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Toward a Multimodal Framework of Brainstem Pain-Modulation Circuits in Migraine

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Review of Marciszewski et al.

Migraines are severe episodic or chronic headaches that can be associated with dizziness, nausea, and increased sensitivity to light and sound. It is a pervasive condition, affecting ~1 in every 7 Americans (Raval and Shah, 2017). Within the brainstem pain-modulation system, several areas are associated with migraine pathophysiology. Growing evidence suggests that migraine pain stems from noxious signals from sensate intracranial and extracranial structures, including cerebral vasculature (Akerman et al., 2011), scalp muscles (Hinsey, 1928), and neck muscles (Jensen, 1993). These signals are associated with migraine-related head pain, dizziness/nausea, and muscle tenderness, and are transmitted by nociceptive peripheral neurons in the trigeminal nerve to ascending central neurons in the spinal trigeminal nucleus (SpV; Olesen et al., 2009). These ascending noxious signals are shaped by descending modulatory signals from brainstem areas, particularly the periaqueductal gray matter (PAG) and the rostral ventromedial medulla (RVM; Russo et al., 2017). In mice, PAG stimulation suppresses SpV neuron activation (Knight and Goadsby, 2001), and reducing modulation by the PAG by blocking calcium channels increases both pain-related and spontaneous neuronal activity in the SpV (Knight et al., 2002). The RVM serves as a throughway for descending PAG neurons that target ascending SpV neurons, perhaps enabling facilitatory/inhibitory signaling between these areas (Akerman et al., 2011). Notably, RVM stimulation has been shown to either enhance or reduce spinal neuron activation, perhaps underscoring the region's nuanced role in descending pain modulation.

How these areas contribute to migraine onset, maintenance, and symptoms remains incompletely understood. Current models of migraine pathophysiology suggest that different headache dimensions—such as onset, maintenance, and symptoms—can be attributed to complex changes in distributed pain-modulation networks across brainstem, subcortical, and cortical regions (May, 2017). These changes likely include aberrant functioning within descending pain-modulation brainstem areas that render pain circuits more sensitive to ascending noxious signals (Raskin et al., 1987). For example, people with migraine show diminished resistance to experimental pain between headaches, which has been attributed to either *reduced inhibition* or *enhanced facilitation* from descending brainstem pain-modulation areas (e.g., PAG, RVM), effectively increasing susceptibility to migraine attacks (Solstrand Dahlberg et al., 2018). Additionally, the PAG–RVM pathway is thought to regulate secondary symptoms associated with migraine headaches (e.g., appetite changes, sedentary behavior, sleepiness, etc.; Akerman et al., 2011). Importantly, however, much of what is known about the functional architecture of brainstem pain-modulation circuits relates to the migraine interictal phase; little is known about the 24 h period immediately preceding a migraine headache. Better understanding about functional relationships among brainstem pain-modulation areas across the migraine cycle is an important step toward establishing effective migraine treatments.

In a recent report in *The Journal of Neuroscience*, Marciszewski et al. (2018) sought to clarify the neural mechanisms underlying migraine by examining functional alterations within the brainstem pain-modulation system among migraineurs across the migraine cycle. Using functional magnetic resonance imaging (fMRI), these researchers measured blood oxygen level-dependent signals in the brainstem during task-based (i.e., noxious orofacial heat stimulation) and task-free (i.e., resting-state) conditions in patients during inter-ictal, pre-ictal, and

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post-ictal phases. It is worth noting that, although some patients were scanned across migraine phases, results reported by Marciszewski et al. (2018) characterize inter-ictal, pre-ictal, and post-ictal brain states using cross-sectional observations from distinct patient groups. Results indicated that, among individual migraineurs, self-reported pain intensity during experimental heat stimulation was associated with impending migraines across groups, such that perceived pain increased incrementally between headaches. In patients scanned during the inter-ictal phase, this period was associated with reduced PAG activation and increased coupling (functional connectivity) between the PAG and RVM. However, in the 24 h period immediately preceding a migraine headache, self-reported pain decreased dramatically among individual migraineurs. In patients scanned during the pre-ictal phase, this period was associated with increased SpV activation and reduced functional connectivity between the SpV and RVM. These outcomes suggest that brainstem function fluctuates considerably across the migraine cycle and that migraine onset is associated with increased SpV activation. The latter finding is consistent with recent work that found visual stimulation increased SpV activation among chronic migraine patients compared with controls (Schulte et al., 2018). Moving forward, longitudinal studies that track individual migraineurs across phases should provide additional clarification regarding cyclical dynamics in migraine-related brainstem function.

Surprisingly, Marciszewski et al. (2018) found no differences in self-reported pain intensity between controls and inter-ictal, pre-ictal, and post-ictal patient groups. Moreover, among individual migraineurs that were scanned across migraine phases, perceived pain during heat stimulation decreased immediately preceding migraine headaches despite increased SpV activation. The authors conclude that endogenous pain-modulation areas may dampen ascending pain signals just before migraine onset. It is possible that these outcomes represent brainstem pain-preventative (or compensatory) mechanisms that become active during the pre-ictal phase. However, given that perceived pain increases during headaches (Burstein et al., 2000), subsequent studies should elaborate on the clinically-relevant transition from reduced pre-ictal pain sensitivity to enhanced ictal pain sensitivity.

How do changes observed in the brainstem pain-modulation system relate to the onset and experience of migraine headaches? One possible explanation is that increasing pain sensitivity during the inter-ictal phase reflects peripheral sensitization in SpV neurons (Bernstein and Burstein, 2012). For example, in mice, preliminary noxious stimulation (i.e., chemical irritation) renders SpV neurons more responsive to subsequent noxious stimulation (i.e., mechanical pressure), even when they were originally not responsive or minimally responsive (Strassman et al., 1996). Similarly, non-headache pain experienced throughout the migraine cycle (e.g., minor neck pain) may have compounding effects on SpV neurons. Indeed, that could explain elevated SpV activation during the pre-ictal phase reported by Marciszewski et al. (2018). Moreover, concomitant increases in PAG activation, coupled with diminished pain sensitivity immediately preceding headache onset, supports the thinking that endogenous pain-modulation mechanisms are recruited in response to elevated SpV activation.

Functional connectivity changes within the brainstem pain-modulation system may contribute to migraine pathophysiology. In addition to modulating pain, the PAG–RVM pathway is associated with homeostatic behaviors such as eating and sleeping; deprivation of which can trigger migraine headaches (Akerman et al., 2011). Therefore, enhanced connectivity within this pathway reported by Marciszewski et al. (2018) may reflect compensatory changes in brain function following repeated homeostatic challenges among migraineurs. Cortical and subcortical brain regions may provide additional pain modulation. For example, one recent fMRI investigation (Dahlberg et al., 2018) found reduced coupling between the PAG and prefrontal cortex, a cortical region with links to descending pain modulation (Wager et al., 2004), among inter-ictal migraine patients. Whether the transition from inter-ictal to pre-ictal to ictal represents a shift from cortical-PAG functional connectivity to PAG–RVM functional connectivity warrants additional consideration.

Growing evidence suggests that migraine pathophysiology is associated with anatomical abnormalities within brainstem areas. PAG volumes are larger in people with episodic migraine headaches than in pain-free controls (Chen et al., 2017). In addition, migraineurs have diminished white matter integrity within the brainstem pain-modulatory system, including the ventral trigeminothalamic tract and PAG, pointing toward potential reductions in fiber organization and efficiency (DaSilva et al., 2007). Lessened white matter integrity along these tracts might predispose migraine patients to aberrant somatosensory processing. On the other hand, it is possible that repeated migraine attacks produce white matter alterations, and associated symptoms, via brain plasticity. Given the dearth of migraine-related structural neuroimaging assessments involving the brainstem pain-modulation system, future research should examine the extent to which regional volume and structural connectivity are related to migraine symptoms, and specifically how these relationships may change over time.

Another important challenge is to determine whether differences in the brainstem pain-modulation system of migraineurs are associated with underlying neurochemical changes across migraine phases. Several brainstem nuclei, including the RVM, are involved in the inhibition and facilitation of incoming pain signals. For example, in rats, RVM glutamate neuron activation increases pain-avoidance behavior during noxious stimulation (Jinks et al., 2007). As reported by Marciszewski et al. (2018), stronger inhibition from the RVM was associated with weaker pain-related responding in the SpV during the pre-ictal phase. Thus, enhanced pain modulation in response to impending migraine headaches may reflect adequate RVM glutamate signaling. In contrast, aberrant RVM glutamate signaling may be associated with increased migraine headache pain or duration. Considering the importance of these (and other) systems in descending pain modulation, future research would benefit from simultaneous consideration of brainstem functional, structural, and neurotransmitter system aberrations associated with migraine headaches.

Although Marciszewski et al. (2018) elucidate functional differences within brainstem pain-modulation circuitry among migraineurs, additional research is warranted to determine how these differences are related to neuroanatomical and neurotransmitter changes to produce migraine headaches. For example, comparing metabolite concentrations between patients and pain-free controls within brainstem nuclei during different migraine phases might identify biomarkers for the development of novel therapeutic interventions. Furthermore, after such interventions, high-resolution structural and functional neuroimaging could identify targets within complex brainstem neural networks. In summary, enhanced understanding provided by multimodal neuroimaging assess-

ments that incorporate neurobiological, neuroanatomical, and neurochemical techniques might provide a comprehensive framework necessary to more-completely characterize migraine headache pathophysiology and develop novel therapeutic interventions that correspond to various migraine cycle phases.

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