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Migraine and Reward System—Or Is It Aversive?

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Abstract Migraine is a debilitating neurological disorder with grave consequences for both the individual and society. This review will focus on recent literature investigating how brain structures implicated in reward and aversion contribute to the genesis of migraine pain. There exist many overlapping and interacting brain regions within pain and reward circuitry that contribute to negative affect and subjective experience of pain. The emotional component of pain has been argued to be a greater metric of quality of life than its sensory component, and thus understanding the processes that influence this pain characteristic is essential to developing novel treatment strategies for mitigating migraine pain. We emphasize and provide evidence that abnormalities within the mesolimbic cortical reward pathways contribute to migraine pain and that there are structural and functional neuroplasticity within the overlapping brain regions common to both pain and reward.

Keywords Pain · Aversion · Reward · Negative affect · Dopamine · Ventral tegmental area · Nucleus accumbens

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Introduction

Chronic pain may be considered an epidemic in our society affecting 25 % of Americans, in which quality of life of chronic pain patients is reported to be lower than other disorders such as heart failure, renal failure and even depression [1]. One category of chronic pain that continues to be an elephant in the room of medicine is migraine [2]. It is problematic because it is massively common, thereby constituting a heavy burden on patients and their healthcare providers [2]. Regardless of significant advances in our understanding of the mechanisms underlying migraine pain, the basis for its persistence and prevalence is unknown. The American Migraine Prevalence and Prevention Study indicates that the cumulative lifetime incidence of migraine in this population is 43 % for women and 18 % for men [3]. Despite its high prevalence and associated disability, migraine is not generally perceived as a serious medical condition. However, evidence suggests that the burden of migraine is substantial, with 61 % reporting severe or very severe pain, and 67 % reporting severe disability [4]. Studies show that migraineurs are commonly underdiagnosed, undertreated, and experience substantial decreases in functioning and productivity, which, in turn, translates into financial burdens to both health-care systems and employers [5]. Despite high levels of disability, as assessed by Migraine Disability Assessment (MIDAS) scores and evidenced by the need for bed rest during attacks, many migraineurs continue to treat their headaches with simple analgesics, and approximately one-half of all migraineurs do not seek medical advice [6]. Even for patients that do consult a physician, the most commonly prescribed treatment is simple analgesics (30 %) [6]. This exemplifies that migraineurs have unacceptable levels of suffering, associated deterioration of health-related quality of life and increased comorbidities. Indeed, migraine is considered a progressive disease that may cause vascular and long-term central nervous system (CNS) damage [5].

Although not commonly recognized, migraine is often accompanied by dramatic sensory disturbances that result in pain hypersensitivity (allodynia and hyperalgesia). Indeed, the measurement of headache in rodents remains elusive, but cutaneous hyperalgesia occurs in most migraineurs [7, 8], and is frequently used to study headache-related pain in rodent models [9, 10, 11•]. However, the fact that migraine pain is associated with adverse affective and emotional states is relevant to this review. Pain is a multidimensional experience comprised of sensory, cognitive, and emotional (subjective) components, which are processed within discreet but interacting brain structures. It is widely accepted that stress contributes to the severity and frequency of migraine attacks. However, this review will posit that disruption in mesolimbic cortical circuitry may also play an important role in migraine pain that is not limited to circuitry engaged by medication overuse headache. Pain and reward are considered opponent processes, but are processed within overlapping or interacting brain structures (e.g., anterior cingulate cortex, dorsal and ventral striatum, and amygdala). It has been demonstrated that rewarding stimuli such as food and pleasurable music decrease pain sensitivity [12], whereas pain can impair reward processing, which can lead to an anhedonic state [13, 14]. The negative affect, or how much the pain is 'bothersome,' significantly impacts the quality of life of the sufferer, and leads to the common comorbidities of psychiatric disorders such as depression. Comorbidity between chronic pain and Axis I disorders of the DSM-V (including depression, anxiety disorders, bipolar disorder, ADHD, autism spectrum disorders, and schizophrenia) has been well documented, where depression is the most common comorbidity, with some studies finding a prevalence rate approaching 100 % among clinical chronic pain samples [14]. In fact, chronic pain is second only to bipolar disorder as the major cause of suicide among all medical illnesses, and the high comorbidity of migraine with depression further highlights the importance of negative affect [15–17]. This is also relevant to migraine patients, as significant associations between suicide and migraine pain were identified even when controlling for concomitant psychiatric conditions [18]. Indeed, patients with severe headache had the highest risk for suicide (6.5-fold) over other chronic pain cohorts [16].

Interplay Between Reward and Pain

Dopamine, serotonin, and norepinephrine are the canonical neurotransmitters involved in affect and reward, and alterations in these neurotransmitters are associated with altered mood states. Imaging studies on human volunteers and chronic pain patients of various etiologies suggest that perturbation of the mesolimbic-cortical dopaminergic reward circuitry contributes to chronic pain. Indeed, a high prevalence of chronic pain is common in disorders linked with deficits in the dopamine system, including disorders of mood and affect, substance abuse, and Parkinson's disease [19]. The interplay between reward pathways and chronic pain is relatively unexplored, but there are sufficient reports to validate the importance of this circuitry in migraine pain.

The mesolimbic reward circuitry comprises projections between the ventral tegmental area (VTA) and ventral striatum (which includes the nucleus accumbens). Dopaminergic neurons within the VTA project to various brain structures; however, their projections to the nucleus accumbens are a critical component of reward circuitry and underlie positive reinforcement. Indeed, dopamine release within the nucleus accumbens from VTA dopaminergic neurons is responsible for hedonic reward associated with many drugs of abuse including cannabis, nicotine, ethanol, cocaine, opioids, amphetamine, etc. However, the mesolimbic cortical dopamine system is involved in mediating not only appetitive, but also aversive behaviors [20, 21]. Dopaminergic projections to the nucleus accumbens encode aversive events and aversive motivated behavior, and there are important studies linking VTA dopaminergic projection neurons to the nucleus accumbens in aversion. Kappa opioid receptor agonists have dysphoric and psychotomimetic properties in humans and will mediate place aversion in rodents [22, 23], which can be elicited by direct injection of receptor selective ligands into the VTA [24]. There is strong evidence that the aversive properties of kappa opioid receptor agonists are mediated by a negative modulation of the mesolimbic dopamine system [22, 25], although conflicting data exists where Land et al. [26] reported that kappa opioid receptors on serotonergic neurons within the dorsal raphe nucleus projecting to the rostral nucleus accumbens are responsible for kappa aversion. Regardless, activity of medium spiny neurons expressing dopamine receptors within the nucleus accumbens appears necessary for kappa opioid receptor mediated aversion. Other behavioral responses to aversive stimuli have been shown to activate midbrain dopaminergic neurons and increase dopamine release in the nucleus accumbens [27]. Similarly, nucleus accumbens dopamine was identified to be instrumental in an avoidance task to escape foot shock, and the avoidance task led to significant elevations of dopamine and dopamine metabolites within the nucleus accumbens, as measured by microdialysis [28]. Taken together, this data suggests that the involvement of nucleus accumbens dopamine is not unique to positively reinforced responses, but constitutes important motivational aversive behaviors that may contribute to the aversive emotional component of pain. Indeed, projections from the midbrain VTA to the nucleus accumbens were suggested to be important in motivational aspects of pain [29].

What remains unclear, and difficult to ascertain, is whether this circuitry is driving the emotional, aversive nature of pain, or is engaged by the rewarding aspects of pain relief.

Dopamine release within the nucleus accumbens occurs following alleviation of ongoing pain, or the expectation of pain relief [30]. However, direct evidence for modulation of dopamine in the nucleus accumbens by aversive stimuli has been demonstrated. Phasic dopamine release, as measured by fast-scan cyclic voltammetry within the nucleus accumbens, was significantly suppressed by aversive stimuli using a classical conditioning procedure that renders sucrose aversive by explicitly pairing it with malaise (lithium chloride) in a conditioned taste aversion paradigm [21]. A recent study dissected distinct VTA circuitry that generates reward and aversion, whereby activation of inputs to the VTA from the laterodorsal tegmentum and the lateral habenula elicited reward and aversion, respectively [31••]. This latter study identified that neurons originating in the laterodorsal tegmentum (presumably encoding reward) preferentially synapsed on dopamine neurons projecting to the nucleus accumbens lateral shell, whereas lateral habenula neurons (presumably encoding aversion) synapsed primarily on dopamine neurons projecting to the medial prefrontal cortex, as well as on GABAergic neurons in the rostromedial tegmental nucleus. Interestingly, a reciprocal efferent projection from the medial prefrontal cortex back to VTA has also been described [32]. Thus, the medial prefrontal cortex can modulate subcortical dopaminergic transmission within the mesolimbic pathway, including via direct inputs to dopaminergic neurons within the VTA [32]. Hence, discrete anatomical circuitry within the mesolimbic cortical system may be engaged by ongoing pain and contribute to the subjective or aversive emotional component of the pain experience (Fig. 1). Dysfunction of this circuitry has been reported in migraineurs where patients with episodic migraine had altered functional connectivity in the basal ganglia (which consists of the caudate nucleus, putamen, nucleus accumbens, globus pallidus, substantia nigra, and subthalamic nucleus), suggesting a pathophysiology of this brain region that may underlie the progression of chronic daily headache seen in this patient population [33].

What Can We Learn from Operant and Behavioral Paradigms Typically Used for Addiction Research?

One well-utilized reward-related paradigm is the conditioned place preference (CPP) test. This test provides an understanding of the contribution of processes underlying motivation and reward [34], and is frequently used to assess affective states by measuring the time spent in an environment previously associated with motivationally salient stimuli (e.g., drugs or food). Pavlovian conditioning is involved in the acquisition of a place preference for a drug (most commonly studied are illicit drugs). The apparatus consists of either a two or three chamber box, where two of the chambers are equal in size but have distinct environments for visual, textural and occasionally olfactory cues. To evaluate whether a drug has rewarding motivational effects, an animal is injected with active drug or vehicle and confined to one of the compartments for a specific period of time. This is usually repeated over a few days, such that the animal develops an association of a specific environment with the subjective effect of the drug. Following conditioning, the animal is placed in the testing environment with free access to all compartments. If the animal spends more time in the drug-paired compartment, the conclusion is that the drug produced a rewarding effect. This same paradigm is also used to assess aversive stimuli (conditioned place aversion), including aversion to acute pain induced by injection of a chemical irritant such as capsaicin or formalin [35]. There is now strong evidence that the CPP paradigm can also be very useful in assessing the effectiveness of potential drug targets to alleviate the tonic-aversive or emotional component of ongoing chronic pain. King and colleagues [36] reported how analgesics used clinically for treating neuropathic pain produced a place preference in an animal model of neuropathic pain, but not in pain-naïve animals. This CPP paradigm has subsequently been used in various animal models of experimental nociceptive, inflammatory, neuropathic pain [37] to investigate mechanisms of affective aspects of pain. The motivational effect for place preference of analgesic drugs is hypothesized to reflect the rewarding component of pain relief, termed negative reinforcement. De Felice and colleagues [38•] recently demonstrated that injection of lidocaine into the rostral ventral medulla elicited a CPP in an animal model of migraine pain; pain was induced by application of inflammatory mediators to the dural membrane. The place preference was validated relevant to migraine pain, because pretreating animals with sumatriptan, a drug used clinically to alleviate migraine pain, or calcitonin gene-related peptide antagonists, blocked lidocaine-induced place preference. Interestingly, sumatriptan also blocked lidocaine-induced release of dopamine within the nucleus accumbens. Also, lidocaine-induced CPP was blocked by pretreatment with intracerebral injection of a non-selective dopamine receptor antagonist (α-flupenthixol) into the nucleus accumbens.

Together, this data suggests that the rostral ventral medulla is important in engaging reward circuitry to alleviate migraine pain. However, this data is paradoxical to clinical literature that supports the use of neuroleptics such as haloperidol, droperidol, and prochlorperazine in treating acute migraine [39, 40], which indeed may outperform migraine drugs such as sumatriptan [41]. Moreover, the levels of dopamine metabolite 3,4-dihydroxyphenylacetic acid in cerebrospinal fluid positively correlated with the duration of a migraine attack and with pain severity [42]. Indeed, the finding that sumatriptan decreased the serotonin concentration in the hypothalamus and increased the turnover of dopamine and serotonin in both the hypothalamus and striatum was suggested to be involved in the anti-migraine effects of this drug [43]. Nevertheless, a

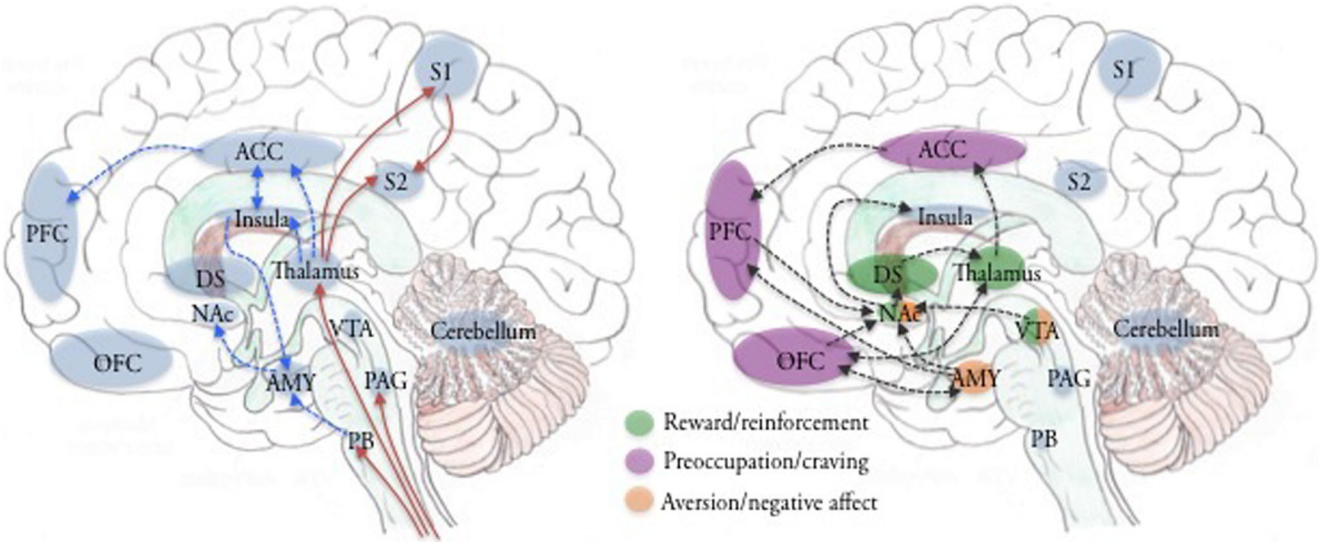

Fig. 1 Cartoon of sagittal brain sections illustrating the networks involved in pain and addiction. Left: Network of sensory (*red lines*) and affective/cognitive (*dashed blue lines*) dimensions of pain. Neurons from spinal cord and trigeminal nucleus project to the thalamus, which send projections to the S1 somatosensory cortex. This pathway conveys information about location and intensity of pain (sensory). Neurons of the spinoparabrachio-amygdaloid and spinoreticulo-thalamic pathways include projecting to the amygdala (fear and emotion), anterior cingulate cortex (fear avoidance, unpleasantness, interoception, and motor orientation), insula (subjective experience and interoception), parabrachial nucleus and hypothalamus (autonomic and neuroendocrine stress response). This circuitry is important for the subjective and emotional component of pain. Right: Networks of circuitry involved in addiction including reward (*green*), negative/aversion (*purple*) and preoccupation/craving (*orange*). The dorsal and ventral striatum (which includes the nucleus accumbens) and thalamus has been implicated in the rewarding (binge/habit forming) phase of addiction. The ventral striatum, amygdala are involved in withdrawal and negative affect and the prefrontal cortex, orbitofrontal cortex, and hippocampus are involved in preoccupation and anticipation of addiction. Note that many brain structures of the sensory and affective pain circuitry overlap with reward/aversion circuitry implicated in addiction. ACC (anterior cingulate cortex), AMY (amygdala), CC (corpus collosum), DS (dorsal striatum), HYP (hypothalamus), NAc (nucleus accumbens), OFC (orbitofrontal cortex), PAG (periaqueductal grey), PB (parabrachial nucleus), PFC (prefrontal cortex), S1 (primary somatosensory cortex), S2 (secondary somatosensory cortex), VTA (ventral tegmental area)

recent review postulated that migraineurs have dopamine receptor hypersensitivity due to a chronic dopaminergic deficit synergistic to serotoninergic impairment, and this may underlie their susceptibility to migraine attacks [39]. Of interest is the observation that migraine pain is often preceded, accompanied and followed by dopaminergic symptoms (premonitory yawning and somnolence, accompanying nausea and vomiting, postdromal somnolence, euphoria and polyuria) [39]. Supporting this hypothesis is the observation that the risk of migraine is positively correlated with a polymorphism of a serine/threonine kinase domain (Ankyrin repeat and kinase domain containing 1 or ANKK1) in the promoter region of the dopamine D2 receptor gene locus and a dopamine beta hydroxylase polymorphism, an enzyme responsible for maintaining a dopamine/noradrenaline ratio [44]. Interestingly, dopamine receptor agonists have proven to be an effective prophylactic treatment strategy in some migraineurs [39]. Since activation of discreet VTA circuitry elicits aversion [31••], it will be essential to dissect the dopaminergic circuitry that may contribute to the aversive component of migraine pain, that is likely distinct from reward.

The CPP paradigm provides a useful tool for understanding the mechanisms responsible for the various dimensions of the pain experience, and preclinical research using this paradigm supports findings from functional imaging studies of clinical populations. Functional magnetic resonance imaging (fMRI) studies of clinical pain cohorts have provided valuable insight into the areas of the brain that differentiate the sensory and emotional (affective) components of pain. One region of the brain that is consistently associated with pain affect and unpleasantness is the anterior cingulate cortex (ACC) [45]. For example, hypnotic suggestions that changed the sensory, but not the affective dimension led to activity changes in the primary somatosensory cortex [46], whereas similar experiments that altered affective without changing sensory perception were correlated with activation in the ACC [47]. Using the CPP paradigm, the ACC was shown to be a critical brain region in the tonic aversive component of neuropathic pain, where lesions of the ACC prevented the acquisition for place preference produced by injection of lidocaine into the rostral ventral medulla [48]. Further evidence that the ACC is important for the integration of the aversive component of pain was demonstrated by the absence of a conditioned place aversion to formalin-induced pain [49, 50•], and attenuated formalin-evoked or bee venom-evoked pain responses [51, 52] following ACC lesions in rodents. Moreover, ACC lesions attenuated pain avoidance to electrical stimulation in macaque monkeys [53]. Interestingly, ACC lesions were not shown to affect pain hypersensitivities in animal models of neuropathic pain [48, 51, 54], but did reduce escape/avoidance behavior

induced by mechanical stimulation of the hindpaw ipsilateral to nerve injury [54]. In an animal model of migraine pain, intracerebral injection of lidocaine into the rostral ventral medulla produced a CPP that was significantly attenuated by lesions of the rostral ACC [38•], demonstrating that this brain structure may also be important in the aversive component of migraine pain.

Anterior Cingulate Cortex in Pain and Reward

Areas of the cortex regulate and orchestrate almost all aspects of behavior, including cognitive function, action, emotion, goal-directed behaviors and reward, and memory. Cortical function is significantly impaired during both acute and chronic stress, and the resulting neuromodulatory changes in these brain regions serve to mediate the cognitive deficits common to mood disorders [55]. With the extensive direct and indirect connectivity of the numerous cortical regions with the mesolimbic pathway, it is not surprising that stress and illness can affect reward and motivational behavior [56, 57]. Research has demonstrated altered cortical structure and function following migraine attacks [58–61], and thus represents one likely pathway by which migraine, stress, the accompanying negative affect, and altered motivational states are intimately linked.

The ACC assists with the integration of emotion, cognition, autonomic function and conflict resolution. Importantly, it is considered part of the limbic system and encodes emotional (dysphoria or negative affect) and motivational aspects of pain [62], as well as behavioral monitoring and response selection relevant to disadvantageous choices in addiction [63]. This region receives direct dopaminergic input from the VTA [64], and as such may reflect upon the altered state of cognitive control and motivation common to mood disorders comorbid with migraine. Abnormal activity patterns in the ACC have been described in chronic pain patients, including patients with fibromyalgia, inflammatory bowel disease and chronic low back pain [65–68]. Altered activity, functional connectivity, and grey matter density of this brain structure have also been reported in migraineurs [60, 69]. Indeed, migraineurs were identified to have structural and functional cerebral abnormalities in the prefrontal cortex, the rostral ACC, the somatosensory cortex, the orbitofrontal cortex, and insular cortex [70, 71]. Migraineurs were found to have reduced cortical thickness in both the ACC and the insular cortex, another brain structure involved in processing the emotional component of pain. In addition to cortical thinning, the functional activity of both the ACC and the insular cortex was significantly reduced in patients with chronic migraine [60]. This result is in agreement with an ^{18}FDG-PET study demonstrating reduced metabolism of these brain regions in migraineurs [61], and an EEG study showing that migraineurs have decreased spontaneous cerebral activity, as measured by the amplitude of low-frequency fluctuation, in the rostral ACC and prefrontal cortex compared to healthy volunteers [72]. The insula has connections with the ACC in addition to the amygdala and the nucleus accumbens, and as such the reduced functionality of this brain region in migraine patients may serve to alter processing of both affect and reward. Given the high comorbidity of migraine and depression, controlled studies will be necessary to determine whether migraine is causative or a consequence of these cortical abnormalities, since reduced cortical thickness is also evident in patients with depression [73, 74].

It was recently proposed that a functional link exists between the nucleus accumbens and the ACC in reward processing [75, 76], and thus activity between these brain regions could reflect affective and motivational aspects of pain [77]. Since the ACC and the nucleus accumbens respond to both aversive and rewarding stimuli, the ability of these structures to influence activity in the other is of interest in the context of modulating the dysphoria or negative affect of the pain experience. A recent fMRI study in healthy volunteers and rodents reported that onset of noxious heat produced a decrease in activity within the nucleus accumbens, whereas offset of acute pain produced an increase in activity within the nucleus accumbens and ACC [77]. Since the ACC receives connections from other cortical and subcortical regions, including the prefrontal cortex, amygdala, and the nucleus accumbens [78], it is likely that the nucleus accumbens plays a role in modulating activity within the ACC, and thereby indirectly regulates the subjective experience of pain through this brain structure.

The ACC, along with the insular cortex and orbitofrontal cortex, is part of a salience network. Aberrant functioning of the brain circuits that assign salience values to stimuli may contribute to chronic pain [79]. Responsive salience networks in the brain are disrupted or dysregulated in chronic pain patients, whereby dysregulated brain salience systems may be overly responsive to certain types of stimuli because they cannot properly filter/process information [79]. This hypothesis is evident in migraineurs where functional imaging studies identified that migraine patients viewing pain-related words exhibited *enhanced* activation in the insular cortex and orbitofrontal cortex, compared to healthy control subjects [71]. The orbitofrontal cortex is involved in judging the affective value of reinforcing stimuli and driving the individual towards goal-directed behavior, and makes substantial connections with the amygdala, striatum, and the ACC [80]. As such, the orbitofrontal cortex is well positioned to process and integrate signals related to reward, behavior and affect. Abnormalities within the orbitofrontal cortex may underlie and contribute to an increased allostatic load and symptoms of associated disease states, such as apathy, in migraine patients. Jin and colleagues [69] reported structural deficits in the

orbitofrontal cortex, as well as increased functional connectivity between the orbitofrontal cortex and ACC in migraineurs. The functional relevance is unclear, but may be fundamental in relating the negative affect of migraine pain to the development of depression and associated apathetic behavior that is prevalent in migraine patients.

Does the Amygdala Contribute to Migraine Pain?

There is overwhelming evidence demonstrating the comorbidity of psychiatric illness in patients with migraine [81, 82]. Studies suggest mood and anxiety disorders generate the most prevalent subset, with more than 47 % of migraineurs meeting criteria for these conditions [83, 84]. Stress also is a symptom unequivocally concomitant with the etiology of both migraine and mood disorders [85]. Some current theories suggest that both the development of disease comorbidity and the progression to chronic migraine are a result of stress-induced plasticity in brain regions heavily integrated with stress, affect and pain [86–88]. The neural substrates underlying emotional aspects of pain processing overlap with those of stress system neuro-adapations associated with addiction, including areas such as the amygdala [89]. It is therefore feasible that a link exists between the neural mechanisms responsible for migraine pain and allostatic emotional changes seen in mood disorders and addiction.

The amygdala is involved in a wide array of functions including decision-making, memory, attention and fear. The amygdala is another limbic structure that is thought to attribute affective significance to environmental stimuli by forming a link between brain regions that process sensory information and areas involved in the production of emotional responses. A number of clinical and animal studies have indicated that the amygdala, along with the ACC, plays a critical role in the processing of affective components of pain [90]. Hence, excitotoxic lesions of the central amygdaloid nucleus or basolateral amygdaloid nucleus suppress intraplantar formalin-induced aversive responses [50•, 91]. Glutamatergic transmission within the basolateral amygdala via N-methyl-D-aspartate (NMDA) receptors has been shown to play a critical role in these aversive responses. The amygdala sends projections to, among other areas, the hypothalamus, VTA, and the cortex, making it a neuroanatomical structure well positioned to mediate the negative affect (aversiveness) associated with migraine pain [92, 93]. Although evidence is sparse, there is suggestion that synaptic plasticity within the amygdala may contribute to migraine pain. For example, Akcali and colleagues [94] demonstrated that stereotactic application of NMDA to the central amygdala produced cortical spreading depression (CSD); strong clinical evidence suggests that CSD is involved in the mechanism of migraine pain [95, 96]. Interestingly, sumatriptan attenuated c-fos expression within the amygdala that was thought to result from the induction of CSD. In addition, freezing behavior, a reaction of fear and/or anxiety mediated by the amygdala, was significantly increased upon induction of CSD, but how this behavior is related to migraine pain remains unclear, as sumatriptan did not alter this behavioral response. Imaging studies provide further evidence that activity within the amygdala contributes to migraine pain. Functional MRI connectivity analysis between the amygdala and cortex in migraine patients identified atypical and increased functional connectivity between these brain regions, which was surprisingly independent of aura, and absent in other chronic pain cohorts and healthy controls [97]. Interestingly, Dehbandi and colleagues [98] reported that synaptic plasticity in the amygdala is induced by CSD propagation, an effect modulated by dopamine D2, but not dopamine D1 receptors. Finally, a more recent study in humans uncovered that migraine attacks result in the sensitization of the amygdala [99]. Since there is broad transmission from the amygdala to other neuroanatomical structures facilitating stress and pain response, this sensitization may underlie the progression of migraine symptoms and mood disorders.

Conclusions

The concept that migraine is a painful neurologic disorder that drives alterations in both brain structure and function provides a basis for understanding the pathological consequences that contribute to the chronicity of this chronic pain condition, as well as the high prevalence of mood disorder comorbidities. We argue that alterations in the mesolimbic cortical reward circuit contribute to the pathophysiology underlying the genesis and persistence of migraine pain. On the surface, a significant amount of research has identified overlapping structural and functional deficits in the individual brain regions and circuits of migraineurs common to both pain and reward. The recent imaging studies in migraine patients have been a boon to elucidating some of these underlying neural pathways. However, many of the specific molecular and neurophysiological details pertinent to understanding not only the pathophysiology of migraine, but how specifically migraine and the associated pain fuel the rapid development of debilitating psychological disorders, remain elusive. Indeed, research into the role of the dopaminergic mesolimbic pathway in mitigating both the sensory and affective components of pain, and the symptoms concomitant to migraine associated mood disorders such as depression, is sparse at best. Future research aimed at elucidating the interplay of the reward circuits and migraine will necessitate not only better animal models of migraine and headache pain that demonstrate greater face validity, but also more methodologically sound reward-driven behavioral paradigms such as the CPP. Migraine and comorbid disorders place a substantial burden not only on society, but also on

the individual forced to cope with migraine pain and the associated negative affect. Insights into reward pathways that mediate these effects will generate a greater understanding of migraine etiology and undoubtedly generate prospects for future treatment.

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Compliance with Ethics Guidelines

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- • Of importance
- •• Of major importance

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