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# View and Perspective

## Beyond Neurovascular: Migraine as a Dysfunctional Neurolimbic Pain Network

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**No single model of migraine explains all of the known features of the disorder. Migraine has recently been characterized as an abnormality in pain-modulating circuits in the brainstem. The periaqueductal gray appears to have a critical role in migraine genesis and has been labeled the "migraine generator." The concept of a "pain matrix," rather than a specific locus of pain, is widely accepted in the pain literature and offers a new dimension to understanding migraine. Recent neuroimaging studies of migraineurs suggest altered functional connectivity between brainstem pain-modulating circuits and cortical (limbic) centers. Numerous clinical observations suggest that limbic influences play an important role in migraine expression. We propose a model of migraine as a dysfunction of a "neurolimbic" pain network. The influence between brainstem and cortical centers is bidirectional, reflecting the bidirectional interaction of pain and mood. Neurolimbic dysfunction may increase as migraine becomes more chronic or refractory. The neurolimbic model expands the model of migraine as a dysfunction of brainstem nuclei. A neurolimbic model may help bridge a gap in understanding the migraine attack, the interictal dysfunctions of episodic migraine, the progression to chronic migraine, and the common comorbidities with other disorders (such as fibromyalgia, irritable bowel syndrome, and mood and anxiety disorders), which may also be considered neurolimbic. A neurolimbic model of migraine may be a useful heuristic that would impact both clinical treatment and research agendas, as well as education of physicians and patients.**

**Key words: migraine, limbic system, chronic migraine, pathophysiology**

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Our conceptualization of migraine has evolved dramatically over the last half-century, from primarily a vascular disorder to a neurovascular disorder and currently to a brain disorder, primarily a disorder of neurons rather than blood vessels.[1,2] Prevailing models focus on peripheral (meningeal) and central (brainstem and thalamic) sensitization,[3,4] as well as cortical hyperexcitability,[5] but relegate the role of the limbic system to being a passive recipient of pain signals. The neurovascular model has significantly advanced our understanding of the individual migraine attack but is incomplete as an explanation both for the migraine attack and for many features known to be present in the "migraine brain." Features inadequately explained by the neurovascular model include: the prominent role of stress and emotions as attack triggers, prodromal and interictal migraine features, the bidirectional influence of psychiatric comorbidity, increasing psychiatric comorbidity and psychosocial influence with chronic migraine, the efficacy of behavioral therapies, and the often dramatic resolution of chronic migraine with a change in life

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milieu. Brainstem sensitization explains much of the snapshot we call "the migraine attack" but not the "video," the migraine patient over time.

Models drive research and clinical behavior. Lance, in reviewing the work in his own lab, commented: "In pursuing the vascular theory of migraine, we studied the effect of all the vasoactive agents that were then known."[6] The paradigm of migraine as neurovascular or brainstem dysfunction, or as a "channelopathy," may foster neglect of a large range of (limbic) factors known to influence migraine expression, as well as neglect of the well-documented efficacy of behavioral therapies.[7-9]

A wealth of studies have documented forebrain and limbic pathways that influence brainstem pain-modulating circuits[10] (Tracey and others, summarized later). Both clinical observation and empiricism suggest that limbic factors may play a role in migraine expression as well. In this manuscript, we review recent functional neuroimaging studies that document altered limbic-brainstem connectivity in migraineurs. We propose a "neurolimbic" model of migraine. This model expands the concept of central sensitization – otherwise thought of as a brainstem event – to include limbic dysfunction as well as cortical hyperexcitability. The neurolimbic model accounts for the dynamic bidirectional influence of pain and mood but does not imply psychiatric causation. We then discuss pragmatic implications of a neurolimbic model as a heurisitic in a clinical context as well as in research and education.

## CURRENT VIEWS OF MIGRAINE

Migraine is best understood as a primary disorder of the brain and not of blood vessels.[1] Following neuroimaging evidence of brainstem activation during a spontaneous migraine attack,[11] migraine has come to be described as "the dysfunction of an ion channel in the aminergic brain-stem nuclei that normally modulates sensory input and exerts neural influences on cranial vessels"[12,13] or ". . . a disturbance of subcortical modulatory systems."[1] The brainstem nuclei most commonly cited are the periaqueductal gray (PAG), a critical region involved in descending pain modulation, the dorsal raphe nucleus (the main serotonergic nucleus), and the locus ceruleus (the main noradrenergic nucleus). In this model, nociceptors in the field of the trigeminal ganglion (first-order transmission) are sensitized, leading to sensitization of the trigeminal nucleus caudalis (second-order transmission), leading to sensitization of brainstem nuclei and the thalamus (third order). Migraine is most commonly familial, and a chromosomal abnormality has been described in the rare syndrome of familial hemiplegic migraine[14] and more recently in an extended family of individuals with migraine with aura.[15]

**Central and Cortical Hyperexcitability.—**Welch et al in 1990 first proposed the concept of migraine as a state of central neuronal hyperexcitability.[16] Using magnetoencephalography, they documented signals observed during migraine attacks, and at times interictally, but not in nonmigraine individuals. They suggested specifically that the long amplitude wave might represent focal spontaneous neuronal depolarization, which in turn might reflect central neuronal hypersensitivity, a basis for migraine susceptibility. Since that time, the most common and consistent interictal abnormality that has been described in migraineurs is lack of habituation to repetitive stimuli in cortical centers.[17]

The concept of migraine as a continuum or spectrum disorder was possibly first proposed by Mathew et al.[18] Aurora has more recently summarized findings of cortical hyperexcitability in individuals with episodic and chronic migraine,[5] lending support to the concept of migraine as a spectrum disorder. For example, visual cortical excitability based on visual evoked responses was found to be abnormal in the interictal state of chronic migraineurs to an extent comparable with the ictal phase of episodic migraine.[19]

**A Thalamic Network.—**More recently, a major network of trigeminovascular-sensitive neurons from the thalamus to widespread regions of the cortex has been identified.[20] Such a parallel network of thalamocortical projections may play a role in the transmission of nociceptive signals from the meninges to the cortex. Individual dura-sensitive neurons project to many functionally distinct and anatomically remote cortical areas, involved in regulation of affect, motor function, visual and auditory perception, spatial orientation, memory retrieval, and olfaction. This

thalamacortical network may explain some of the common disturbances in neurological functions during migraine. Thalamic sensitization also likely mediates widespread allodynia that often occurs during a migraine attack.[21]

**Other Brain Regions.—**Functional imaging also suggests that the basal ganglia may play a role in the transformation of low-frequency to high-frequency migraine.[22] Undoubtedly, other brain areas and networks will be described with relevance to the migraine process.

## DESCENDING MODULATION OF PAIN AND THE LIMBIC SYSTEM

The brainstem nuclei most clearly involved in descending modulation of pain (Fig. 1[23]) are the PAG and rostralventral medulla (RVM).[24] The PAG is heavily interconnected with the hypothalamus and limbic forebrain structures (detailed later) and projects to the RVM, which in turn sends its output to dorsal horn laminae important in nociceptive function. This system has a pivotal role in organizing strategies for coping with intrinsic and extrinsic stressors, and is also recognized as the central site of action of analgesic agents including opioids, cyclooxygenase inhibitors, and cannabinoids.[24] Descending inhibition from the PAG is preferential for C-fibers rather than A-delta fibers,[24] but RVM output may be facilitatory or inhibitory. This latter property is based on the presence of "On" and "Off" cells in the RVM, ie, cells which facilitate ("On") or inhibit ("Off") pain transmission.[25] On and Off cell populations fire synchronously, with the 2 classes out of phase, exerting a "mass-action" regulation of dorsal horn function. Nociceptive threshold varies with the balance between the output of the 2 cell populations. C-fibers are specifically involved in the development of chronic pain states, and failure to inhibit C-fiber input

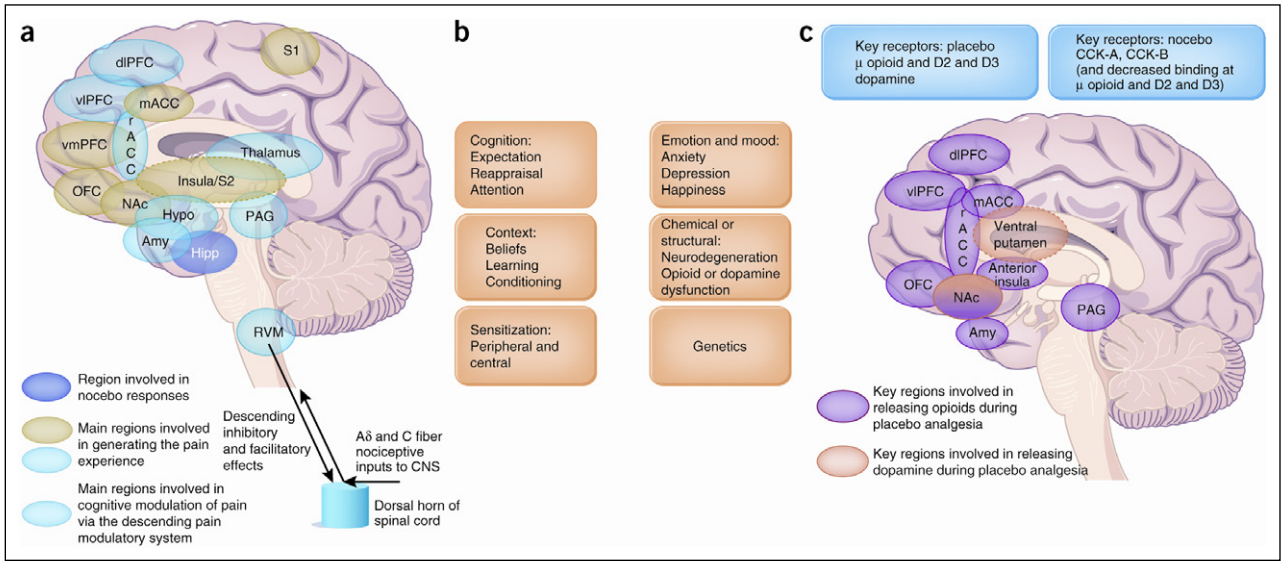


**Fig 1.—Factors influencing pain perception and the neural basis for endogenous pain modulation, placebo and nocebo effects. (a, b) Schematic illustration of key brain regions involved in generating a pain experience and core brain regions that comprise the cognitive and descending pain modulatory networks (a) and a description of the various factors that influence the pain experience listed in the text boxes (b). The hippocampal region is important for amplifying pain experiences during nocebo or increased anxiety. (c) Schematic illustration indicating where endogenous opioid and dopamine neurotransmission occurs in the human brain during placebo analgesia. For some brain regions (NAc), there is a bidirectional response of both opioid and dopamine release that produces either placebo (increased release) or nocebo (decreased release) effects. Amy = amygdala; CCK = cholecystokinin; CNS = central nervous system; dlPFC = dorsolateral prefrontal cortex; Hipp = hippocampus; Hypo = hypothalamus; mACC = midanterior cingulate cortex; NAc = nucleus accumbens; OFC = orbito-frontal cortex; PAG = periaqueductal gray; rACC = rostral anterior cingulate cortex; RVM = rostral ventral medulla; Sl = primary somatosensory cortex; S2 = secondary somatosensory cortex; vlPFC = ventrolateral prefrontal cortex; vmPFC = ventromedial prefrontal cortex. (used with permission from Tracey I. Getting the pain you expect.[23]).**

may permit recruitment of descending facilitation, leading to central sensitization.[24]

**The Limbic System.—**Following Broca's original designation of the "limbic lobe" in 1878, Papez and Maclean are credited with first designating the "limbic system" as the functional organization of emotions.[26] The limbic system today is generally thought of as including the amygdala, the anterior cingulate cortex (ACC), the orbital and medial prefrontal cortex (PFC), the insula, and hypothalamus (for detailed review, see Price and Drevets[26]). Because of the interconnectivity of the PAG-RVM system with limbic structures, some authors include these brainstem nuclei as well as part of the limbic system.[27]

A brief review of limbic system function and proposed neural pathways for modulation of pain may help shed light on possible roles for the limbic system in migraine. Wiech and Tracey summarized the influence of the limbic system on pain modulation, as follows later.[28]

The *amygdala* influences attention, conditioning, and memory retrieval, and plays a critical role in fear conditioning. Feedback from the amygdala to the human sensory cortex can facilitate attention and perception, which may result in enhanced perception of stimuli that have acquired emotional properties. The *entorhinal cortex*, a pivotal structure for memory consolidation, is highly interconnected with the amygdala. Entorhinal activation prior to the onset of a noxious stimulus predicts the perception of pain, and increased activation of the entorhinal cortex (along with the amygdala and anterior insula) has been found in patients with somatoform disorders.

The *ACC* is involved in numerous emotional functions, including evaluation of pain (ie, the assessment of pain as unpleasant), reward processing, evaluation of socially relevant information, and conflict resolution.[29] More generally, the ACC helps to prioritize behavior when dealing with emotional or painful stimuli. The dorsal ACC activates with cognitive modulation of pain affect, while the perigenual ACC activates during placebo analgesia. Distraction from pain reduces pain intensity, modulated by the orbitofrontal and perigenual ACC, as well as the PAG and thalamus.[30]

While the ACC is primarily involved in modulating the affective component of pain, the *anterior insula* is involved when attention modulates pain. The anterior insula is involved in interoception (the subjective evaluation of the internal state of the body) and is activated when subjects are asked to rate (ie, pay attention to) the intensity of pain. Interoception is associated with "anxiety sensitivity" (the tendency to view internal sensations as threatening). The anticipation of unpleasant stimuli activates right insular cortex; anxious individuals have increased insular activation during emotional processing, and anterior insula activation is reduced by anxiolytic medication. In addition to the insula, the ACC and nucleus cuneiformis are involved in the modulatory effect of expectation on pain transmission.[31]

The *PFC* serves a critical role in controlling pain modulatory circuits, specifically by driving endogenous pain-inhibitory circuits. The PFC governs the function of the PAG, amygdala, and anterior insula. Individuals taught to emotionally distance themselves from pain show increased activation of the ventrolateral PFC, which is also activated when individuals perceive reduced pain during perceived control over pain. Impaired prefrontal activity, and therefore increased pain, may be seen in anxiety states. The medial PFC is preferentially connected to the cingulate cortex and also appears to comprise the "default mode network," ie, the part of the brain active during the resting state ("daydreaming").[29]

The described pathways earlier appear to have direct relevance for migraine, where anticipation of pain, somatic preoccupation, anxiety, and locus of control all bear influence on headache control.[32]

## HISTORICAL HYPOTHESES LINKING THE LIMBIC SYSTEM TO MIGRAINE

Historical and cultural references have long given psychosocial factors prominence in our conceptualization of migraine. Rafaelli and Menon may have been the first to suggest, in 1975, that much of "chronic headache or migraine" could be explained by limbic system dysfunction.[33] They suggested specific anatomic localization of migraine symptoms and phenomena, especially to the hypothalamus (hormonal triggers), reticular activating system (sleep),

and the limbic system in general (emotional features). Without specifying the limbic system, Lance wrote: ". . . we believe that there is an upstream projection from brainstem monoaminergic nuclei to the cortex that can regulate blood flow, and downstream projection that plays an important part in the descending pain control system."[6] Salloway and White included migraine in the differential diagnosis of "paroxysmal limbic disorders."[34] More recently, Schoenen suggested that inhibitory serotonergic afferents from the raphe magnus nucleus were influenced by excitatory input from the periaqueductal grey and "other limbic structures."[35] O'Carroll has argued eloquently for the importance of considering limbic factors in our understanding and treatment of migraine.[36]

Burstein and Jakubowski proposed a "Unitary Hypothesis" that suggests a primary role for cortical and limbic structures.[37] They proposed that the well-known multiple triggers of migraine could be accounted for through the activation of the superior salivatory nucleus (SSN) by cortical and limbic centers. The SSN is a preganglionic parasympathetic nucleus that receives projections from multiple hypothalamic, limbic, and cortical areas. The SSN in turn activates the postganglionic parasympathetic nucleus, the sphenopalatine ganglion, which triggers vasodilation of meningeal vessels with release of inflammatory chemicals initiating migraine pain.

## MIGRAINE AS A DYSFUNCTIONAL NEUROLIMBIC PAIN NETWORK

As noted earlier, there is abundant evidence of the role of forebrain/limbic structures in modulating nonmigraine pain. Is there sufficient evidence to include forebrain structures and the limbic system in the pathophysiology of the migraine attack or the chronic disorder of migraine? (see Fig. 2).

**The Role of the PAG in Migraine.—**Weiller et al performed positron emission tomography scans on 9 subjects who experienced spontaneous migraine attacks.[38] Both brainstem (including PAG and dorsal pons, near the locus ceruleus) and cortical (ACC)

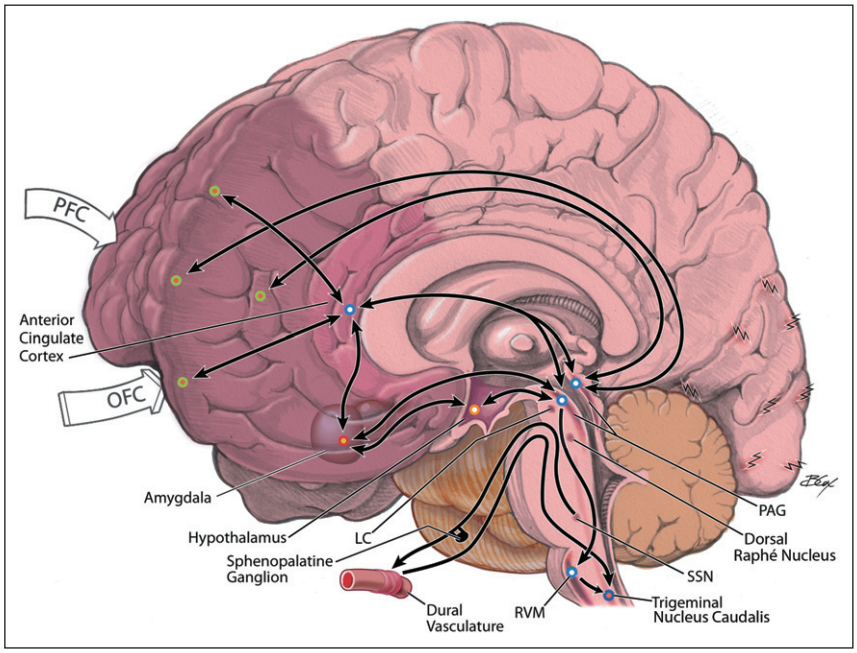


**Fig 2.—Proposed pathways of neurolimbic model of migraine. The concept of periaqueductal gray (PAG) as "migraine generator" is expanded to a neurolimbic pain network. Brainstem pain-modulating circuits have bidirectional connections with the limbic system (anterior cingulate cortex, amygdala, insula, orbito-frontal cortex [OFC] and prefrontal cortex [PFC], hypothalamus), and tonically influence migraine expression. Cortical hyperexcitability (shown in occipital cortex) is also influenced by brainstem circuits. See text for detailed description of interrelationships. ACC = anterior cingulate cortex; RVM = rostral ventral medulla; SSN = superior salivatory nucleus.**

structures activated during the attack, but only the brainstem, specifically the region of the PAG, remained active after sumatriptan injection relieved migraine symptoms. The persistence of the brainstem activation was thought to signify continuing vulnerability to migraine and led to the designation of the PAG as the "migraine generator." The activation of the ACC was attributed to "the emotional reaction to pain."

While the PAG is also involved in other chronic pain disorders, other lines of evidence, in addition to the Weiller study, suggest that the PAG may play a uniquely prominent role in migraine. First, the duration of illness correlates with iron deposition (a marker of dysfunction) near the PAG,[39] as well as in the caudate and putamen.[40] Dihydroergotamine binds to the PAG as well as the midbrain dorsal raphe nucleus,[41] and injection of naratriptan into the PAG produces an antinociceptive effect.[42]

**Evidence of Abnormal Limbic-Brainstem Connectivity in Interictal Migraine.—**Mainero et al using functional magnetic resonance imaging (fMRI) recently demonstrated interictal dysfunctional dynamics in the pain network of migraineurs.[43] Compared with controls, migraineurs displayed increased resting-state connectivity between the PAG and several cortical regions primarily involved in nociceptive and somatosensory processing (thalamus, posterior parietal cortex, anterior insula, somatosensory cortex). Migraineurs with higher frequency of attacks showed greater connectivity between the PAG and specifically anterior insula, nucleus cuneiformis, and hypothalamus. Conversely, high-frequency migraineurs displayed prominent reduced functional connectivity between the PAG and PFC, and to a lesser degree with ACC, amygdala, and medial thalamus. Migraineurs with allodynia showed decreased connectivity between the PAG, PFC, ACC, and anterior insula.

Consistent with these results, 2 additional studies found reduced limbic connectivity to the PAG in high-frequency compared with low-frequency migraineurs,[44] and in adult compared with childhood migraineurs.[45] Specifically, high-frequency migraineurs showed reduced functional connectivity of the PAG to anterior and posterior cingulate cortex, hippocampus, putamen, and posterior insula. Adult migraineurs displayed reduced connectivity to the PAG with the amygdala, accumbens/ventral pallidum, and ACC. In addition, the same group found gender differences, with females showing reduced functional connectivity of the PAG with the posterior cingulate cortex and amygdala.[46]

**Other Evidence of Limbic Abnormalities in Migraine.—**Another study of migraineurs interictally, using 18 fluoro-deoxy-glucose (FDG) imaging, showed hypometabolism in several regions of the limbic system, specifically insula, anterior and posterior cingulate cortex, and left premotor and PFC.[47] The abnormalities in the insula and ACC were correlated with disease duration and lifetime headache frequency. Migraineurs also display a hypoactive response to noxious stimuli in brainstem centers near the nucleus cuneiformis.[48]

Abnormalities of excitatory (glutamatergic) neurotransmitters in the ACC and insula have also been found in the interictal phase of migraineurs.[49] In a study of nonmigraine pain, Wiech et al found that activation of the anterior insular cortex predicted the likelihood that a subject perceived a near-noxious stimulus as painful; they referred to the insula-cingulate cortex conection as a "salience network."[50] A stronger functional connectivity of the anterior insular cortex with the PAG predicted that the stimulus would be perceived as not painful. Further, trait measures of anxiety and attention to pain negatively correlated to insular-PAG connectivity.

Recent functional imaging found reduced activation of the basal ganglia in high-frequency compared with low-frequency migraineurs.[22] The basal ganglia integrate information between cortical and thalamic regions and, in particular, the 3 domains of pain processing – sensory, emotional/cognitive, and endogenous/modulatory.

Holland and Goadsby have further proposed a role for the hypothalamus in migraine.[51] In addition to its known critical role in circadian rhythms, autonomic function, and aspects of homeostasis, the hypothalamus has significant connectivity with the limbic system, as well as PAG and RVM. Increasing connectivity between PAG and hypothalamus in high-frequency migraineurs may reflect a stress response

of the brain to worsening disease (conversely – disease progression may reflect the brain's adaptation to long-term stress).[43]

Cortical excitability may also be modulated by brainstem centers and thus indirectly by the neurolimbic network. In patients with chronic migraine, increase in visual cortical excitability accompanies brainstem activation and inhibition of PFC and somatosensory areas, again suggesting a dysfunction of inhibitory pathways.[52]

**Relating Functional Imaging to Function.—**It is important to note that visualizing changes in activity or connectivity do not tell us what is occurring functionally. PAG is normally thought of as inhibiting pain, but PAG activation in migraine is thought to indicate the "migraine generator." Similarly, some of the earlier studies had seemingly contradictory findings: PAG-insula connectivity is increased in high-frequency migraineurs but decreased in the presence of allodynia.

**Reexamining ACC Activation in Migraine.—**The persistent activation of the PAG but not the ACC found by Weiller et al[38] has been interpreted to support the idea of the PAG as migraine generator and the ACC as an emotional response to pain. However, hemodynamic responses of brain regions to pain may reflect both cognitive/affective response to pain as well as pain modulation (for review, Peyron et al[53]). For instance, Wagner et al using a thermal pain model showed that the ACC and PAG are *increasingly* activated by remifentanil analgesia, providing support for top-down influence of the ACC on the PAG.[54] fMRI studies demonstrate activation of the ACC and PAG during distraction-induced reduction of pain.[28] Most recently, functional connectivity MRI suggests that the ACC-PAG-RVM is a coherent network of pain modulation.[55] The ACC activation noted in the Weiller study may well represent descending modulation of pain, and abnormal connectivity in this pathway may represent migraine vulnerability.

What occurs in the earliest phases of a migraine? Woods et al published the first report of imaging of spontaneous migraine, demonstrating cortical hypoperfusion consistent with spreading depression.[56] He rejected the possibility that the blood flow changes were due to neuronal mediation. However, Cetas et al showed, in a rat model, that the RVM is active in regulating cerebral blood flow both at rest, as well as during an experimental model of subarachnoid hemorrhage.[57] This observation suggests the possibility that activity of brainstem nuclei (which in turn are subject to top-down regulation) underlie cerebrovascular changes associated with cortical spreading depression.

## CLINICAL IMPACT OF PSYCHIATRIC COMORBIDITY AND OTHER LIMBIC FACTORS

Both depression and anxiety are more prevalent in individuals with migraine than those without,[58,59] and the prevalence increases in those with chronic migraine.[60] Depression is associated with cutaneous allodynia, a marker of central sensitization in population-based studies,[61] and both anxiety and depression are associated with cutaneous allodynia in clinic-based studies.[62] Major depression is an independent predictor of persistence of chronic daily headache in adolescents.[63] In an emergency department setting, depression is an independent predictor of poorer 24-hour outcomes.[64]

Limbic influence is not limited to psychiatric comorbidity. Emotional stress is the most commonly reported trigger of migraine attacks, reported by 59% in a clinic-based population.[65] Stressful life events, as well as both anxiety and depression,[66,67] are modifiable risk factors for migraine progression. The trait of suppressed anger is significantly associated with migraine[68] and is a strong predictor distinguishing individuals with and without headache.[69] Alexithymia (the inability to talk about feelings and a trait strongly correlated with somatization) correlates with the presence of anxiety and depression in migraineurs,[70] and in one study was strongly associated with migraineurs who made frequent visits to the emergency department.[71] Cutaneous allodynia is associated with the personality trait of harm avoidance, as well as with anxiety and depression.[72] A history of adverse childhood experiences (childhood trauma) is linked to frequent headaches in a "dose-dependent" manner.[73]

The PAG not only receives input from limbic centers but also participates in regulation of mood and emotion. In a virtual threat paradigm, activation shifts from the forebrain (PFC) to the midbrain (PAG) as threat becomes imminent, consistent with studies showing abnormalities in this circuit in individuals with panic and anxiety.[74] Distinct anatomic circuits of the PAG may mediate active vs passive coping strategies to stressful, threatening, or noxious stimuli.[75]

Kong et al also found significant PAG connectivity with the anterior insula.[55] PAG-anterior insula connectivity may reflect the susceptibility of an individual to a noxious stimulus and correlates with traits of anxiety and attention to pain.[50]

## THE NEUROLIMBIC MODEL AS A HEURISTIC

The headache clinician will recognize variations of the following clinical scenario:

> The new patient is a middle-aged woman with chronic migraine and medication overuse, as well as fibromyalgia. In addition, there is anxiety and depression, fatigue and insomnia, and the familiar exhaustive list of psychotropics and antiepileptic drugs tried and failed.

We may consider for this patient 2 conceptualizations of migraine and how they might guide the therapeutic approach: the hypothesis of migraine as a dysfunction of brainstem monoaminergic nuclei and a neurolimbic model of migraine. Most clinicians intuitively accept that the vicissitudes of life are important in the presentation of migraineurs; a model to integrate this clinical wisdom may be useful.

Rome and Rome proposed a construct – the limbically augmented pain syndrome (LAPS) – to account for the complex chronic pain patient.[76] The construct refers specifically to: ". . . the distal end of the spectrum of chronic pain patients who have psychiatric comorbidity – patients whose history, clinical presentation, and treatment course reveal a complex linkage between the sensory and affective domains of their illness." The model suggests *corticolimbic sensitization* to explain the distinguishing features of the LAPS patient, which include "alterations in pain perceptions that are chronic, often atypical, and resistant to analgesic treatments in association with disturbances of mood, sleep, energy, libido, memory/concentration and stress intolerance." They suggest kindling and related models of neuroplasticity may help to explain the development of a sensitized corticolimbic state. Post and Silberstein previously had proposed kindling as a heuristic model to explain progression in affective disorders and migraine.[77]

In contrast with the LAPS model, we view limbic influence and augmentation as occurring along a spectrum of migraine dysfunction, not limited to one end of the spectrum but more prominent in the chronic/refractory migraineur. Limbic factors (mood/emotion/stress/personality/coping styles) may well-trigger a migraine attack. But more importantly, they influence the interictal state of the neurolimbic pain network, which influences ones vulnerability to an attack regardless of the trigger. Limbic factors mediate the placebo response,[78] a consistently prominent feature of headache therapies.[79] As episodic migraine progresses to chronic migraine and "refractory" migraine, neurolimbic dysfunction often increases. Patients with chronic migraine report more fatigue, sleep disturbance, bowel and gastrointestinal disturbances, and nonheadache pain than do patients with episodic migraine.[80] Psychiatric comorbidity is increased in individuals with chronic migraine, as are comorbidities, such as fibromyalgia. Dysfunction in multiple domains – family, social, work, sleep – is noted.

Heuristics may be defined as: ". . . experience-based techniques for problem solving, learning, and discovery. Heuristic methods are used to come to an optimal solution as rapidly as possible."[81] Clearly, a neurolimbic model helps us to understand and hopefully to address more comprehensively the triggers, behaviors, and therapeutic elements needed to relieve both the pain and suffering of migraine. Support for the therapeutic value of a neurolimbic model comes from Holroyd et al, who showed that behavioral therapies combined with pharmacotherapies provide superior outcomes for migraine than either treatment alone,[82] and that the influence of headache management self efficacy was an important moderator in treatment outcomes.[83]

The migraineur with comorbid psychiatric illness and chronic pain (fibromyalgia) may well be at the far end of a spectrum of neurolimbic dysfunction. The association of migraine with fibromyalgia, irritable bowel syndrome (IBS), and depression has led to the suggestion that each of these is part of an affective spectrum of disorders.[84]

However, the neurolimbic model does not imply that migraine is a psychiatric disorder or that isolated treatment of psychiatric distress will resolve migraine attacks. Rather, the model suggests that we view migraine as a dysfunctional network of pain and emotional modulation, where altered limbic connectivity may result from or contribute to migraine dysfunction as well as altered mood.

## PRAGMATIC IMPLICATIONS OF A NEUROLIMBIC MODEL

A neurolimbic model suggests more than identifying and addressing psychiatric comorbidity. Embracing a neurolimbic model would influence: (1) clinical evaluation, (2) patient education, (3) physician education, (4) treatment, (5) research agendas, and (6) definitions of the refractory headache patient.

**Clinical Evaluation.—**The high prevalence of psychiatric comorbidity and impact on quality of life are compelling reasons to promote psychiatric screening. In addition, personality style (eg, perfectionism, caregiver), lifestyle factors ("pressure cooker"), life circumstances (eg, an abusive relationship), as well as stressors and coping skills appear important to identify in the overall management of the migraineur.

**Patient Education.—**An explanation of the bidirectional influence of neurolimbic factors on mood and pain may be useful for both patient and physician. Understanding that depression and anxiety may be important risk factors for migraine transformation[67] lays a foundation for treatment.

**Physician Education.—**We believe that the foundational question of neurology – "Where is the lesion?" – readily applies to migraine, but the answer is found in conceptualizing migraine as dysfunction of a pain network rather than a specific brainstem nucleus.

**Treatment.—**Although there is not as yet evidence to show that treating psychiatric comorbidity influences headache outcomes, it appears clinically prudent to do so. Nonpharmacologic therapy is an often neglected aspect of treatment.

**Research.—**In addition to further neuroimaging studies, clinical studies may further our understanding by systematically including psychiatric measures in studies of both acute and preventive agents.

**Definition of Refractory Headache.—**Lipton et al proposed 6 reasons why standard headache treatments might fail and psychological factors were included in 3 of the 6 (unrecognized exacerbating factors, inadequate nonpharmacologic treatment, and presence of comorbid conditions [anxiety and depression]).[85] However, most recent proposals for definition of refractory headache consider only lack of response to pharmacologic therapies.[86-89] As more invasive procedures become available, the definition of refractory becomes important in protecting patients from potentially unnecessary and harmful procedures. As an example, one group suggested that surgical treatment should be considered for children in a pediatric neurology clinic with migraine refractory to medical treatment; 24% of children with migraine in this clinic were considered refractory and therefore surgical candidates.[90]

## DOES "NEUROLIMBIC" APPLY UNIQUELY TO MIGRAINE?

Abnormalities of central pain processing, with attendant limbic influences, are clearly not unique to migraine, and are thought to underlie a group of clinical entities labeled *central sensitivity syndromes* (*CSSs*).[91] These disorders include fibromyalgia, IBS, temporomandibular disorder, and others. Many clinical features of the migraine attack distinguish it from other pain disorders, including the associated nausea; sensitivity to light, noise, and odors; and cognitive impairments. The challenge for the future will be to elucidate how the function of the neurolimbic pain network differs among these and related disorders. Perhaps similar labels may be applied to other CSSs, such as "somatolimbic" for fibromyalgia and "gastrolimbic" for IBS. In this sense, "limbic" connotes not

merely dysfunctional emotional pathways but the inherent integration of limbic and brainstem pain-modulating pathways.

## CONCLUSION

Recent demonstrations of altered connectivity between forebrain/limbic cortex and brainstem nuclei support the view of migraine as a disorder of a neurolimbic pain network. Neuroimaging studies of the migraine attack demonstrate activation of the PAG and limbic system. Further, studies during the interictal period demonstrate abnormal connectivity between the PAG and limbic system, which appears to be progressive with duration and severity of illness. We propose the concept of migraine as a dysfunctional neurolimbic pain network, with increasing dysfunction as migraine becomes more chronic or refractory. Neurolimbic influence is bidirectional; limbic pathways may modulate or trigger a brainstem process that initiates a migraine attack, and brainstem dysfunction may alter limbic function, influencing mood and coping strategies. Consideration of migraine as a spectrum of neurolimbic influence may promote changes in clinical, research, and educational approaches, and ultimately benefit the migraine patient.

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**(a) Final Approval of the Completed Article**
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