Y, Xing G-G, Cai J, Wan Y (2011) Phase-amplitude coupling between θ and γ oscillations during nociception in rat electroencephalography. Neurosci Lett 499:84–87.

Wang J, Wang J, Xing G-G, Li X, Wan Y (2016) Enhanced Gamma Oscillatory Activity in Rats with Chronic Inflammatory Pain. Front Neurosci 10:489.

Xu H, Jeong H-Y, Tremblay R, Rudy B (2013) Neocortical somatostatin-expressing GABAergic interneurons disinhibit the thalamorecipient layer 4. Neuron 77:155–167.

Yue LP, Iannetti GD, Hu L (2020) The neural origin of nociceptive-induced gamma-band oscillations. J Neurosci 40:3478–3490.

Zhang ZG, Hu L, Hung YS, Mouraux A, Iannetti GD (2012) Gamma-band oscillations in the primary somatosensory cortex–a direct and obligatory correlate of subjective pain intensity. J Neurosci 32:7429–7438.

Zhou R, Wang J, Qi W, Liu F-Y, Yi M, Guo H, Wan Y (2018) Elevated resting state gamma oscillatory activities in electroencephalogram of patients with post-herpetic neuralgia. Front Neurosci 12:750.