POTENTIAL MECHANISMS LINKING MIGRAINE AND PSYCHIATRIC COMORBIDITIES AND TREATMENT IMPLICATIONS

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Potential Mechanisms linking Migraine and Psychiatric Comorbidities.
The association of migraine and psychiatric conditions has been well documented but the neurophysiological link between migraine and its comorbidities remains unknown. Potential mechanisms involve 1) Shared genes, 2) Commonality of environmental factors, and 3) Epigenetic processes by which environmental factors effect alterations in gene expression.

1. Genetic links between migraine and psychiatric conditions

The epidemiological connection of migraine and psychiatric illness, such as depression, anxiety and bipolar disorder, suggest a contribution of genotype, but due to heterogeneity of these conditions this has been difficult to ascertain. It is likely that in many instances the development of these comorbidities is due to multiple genetic factors interacting with a variety of environmental factors (e.g. stress, inflammation). Genome wide association studies (GWAS) have revealed a number of variants, which were associated with migraine in pathways for pain sensing, glutaminergic neurotransmission, vasculature and synaptic plasticity [1]. In monogenic migraine syndromes (CADASIL, FHM, CHARIOT,and FASPS), which are rare, six genes with large effect size have been uncovered, but these are mostly related to vasculature and not mood disorders. In the case of depression, GWAS have not revealed a single gene or genetic variation that substantially increases the risk of depression. There are, however, validated candidate genes involved in both depression and pain, although not specifically migraine [2]. These include HTR1A, HTR1B, HTR2A,TNF, BDNF, DRD2, SLC6A4, COMT, TAC1, and GRIN2B. Among this list are genes that coding for inflammatory cytokine receptors, which have been implicated in both pain mechanisms and in the etiology of mood disorders. The candidate genes also include those that encode for serotonin receptors, which are important targets in migraine treatment. The SLC6A4 gene (also known as SERT or 5-HTT) encodes the serotonin transporter, a membrane protein that takes up serotonin in pre-synaptic neurons. A degenerate repeat polymorphic region in SLC6A4, 5-HTTLPR (serotonin-transporter-linked polymorphic region) has been the subject of study in both depression and migraine. A polymorphism with the short allele is purported to predict major depressive disorders in association with stress in childhood and adulthood [3], an example of a gene x environment interaction. There is no evidence for a significant association of this polymorphism with migraine [4,5] but the gene x environment interaction of early adversity and migraine has not been studied. Pain and mood disorders may also share genes involved in stress responses. Genes connected to the predominant neuroendocrine stress response system, the hypothalamic-pituitary-adrenal (HPA) axis, include *CRHR1*, *NR3C1* (encoding glucocorticoid receptor [GR]), *NR3C2* (encoding mineralocorticoid receptor [MR]), and *FKBP5* (encoding a GR regulator), which are highly expressed throughout the limbic system. Genetic variants of *CRHR1* may alter HPA axis activation and corticosteroid release, whereas variants of *NR3C1, NR3C2,* and *FKBP5* have an effect on cortisol negative feedback. There has been growing evidence that certain polymorphisms within genes that code for proteins affecting HPA axis function have the potential to predict vulnerability to environment stressors, including early adverse experiences, such as childhood maltreatment.

2. Environmental factors links between migraine and psychiatric disorders

Exposure to stress early in life increases susceptibility to a number of health conditions in adulthood. A history of severe childhood stress is one of the most robust risk factors for development of depression and anxiety in adulthood. Also associated with migraine in several large population studies, adverse childhood experiences (ACEs) include abuse (sexual, physical and emotional), neglect (physical and emotional) and dysfunction within the family (domestic violence, substance abuse, separation/abandonment, depression, and incarceration). The impact of early exposure to stressors, such as abuse, depends on abuse type(s), severity, duration, and stage of brain development at time of abuse, as well as gender and genetic predisposition to stress-induced changes. In migraine, stress has long been postulated to be an important trigger, although the evidence establishing this has been scarce, both in clinical [6,7] and basic science arenas [8]. Studies in migraine have predominantly focused on the temporal association of acute stress and the migraine attack, rather than on the effects of early life and

chronic stress on susceptibility to later life stressors. There are a number of inter-related homeostatic systems which mediate the stress response. These include the neuroendocrine, endocannabinoid, serotonergic, oxytonergic, inflammatory systems:

a. Neuroendocine system. The HPA axis is the most important regulator of the physiological stress response. A well-characterized short term response to acute stress, the fight-or-flight response, involves hypothalamic signaling of catecholamine release from the adrenal medulla via the sympathetic nervous system. As part of a more persistent stress response, corticotropin releasing hormone (CRH) and vasopressin (AVP) are released from the hypothalamic paraventricular nucleus (PVN), which in turn stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) into the circulation. ACTH binds to receptors in the adrenal cortex and promotes release of mineralocorticoids and glucocorticoids (cortisol in humans, corticosterone in rodents). Mineralocorticoids influence salt and water metabolism, and glucocorticoids mobilize stored glucose and lipids and modulate immune/inflammatory, and neural systems. The HPA axis maintains homeostatic balance through negative feedback mechanisms tightly regulated by mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) in the limbic system (particularly the hippocampus) and well as by GR in the PVN and anterior pituitary. Chronic stress, encompassing sensitive periods early in life, may lead to loss of negative feedback control with long-term changes in HPA regulation and persistent alterations in stress responsivity. This dysfunction of the HPA axis has been associated with increased and enduring vulnerability to a wide-range of illnesses, particularly neuropsychiatric conditions [9].For instance, hyperactivity of the HPA axis has been one of the most consistent findings in major depression.

b. Endocannabinoid system.The endocannabinoids are atypical neurotransmitters that play a crucial role in the stress response by maintaining neural homeostasis and producing analgesia via inhibition of dural trigeminovascular nociceptive responses. A reduction of endocannabinoid signaling, which can be induced by early life stress, may predispose to the development of migraine and other painful conditions, such as fibromyalgia, irritable bowel and interstitial cystitis [10]. Endocannabinoid signaling mechanisms have also been implicated in the neurobiology of depression.

c. Serotonergic system. Migraine has also been characterized by a low serotonergic state, a condition which facilitates activation of the trigeminovascular nociceptive pathway. Stress induces decreases of serotonin in the amygdala and nucleus accumbens [11], as well as decreased serotonin 1B receptor expression [12], which may increase vulnerability to migraine. Low serotonergic response also increases vulnerability to depression. Modulations in the 5 HT 1a receptor have been demonstrated to lead to the expression of the major depressive disorder phenotype [13].

d. *Oxytonergic system*. Oxytocin is a hypothalamic neuropeptide, which modulates the HPA stress axis, and has an important role in social behavior and bonding. ACEs, especially emotional abuse in women, disrupts regulation of oxytocin and results in lower levels within the CSF [14,15]. Oxytocin receptors are expressed by neurons in many parts of the brain, including the amygdala and ventromedial hypothalamus. Specific oxytocin receptor genotypes increase vulnerability to psychiatric conditions in the setting of childhood maltreatment, likely in conjunction with epigenetic mechanisms [16] described below. There is a paucity of research of the role of oxytocin in migraine but the finding that oxytocin receptor expression in calcitonin gene-related peptide (CGRP) containing trigeminal ganglion neurons, as well as the blockade of CGRP release from trigeminal dural afferents suggests that receptor activation may be useful in migraine treatment [17].

e. *Inflammatory system*. Inflammatory cytokines activate the HPA axis, which in turn modulates inflammation and immunoreactivity. Cytokines also interact directly with the neuronal environment in addition to targeting downstream pathways (excitation of NMDA receptor, excessive levels of glutamate, change in GABAergic neurotransmission from inhibitory to excitatory), which disrupts neural function. An elevated basal rate of inflammation is well documented to occur in adults maltreated as children [18] and inflammation has also been implicated in the pathophysiology of depression, bipolar disorder, and migraine [19]. Inflammatory markers are elevated in the interictal (compared to controls) [20] and ictal states (compared to interictal levels) of migraine [21] and inflammatory marker levels correlate directly with a measure of severity of childhood maltreatment, the ACE score [22]. The inflammatory system likely plays a pivotal role in linking stress to migraine and depression.

Support for the theory that maltreatment-related stress occurring early in life is a mechanism in the later development of migraine and psychiatric disorders is the finding of *structural* and *functional* similarities of limbic regions in these conditions.

Structural Similarities. In animal models prolonged elevation of glucocorticoids leads to dendritic remodeling of limbic system structures, with the most prominent changes being atrophy of the hippocampus [23] and hypertrophy of the amygdala [24,25]. Other limbic system structures include the septal nuclei, cingulate cortex, and portions of the temporal lobe (entorhinal cortex, perirhinal cortex, and parahippocampal cortex). Structural changes in the limbic system lead to dysregulation of the HPA-axis by interfering with the tightly controlled feedback mechanisms normally in place. With the advent of MRI there has been much interest in radiological changes in persons suffering childhood abuse and in persons with migraine.

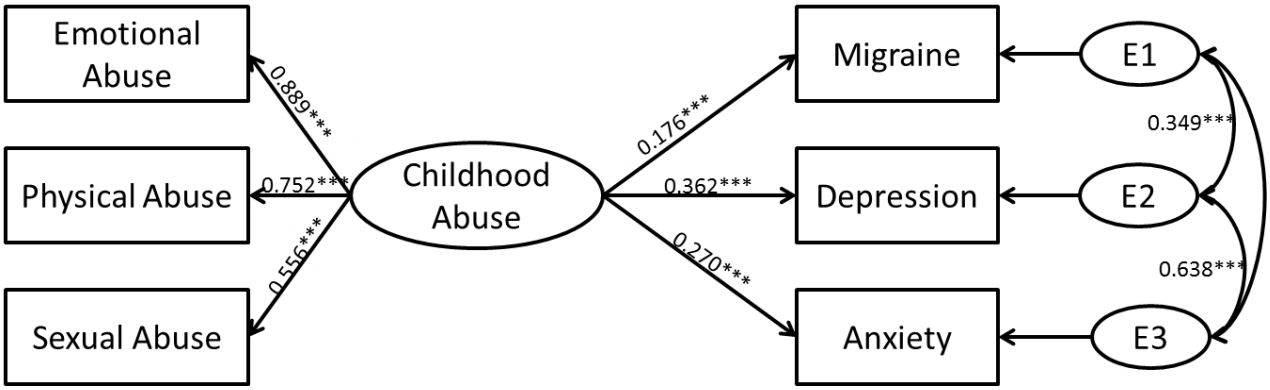
Childhood maltreatment. In voxel based morphometric MRI studies of adults who were maltreated as children there are smaller hippocampal volumes as well as decreased thickness of the amygdala, anterior cortex cinguli (ACC), orbitofrontal cortex (OFC), dorsolateral and ventromedial prefrontal cortex, and corpus callosum [26]. Radiographic hippocampal changes in abused children are less pronounced than those seen in adults reporting to have experienced abuse as children, but there is evidence of reduced cortical thickness of the ventral anterior cingulate, superior frontal gyrus, and the OFC, as well as of the left middle temporal area and lingual gyrus [27]. Studies support the theory that different brain regions show unique sensitive periods to the effects of stress. In a recent brain MRI volumetric analysis young women with a history of childhood sexual abuse were compared to healthy female controls. Abuse was associated with volume reductions in 1) the hippocampus at ages 3–5 years and 11–13 years, 2) the corpus callosum at ages 9–10 years, and 3) the frontal cortex at ages 14–16 years [28].

Migraine and Depression. Similar to the radiological profile described in abused persons, MRI changes in migraineurs predominantly involve structures in or connected to the limbic system. A study of MRIs from children with migraine for 3 years showed changes in these structures. A 2015 meta-analysis of radiological studies from adults found that, compared to healthy controls, those with migraine had decreased gray matter thickness in the posterior insular-opercular regions, the prefrontal cortex, and the anterior cingulate cortex [29]. A recent single center case control MRI study of migraine found cortical thinning in areas participating in affective and cognitive aspects of pain processing (anterior cingulate cortex, medial orbital, frontal gyrus, entorhinal cortex, and pars triangularis) as well as in areas involved in multisensory integration (temporal pole and superior temporal lobe) [30]. The changes allowed for classification of chronic migraine versus episodic migraine or no migraine, but it is important to note that it remains unknown as to whether these structural changes predispose to migraine or whether they are a result of disease progression. Despite the overlap in radiological features of persons with maltreatment and those with migraine, there are no published studies comparing MRI changes in persons with migraine stratified by abuse history. Of interest, a case control MRI study of hippocampal morphometry found no difference related to major depression diagnosis (MDD) if childhood maltreatment was regressed out, suggesting that reduced hippocampal volumes in MDD may be due to early life adverse experiences [31]. The same might be true in migraine, and this could best be elucidated by longitudinal studies.

Functional similarities. Functional brain changes reported in maltreatment, migraine and depression may result from the stress-induced structural limbic system changes described above [9].

Childhood maltreatment. In a functional magnetic resonance imaging (fMRI) study of young men, multiple linear regression analyses showed that early life stress, specifically emotional abuse, predicted reduced resting state functional connectivity between the right amygdala and pregenual anterior cingulate cortex (pgACC). This, in turn, predicted elevated state anxiety after acute psychosocial stress [32]. Positron emission tomography (PET) studies in subjects reporting low maternal care early in life demonstrate that acute stress causes dopamine release into the ventral striatum [33].

Migraine and Depression. In a 2011 study, persons with migraine showed a decrease in resting-state connectivity between the amygdala, which modulates pain activity and perception, and the periaqueductal gray matter (PAG), an important site in both ascending pain transmission and the descending pain inhibitory system, suggesting migraine might be modeled as a dysfunctional “neurolimbic” pain network [34, 35]. A higher monthly headache frequency was associated with a significant decrease in the PFC and ACC resting-state connectivity with the PAG. Studies have also demonstrated a negative correlation in PFC activity with pain severity [36,37]. A 2016 depression study demonstrates disrupted structural and functional connectivity in PFC-hippocampus circuitry in medication-naïve adolescents experiencing a first episode of depression. These findings suggest that abnormal neural circuitry may play an important role in the neuropathophysiology of MDD [38]



Structural equation modeling (SEM) of the relationship of childhood abuse, migraine, depression, and anxiety was performed using Wave 4 Add Health data, including 2,061 (14%) persons with migraine. SEM analysis demonstrated that childhood abuse has a significant direct impact on migraine, anxiety and depression. This supports the theory that environmental factors (in this case, abuse) act in such a way to directly lead to the comorbid disorder, rather than having one disorder mediate the others.

3. Epigenetic mechanisms linking environment to gene expression. Epigenetics processes govern expression of genes through alterations unrelated to the DNA sequence. Epigenetic modifications include DNA methylation, post-translational histone modifications, and gene regulation by microRNAs. These stable alterations in gene expression are likely amongst the key mechanisms by which early life stress effects neurobiology and disease vulnerability throughout the lifespan and even across generations. Chronic stress can influence epigenetic patterns of approximately 2000 genes, yet relatively few epigenetic studies have been conducted in this area. In animal models stress-induced epigenetic changes have been shown to occur in genes directly impacting HPA axis function (*NR3C1, FKBP5, Crh, Avp*), as well as those genes regulating functions outside the HPA axis, including *5-HTT, GAD1, ESR1, BDNF* [39]. Human studies have thus far focused on genes for the glucocorticoid receptor and serotonin transporter. The role of stress-induced epigenetics processes have largely focused on psychiatric conditions. While the impact of epigenetics on the pathophysiology of migraine remains largely unknown, there have been a few intriguing findings [40]. A meta-analysis of MTHFR polymorphisms, demonstrated that the 677TT genotype is associated with an increased risk for migraine with aura [41]. The MTHFR gene, which encodes for 5',10'-methylene-tetrahydrofolate reductase, is involved in DNA methylation. Of note, both valproic acid and topiramate, which are commonly used in migraine prophylaxis, have been shown to inhibit HDAC [42].

Treatment Implications of gene x environment interaction linking migraine and psychiatric comorbidities, Although no migraine clinical trials have stratified participants by history of childhood maltreatment, adverse early life experiences may guide migraine therapy, particularly in persons who have been refractory to multiple treatments.

Serotonin Modulating Agents. Studies suggest that early life stress can produce long lasting reductions brain serotonin, and this is a putative mechanism by which childhood maltreatment is linked to psychiatric disorders. Although serotonin-specific re-uptake inhibitors, a mainstay of depression treatment, are not particularly effective in migraine prophylaxis, the older tricyclic antidepressants, which inhibit reuptake of both serotonin and noradrenaline, have proven efficacy [43]. Newer dual action drugs, such as venlafaxine, duloxetine, and mirtazepine have been shown to treat both depressive symptoms, and pain, although data in migraine is scant. The most effective agents in acute migraine treatment, the triptans, were specifically designed to act as serotonin agonists at the $5HT_{1D}$ receptor, thereby inhibiting release of neuropeptides, including CGRP and substance P, which mediate the inflammatory response.

Anti-inflammatory Agents. Drugs which inhibit inflammation, such as the nonsteroidal anti-inflammatory drugs (NSAIDs), are widely used in acute migraine but side effects limit their use in prophylaxis. Increased endocannabinoid activity has been proposed as a critical component of NSAID-mediated pain alleviation and in rodent pain models, inhibition of endocannabinoid metabolism via enzymes fatty acid amide hydrolase and monoacylglycerol lipase have shown promise. Oxytocin, a hypothalamic neuropeptide that modulates the HPA stress axis, also reduces migraine-related inflammation. Expression of oxytocin receptors, which are on trigeminal

nerve neurons, is known to be driven by inflammatory cytokines, and IL- 6, in particular. A study of single-dose intranasal oxytocin in persons with chronic migraine demonstrated decreased pain in 2 hours in 42% of migraineurs in the treatment group (vs 11% in the placebo group) and also decreased photophobia and phonophobia [44]. CGRP antagonists, which inhibit inflammation, were shown to be effective for the acute treatment of migraine, but issues of toxicity with chronic use halted further development [45]. Currently undergoing testing in clinical trials for migraine prevention are monoclonal antibodies which inhibitor CGRP or its receptor, and preliminary data is promising [45].

Histone deacetylase (HDAC) inhibitors. Several anti-epileptic drugs have efficacy in migraine prophylaxis, and valproic acid and topiramate are FDA-approved for this indication. Interestingly, valproic acid, topiramate and 2-pyrrolidinone-n-butyric acid, a major metabolite of levetiracetam, all function as HDAC inhibitors [42]. In the case of valproate, this mechanism has been proposed as a mechanism for its effectiveness in treating bipolar disorder. It has yet to be tested whether HDAC inhibitors and other treatments which alter epigenetic modifications, are a key mechanism in migraine treatment, and whether this approach might be particularly effective in migraineurs with a history of childhood abuse.

Aerobic Exercise. Although moderate aerobic exercise is widely recommended as a preventive strategy for migraine, there is a paucity of well-designed studies supporting this recommendation. A recent systematic review, which yielded only nine studies that evaluated aerobic therapy as part of a migraine preventive regimen suggested at least a modest benefit in frequency and intensity, and found it to be perhaps as good as other pharmacological and non-pharmacological treatments [46]. A prophylactic trial of exercise compared to topiramate in persons with low to medium frequency episodic migraine showed similar benefits of both strategies but there was better adherence and fewer side effects in the exercise group [47]. Aerobic exercise enhances endorphins, decreases inflammation and increases serotonergic activation and neurogenesis. It is believed to involve endogenous opioids, endocannabinoids as well as CGRP. In rodents, exercise has been shown to reverse the HPA axis dysfunction caused by early life stress [48]. This has also been proposed as a mechanism for the beneficial effects of exercise on depression. Thus, exercise may be particularly effective as a treatment for migraine patients with a history of childhood maltreatment.

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