Understanding Migraine through the Lens of Maladaptive Stress Responses: A Model Disease of Allostatic Load

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The brain and body respond to potential and actual stressful events by activating hormonal and neural mediators and modifying behaviors to adapt. Such responses help maintain physiological stability (“allostasis”). When behavioral or physiological stressors are frequent and/or severe, allostatic responses can become dysregulated and maladaptive (“allostatic load”). Allostatic load may alter brain networks both functionally and structurally. As a result, the brain’s responses to continued/subsequent stressors are abnormal, and behavior and systemic physiology are altered in ways that can, in a vicious cycle, lead to further allostatic load. Migraine patients are continually exposed to such stressors, resulting in changes to central and peripheral physiology and function. Here we review how changes in brain states that occur as a result of repeated migraine may be explained by a maladaptive feedforward allostatic cascade model and how understanding migraine within the context of allostatic load model suggests alternative treatments for this often-debilitating disease.

Migraine, Stress, and Allostasis

Migraine is a disabling headache disorder characterized by intermittent attacks with a number of physiological and emotional stressors associated with or provoking each attack (i.e., pain, tiredness, nausea, vomiting, photophobia, or phonophobia, etc.). The disease affects millions of individuals, by some estimates 45 million Americans (Stewart et al., 1994) or 11%–17% of adults in Western societies (Lipton et al., 2001). Estimated healthcare costs related to migraine are around $1 billion in the United States, and estimated costs to United States society is $13 billion annually (Hu et al., 1999). Migraine may be divided into two subgroups: those with aura (focal neurophysiological symptoms that usually precede or sometimes accompany the headache, e.g., visual aura) and those without aura (http://ihs-classification.org). Frequency of headaches has been used to further differentiate episodic migraine (attacks with or without aura that occur 1–14 days/month for >3 months) or chronic migraine (attacks that occur >15 days/month for >3 months) (Figure 1). The division is somewhat arbitrary in terms of the disorder but reflects increasing deterioration of a patient’s condition as the chronic form is associated with increased comorbid features (Scher et al., 2005). In terms of features associated with the disease, migraine differs from other primary headaches that include tension-type headaches (the most common headache disorder), trigeminal autonomic cephalalgias (e.g., cluster headaches), and secondary headaches related to a specific condition (e.g., infection, trauma, drug withdrawal, analgesic overuse, cranial neuralgias, etc.). Further details on these can be found at http://ihs-classification.org.

The underlying pathophysiology of the migraine is largely unknown. As a neurological condition, migraine may be considered as a continuum not only in terms of the perihedache changes with each attack but also in the progression to high frequency and chronic daily headache that takes place in some patients (Manack et al., 2011) (Figure 2). Current evidence suggests that the brains of patients with migraine are significantly different from healthy controls. Some of these differences are in the form of abnormally increased cortical excitability to pain (Moulton et al., 2011), light (Denuelle et al., 2011), or smell (Demarquay et al., 2008). Other differences relate to abnormality in responses that should be adaptive but become impaired or maladaptive, such as altered brainstem processing (Moulton et al., 2008). In addition, associated changes in gray matter volume (May, 2009), impaired adaptive cerebral hemodynamic mechanisms (Silvestrini et al., 2004), and habituation deficiency (Coppola et al., 2005) have been described. Thus, migraine should be considered a brain disease and not simply a recurrent acute pain syndrome.

The brain is a central organ of stress (McEwen and Gianaros, 2011). The brain determines what is stressful or potentially stressful and initiates responses that could be in the form of behavioral and/or physiologic responses that could be either adaptive or maladaptive. Brain responses are mediated via the autonomic nervous system and neuroendocrine mechanisms. In this context, allostasis is the ability to protect the body through increased activity of mediators that normally promote adaptation (McEwen and Stellar, 1993), and allostatic load and overload refers to the wear and tear on the systems (including the brain) that normally support adaptation and normal function as a result of repeated stress and/or allostasis. This conceptualization has a number of advantages: first, it emphasizes that the mediators that help the organism survive can also contribute to pathophysiology; second, it incorporates the effects of health-related behaviors such as diet, exercise, and physical activity; third, it...
takes into account the effect of secondary behaviors (e.g., smoking and substance abuse) that are often triggered by stressors and that also activate and often dysregulate the same mediators. In the context of modeling brain disorders in the framework of allostatic load, allostatic load is illustrated by reduced hippocampal volume and altered white matter integrity in type 2 diabetes (Gold et al., 2007; Yau et al., 2010), in chronic inflammation (Marsland et al., 2008a, 2008b), and in major depression (Sheline et al., 1996), by metabolic syndrome associated with bipolar disorder (Brietzke et al., 2011b) and by alcohol-induced dopamine deficiency in the mesolimbic system that is due to a growth-derived neurotrophic factor (GDNF) deficiency (Brietzke et al., 2011a). Such alterations in systemic and brain physiology modulate and change brain function and structure in the developing and adult brain (Ganzel and Morris, 2011; McEwen, 2002, 2007).

Allostatic load is not an entity unto itself but is defined by specific system responses. Different disease states (including subtypes of disease) may have different types or intensities of "stressors" that may contribute to the allostatic load. Multiple...
systems may be targeted, including the brain (e.g., prefrontal cortex in drug dependence [George and Koob, 2010]), or there may be changes in systemic metabolic networks affecting brain function and mood (McIntyre et al., 2007). Adaptive processes normally come into play with the onset of a stressor and may be measurable in some physiological responses (e.g., circulating catecholamines or glucocorticoids). Under normal circumstances, the adaptive process habituates to repetitive stimuli. While the consequences of an individual stressor may be subtle, changes at the cellular and systems levels that then accumulate over time can result in a new steady state that may be adaptive (allostasis) or maladaptive (allostatic load). As summarized elsewhere (McEwen and Wingfield, 2003), allostatic load and its more extreme form, allostatic overload, are even seen in animals in the wild, where they can play adaptive roles (e.g., bears putting on fat for the winter as an example of allostatic load that occurs when energy demand exceeds supply; allostatic overload is illustrated by migrating salmon dying after mating because of excess glucocorticoids).

In the case of a condition like migraine, it is the internal state of dysregulation as depicted in Figure 3 that creates an allostatic load with consequences for brain, behavior, physiological regulation, and systemic physiology that is maladaptive and progressively damaging in a feedforward cascade. This cascade is characterized by (1) alterations in normal homeostatic mechanisms (e.g., altered sleep, abnormal autonomic function), (2) failure to habituate to repeated stressors of the same kind, (3) failure to shut down the stress response in a normal manner, and (4) altered or inefficient response to stress that eventually leads to compensatory increased responses to other mediators at the cellular level (e.g., central sensitization, chronification, and stroke). These concepts will be discussed in the following sections of this paper. There are similar examples of such dysregulation on brain systems in other conditions, such as the effects of chronic opioids on brain systems at a cellular/receptor level (Gintzler and Chakrabarti, 2004), as well as spinal morphology (Skil-Tavron et al., 1996) and alterations in behavior, including addiction (Nestler, 2004) and other aspects of brain function and brain morphology (Upadhyay et al., 2010). In migraine, the disease state alters brain function and structure, and repeated attacks can lead to disease progression, transformation, or chronification (see Migraine Progression and Transformation, below). This review is an analysis of migraine, a vexing disorder that affects many individuals, but it is also a paradigm for understanding allostatic interactions in other clinical disorders.

Allostatic load resulting in cumulative physiological dysfunction has been considered in other diseases (McEwen, 2003, 2004), as well as in chronic pain (see Allostatic Load and Other Pain Conditions, below). Specific examples of the latter conditions (McEwen and Kalia, 2010) include arthritis (Von Korff et al., 2009) and fibromyalgia (Martinez-Lavin and Vargas, 2009). In the latter, for example, early onset of depression or anxiety disorders correlated with increased risk of adult-onset arthritis, suggesting that psychological stressors may initially affect the brain and may contribute to a nonbrain disease state. As discussed in the following sections, migraine offers a unique model of the effects of allostatic load on a primary brain disorder.
that includes the following: (1) it is a repetitive brain attack; (2) it shows progression and transformation from acute to chronic forms; (3) it alters the function and structure of multiple brain systems; (4) it can be worsened by medication overuse; and (5) the feedforward cascade is a summation of a number of factors (viz., frequency, pain, associated symptoms) that results in a viscous cycle that may increase the allostatic load. Altered allostasis in migraine is also a consequence of multiple processes, including biological (e.g., gender [Weitzel et al., 2001], genetic [Maher and Griffiths, 2011]), psychological (e.g., depression, anxiety [Casucci et al., 2010]), or social (e.g., household income [Lipton and Bigal, 2005]) in nature.

**Allostatic Load Criteria and Migraine**

As explained previously, allostatic load is the biological consequence (alterations in structure, function, or both) of chronic exposure to repeated or chronic stress conditions. We propose that headaches, foremost migraine, are a disease of allostatic load, with many of the characteristics of migraine fulfilling criteria that lead to allostatic load. These criteria will be elaborated below.

**Repeated Frequency of Stress Response to Multiple Stressors**

In episodic migraine there is a stress response to multiple headaches, which may themselves be triggered by stressors. Specific stressors associated with migraine include psychological/emotional (e.g., anxiety) and physiological (e.g., noise, food, odors, bright light). Perceived stress is what migraineurs list as the most common trigger of their attack (Sauro and Becker, 2009).

**Failure to Habituate to Repeated Stressors of the Same Kind**

Repeated migraine attacks can act as stressors and lead to a vicious cycle. Failure to habituate to physiological stimuli in the interictal period is well known. For example, abnormal habituation to stimuli is observed in migraine (Afra et al., 2000; Coppola et al., 2009; Schoenen et al., 2010; Wang and Schoenen, 1998), although in some types of migraine (viz., familial hemiplegic migraine), there is increased habituation (Hansen et al., 2011). Although the underlying mechanism(s) is unclear, it has been proposed that lack of habituation in migraine may reflect increased neuronal excitability, decreased inhibition, or decreased preactivation levels.

**Dysregulation of Normal Adaptive Responses**

In migraine, both central (brain) and peripheral processes are altered. The interictal brain is hyperexcitable in migraine, and there is a lack of habituation in neuronal information processing (Burstein et al., 2010; Chen et al., 2011; Coppola et al., 2009). This concept applies to both migraine chronification and migraine regression. Chronification of migraine, in which headaches become more frequent (>14 headache days/month), is a result of abnormal repeated stressors and use or overuse of certain medications (e.g., triptans, opioids) and is likely to be exacerbated by genetic factors. Chronification of migraine is suggestive of progressive maladaptation of the brain. Elimination of stressors may diminish chronification, as reported in women whose menstrual periods were effectively controlled by hormonal preventives, leading to a reversal from chronic migraine to episodic migraine in nearly 60% of individuals [Calhoun and Ford, 2008]. Similarly, exercise can diminish the frequency of migraine attacks [Malpass, 2011]. It should be noted that although there are no known mechanisms for migraine transformation, a number of defined stressors may contribute to this, including childhood abuse [Tietjen and Peterlin, 2011], socioeconomic status/social stress [Chyu and Upchurch, 2011], and posttraumatic stress disorder (PTSD) [Peterlin et al., 2011].

Given the above points, we argue that migraine is perhaps an “ideal” brain allostatic load disease model. The allostatic load associated with migraine arises from the disruption of behavior and dysregulation of adaptive physiological systems that appears with severe headache pain and subsequent responses. Because migraine affects behavioral and systemic health for a significant portion of the patients’ lives (>15 years [Kelman, 2006]), it is a compelling model of increased allostatic load (McEwen and Gianaras, 2011). If studied more systematically with this approach in mind, such thinking may provide new approaches to modulating or treating the condition, including the definition of a migraine allostatic load index (Juster et al., 2011).

What differentiates tension-type headaches (TTH) (http://ihsm-classification.org), the most prevalent primary headache condition [Jensen, 1999], from migraine includes: usually bilateral, not aggravated by routine, physical activity; only one of the symptoms related to sensitivity to sound, light, or smell; and few autonomic symptoms (nausea and vomiting). The same allostatic model may be applied to TTH, because the disease may produce significant changes in brain function and structure: altered gray matter volume in pain processing areas (Schmidt-Wilcke et al., 2005), chronification (Ashina et al., 2010), impaired pain modulation (Buchgreitz et al., 2008), and central sensitization (Filatova et al., 2008). Allostatic load and other pain conditions are discussed in the Allostatic Load and Other Pain Conditions section, below.

There are two major processes relating to allostasis in migraine: (1) adaptive (allostatic) responses to each migraine attack and its perimigraine phenomena (see Figure 2) and (2) maladaptive responses (allostatic load) over time with disease modification (i.e., progression or chronification). Major adaptive and maladaptive perturbations of brain and body systems occur in migraine in a number of ways. These include pain (Kelman, 2006), cardiovascular changes (Melek et al., 2007), and immunological changes (Pradalier and Launay, 1996) that over time lead to an altered brain state characterized by increased cortical excitability, changes in brain morphology, and changes in behavior. In this context, the brain “is the key organ of stress processes. It determines what individuals will experience as stressful, it orchestrates how individuals will cope with stressful experiences, and it changes both functionally and structurally as a result of stressful experiences” (McEwen and Gianaras, 2011). Better understanding the cascading pathophysiological changes in brain structure and function with the progression of migraine attacks may contribute to an improved understanding of full nature and consequences of this condition that frequently affects an individual’s brain and body.
Migraine in the Context of Allostatic Load: Reverberating Consequences

As noted above, migraine fits an allostatic load model in a number of ways. In this section we evaluate pathological changes in brain systems that may take place in the condition that contribute to the allostatic changes in migraine, including that migraine attack is a stressor, that the perimigraine events may contribute to alterations on brain systems, and that alterations in brain function and structure may occur as a consequence of repeated migraine attacks (see Figure 4). The lack of a normally responsive allostasis (i.e., efficient turning on and shutting off of responses) in migraine results from a constellation of processes that include disease-related pathophysiology (e.g., central sensitization, chronification, stroke), treatment effects or endogenous hormonal changes (e.g., medications that may contribute to chronification), and alterations in normal homeostatic mechanisms (e.g., altered sleep, abnormal autonomic function).

Stress and Migraine

Migraine is itself a stressful event. Migraine is a continuum of processes that precede and succeed the headache phase and as such should be considered as a multi-event process around the headache itself (Figure 4). Stressful experiences related to activities of daily living (i.e., emotional and physical) may trigger migraine (Sauro and Becker, 2009) in a high percentage (nearly 70%) of individuals (Theeler et al., 2010). Between 50% and 70% of subjects show significant, substantial, meaningful temporal correlations between their daily levels of stress and their daily migraine activity (Holm et al., 1997). Individuals respond to migraine stressors in various ways. Some responses may be considered as protective, involving sensory avoidance (e.g., photophobia [Purdy, 2011]) or sleep (Herbert and Holzer, 2002; Sahota and Dexter, 1990). Others reflect modulation of underlying physiological responses, such as activating protective responses associated with neurogenic inflammation that may be associated with migraine (Herbert and Holzer, 2002) or decreasing physical activity (Kelman, 2006). However, in all cases these responses may be overwhelmed as a viscous cycle of repeated stress continues to either alter, or perhaps damage, the brain, both structurally and functionally.

Intermittent and Persistent Modulators in Migraine

Migraine should not only be considered a process in which acute stressors “attack” the brain. Some of these insults may produce effects after migraine attack ends. Indeed, accumulating evidence suggests increased alterations in brain with migraine (see Brain Regions in Migraine: Targets of Allostatic...
Load, below) particularly with increased frequency or chronic migraine (Kruit et al., 2010). One example is the effects associated with aura. Patients with aura have more deleterious effects on their brains than those without aura (Wolf et al., 2009). Aura may be a subjective symptom associated with cortical spreading depression (CSD). CSD is a process in which a wave of spreading depolarization spreads through gray matter. Although it is unclear whether cortical spreading depression occurs in all migraine patients, because it may be subclinical, in animal models CSD produces swelling of neurons, distortion of dendritic spines, a large change of the slow electrical potential, and silencing (depression) of brain electrical activity. While there is an acute reversal or recovery of the process (clinically manifest in migraine with aura), subclinical events may contribute to underlying brain dysfunction with persistence of changes (Fioravanti et al., 2011). In familial hemiplegic migraine mice mutants, there is an increased susceptibility to CSD, and spreading depression is observed in cortex, basal ganglia, diencephalon, and hippocampal regions (Eikermann-Haerter et al., 2011).

CSD may induce spreading ischemia (Dreier, 2011). Somewhat related to the potential alterations on brain systems induced by CSD (i.e., neuronal death [Sadeghian et al., 2011]) is the increased incidence of subclinical brain lesions or stroke associated with migraine, particularly in migraine with aura (Kruit et al., 2010; Pezzini et al., 2007). This is an example of a feedforward allostatic load process associated with migraine. The process may result from platelet activation or an altered endothelial or coagulopathic state (Cavestro et al., 2011; Pezzini et al., 2007). While thrombosis and migraine may be comorbid, the usually microthrombotic events contribute to microinfarcts in this population and also major strokes, usually occurring in the posterior circulation.

**Brain Functional Disruption**

Increased responses to sensory stimuli in migraineurs are observed interictally and include pain (allodynia), phonophobia, photophobia, and osmophobia. All of these changes are as a consequence of maladaptation with the disease. With repeated attacks there is evidence of central sensitization of sensory systems. Acute allodynia (pain to a normally nonnoxious stimulus) is present in over 50% of patients; interictal allodynia is present in over a quarter of patients, greater still in patients who have aura (Lovati et al., 2008). The lowering of the pain threshold with repeated attacks may then allow for further attacks that contribute to chronification that is mediated in part by medication overuse (Zappaterra et al., 2011). During the interictal period, episodic and chronic migraineurs are more sensitive to thermal stimulation than nonmigraine controls (Schwedt et al., 2011). In children with migraine, quantitative sensory testing to tonic heat applied to the trigeminal area shows increased sensitivity (Zohsel et al., 2006). Thus, alteration in sensory processing reflects changes in brain systems that are a consequence of migraine load. Some have suggested that cutaneous allodynia is associated with migraine progression (Bonavita and De Simone, 2010). Other systems also show central sensitization even during the interictal period: phonophobia, osmophobia (Sjöstrand et al., 2010), and photophobia (Purdy, 2011). Abnormal brain activity is present in studies of allodynia (Burstein et al., 2010), olfactory hypersensitivity (Demarquay et al., 2008), and photophobia (Denuelle et al., 2011), all showing increased excitability. Such changes point to significant functional rewiring of the brain.

**Migraine Progression and Transformation**

Perhaps disease progression (increased frequency of attacks), transformation, or chronification (transformation from episodic to chronic migraine) of the brain state from low-frequency episodic migraine to high-frequency episodic migraine and then to chronic migraine (Bigal and Lipton, 2011) is the sine-qua-non of a measure of allostatic load in this clinical condition. About 6% of migraineurs progress to high-frequency episodic headaches, characterized by 105–179 headache days/year (Bigal and Lipton, 2008). Three percent of individuals in the general population with infrequent episodic headache progress to chronic daily headache (CDH) each year, and approximately 2.5% of patients with episodic migraine develop new-onset chronic migraine (Manack et al., 2011). Given the approximately 8 per 1000 of the population (Lyngberg et al., 2005), or a one-year prevalence of episodic migraine in the US of nearly 12% (Lipton et al., 2007), these percentages translate into millions of patients at risk for progression or transformation. In addition, given the lack of a specific marker, these numbers may be underestimated. Progression may be due to mechanisms generating the migraine attacks or to the consequences arising from the attacks (Aguggia and Saracco, 2010). This is a typical model for brain-induced maladaptation to stress that is the establishment of an “allostatic state” of elevated and dysregulated activity of mediators that normally produced adaptation. From a biological point of view, neural systems have become less responsive to treatments, more sensitive to stressors, and overall less adaptive to normal activities of daily living (Raggi et al., 2010).

**Downstream Effects of Brain Changes on Systemic Physiology**

Migraine can also produce effects that influence systemic physiology as well as the brain (e.g., insulin dysregulation, leptin, ghrelin, inflammation). These systemic mediators of allostatic load may have effects in the periphery and in the brain and may also interact to regulate each other, resulting in nonlinearity of effects (McEwen, 2006a, 2007). Two examples are alterations in cytokines and insulin resistance, which are briefly discussed here. Proinflammatory cytokines are involved in migraine (Bockowski et al., 2009). For example, significant increases in IL-6 are observed in migraine (Gergont et al., 2005), and increases in brain-derived neurotrophic factor (BDNF) (Tanure et al., 2010) during migraine attacks have been reported in migraine patients. The roles of cytokines such as IL-1 seem to be many, including the observation that IL-1 stimulates CGRP release in the trigeminal ganglia cells (Neeb et al., 2011). Such insights are important because therapies can alter cytokine levels (Hirfanoglu et al., 2009) that may correlate with the clinical response and treatments targeted in this area, including anti-leukotrienes (Ricciioni et al., 2007). Such pharmacotherapeutic approaches have been suggested in other stress-related disorders (Covelli et al., 2005). In the second example, insulin resistance is reported in migraine patients (Guldiken et al., 2008). In one report, migraine occurred with the onset of...
non-insulin-dependent diabetes mellitus (NIDDM), suggesting that a metabolic insult contributed to the CNS manifestation of headache (Spill and Szydlowska, 1997). Impaired tolerance to glucose is present during migraine attacks (in patients who acted as their own controls) (Shaw et al., 1977). Such data, taken together with more recent information, suggest specific changes related to hyperinsulinemia in migraine (e.g., elevated levels of glucagon-like peptides and leptin, even in nonobese female migraineurs [Barmecker et al., 2010]). Targeting such risk factors that are easily measured may offer new therapeutic opportunities.

Disturbance of the autonomic nervous system is a primary characteristic of migraine, and some authors have suggested an underlying chronic sympathetic dysfunction in the disorder (Peroutka, 2004). Spontaneous baroreflex sensitivity and heart rate variability (HRV) are different in migraine patients compared to healthy controls (Nilsen et al., 2009). Neural systems, including the prefrontal cortex, control parasympathetic control of the heart via the vagus nerve and also regulate inflammation (Thayer, 2009); in addition, decreases in heart rate variability are associated with a variety of changes (e.g., increased proinflammatory cytokines, acute phase protein, increased cortisol, increased fasting glucose), all of which relate to increased allostatic load.

Migraine is associated with alterations in sleep (Rains et al., 2008). In chronic migraine, altered hormone secretion has been reported for prolactin (decreased nocturnal peak), melatonin (delayed nocturnal peak), and cortisol (increased concentrations) (Peres et al., 2001), suggesting that the condition has produced changes in circadian regulation. Sleep deprivation and circadian disruption is itself a source of stress and allostatic load (Spiegel et al., 1999). “The way sleep impacts next day mood/emotion is thought to be affected particularly via REM-sleep, where we observe a hyperlimbic and hypoactive dorsolateral prefrontal functioning in combination with a normal functioning of the medial prefrontal cortex, probably adaptive in coping with the continuous stream of emotional events we experience” (Vandekerckhove and Cluydts, 2010). Indeed, migraine (along with disorders such as depression and gastric ulcers) is an independent predictor of excessive daytime sleepiness (Stroe et al., 2010). The basis for this may be an abnormal (reduced) arousal index in rapid eye movement (REM) sleep, which implicates dysfunction in hypothalamic and brainstem regions (Della Marca et al., 2006). Abnormal sleep or sleep restriction can have negative consequences for brain function and peripheral physiology (Kim et al., 2007), including increased appetite and energy expenditure, increased levels of proinflammatory cytokines, decreased parasympathetic and increased sympathetic tone, increased blood pressure, increased evening cortisol levels, and elevated insulin and blood glucose (McEwen, 2006b). Clearly, sleep disturbances and migraine (both allodynic and nonallodynic) have complex interactive effects on each other (Lovati et al., 2010) that suggest that implementing congruent therapeutic approaches may be of significant importance.

**Pharmacological Disruption of Allostasis**

Medications may be allostatic moderators or exacerbators. In migraine, the overuse of triptans and opioids seems to induce or contribute to chronic migraine (Bigal, 2009). Corticotrophic and somatotrophic functions are significantly impaired in chronic migraine medication overuse (CM-MOH) patients: after human corticotrophin-releasing hormone (hCRH) administration, ACTH and cortisol concentrations are significantly higher in CM-MOH cases than in controls (Rainero et al., 2006). Drugs such as sumatriptan induce a significant decrease of ACTH, cortisol, and prolactin concentrations, both in patients with migraine and in controls (Rainero et al., 2001). Acute subconscious administration of sumatriptan activates the pituitary-adrenal axis: significant increases in β-endorphin and cortisol concentrations are reported across all subjects receiving sumatriptan (Facchinetti et al., 1994), and these would produce secondary effects. Migraine medications may also alter sensory processing. For example, the administration of sumatriptan to healthy volunteers produces abnormal psychophysiological (diminished pleasantness) and fMRI signal (in anterior insular, lateral orbitofrontal, and anterior cingulate cortices and medial thalamus) changes that are observed only following sumatriptan, not saline (Krämer et al., 2007).

In addition to exogenously administered drugs, endogenous chemical (hormonal) milieu can also be a significant issue in migraine. About 17% of women versus 6% of men get migraines (Rasmussen et al., 1991). Perhaps the best example of induced stressors on brain systems is the female menstrual cycle (Farage et al., 2008). Menstrual migraine (MM) is common in women and may relate to hormonal modulations in the GABA-A receptors decreasing normal inhibitory control (Epperson et al., 2002). Menstrual migraine may be more difficult to treat than nonmenstrual migraine in women, suggesting a role of induced resistance as a result of their hormonally induced migraine. Menstrual migraine may also be a contributor to the evolution of chronification of headache (Lay and Broner, 2008). Conversely, elimination of MM with the use of hormonal preventive medications can be achieved in a large percentage of patients, and this further decreases chronic migraine that is present in over 90% of women (Calhoun and Ford, 2008). It would thus seem that the alterations induced in brain systems that induce menstrual migraine may add to the allostatic load/overload. Estrogen (estradiol) and progesterone (via allopregnanolone) affect neuronal systems with opposite effects, with estrogen generally being excitatory—enhancing glutamatergic systems and progesterone inhibition—through GABA systems (Finocchi and Ferrari, 2011). Progesterone usually antagonizes estradiol in synaptic remodeling in brain regions, including the hippocampus (Wong et al., 2009). Increased brain sensitivity in women includes catamenial epilepsy, in which hormonal changes, particularly estrogen, contribute to increased seizures (Guille et al., 2008). A similar process may take place in migraine. The effects of estradiol on brain systems is complex and may induce excitatory-induced neuronal changes (Blacklock et al., 2005) but may also be protective of adrenal steroids (Garcia-Segura et al., 2007). The higher prevalence of stress-related disorders in women may relate to estrogen effects on brain systems that have high levels of both genomic and nongenomic estrogen receptors (viz., hypothalamic, amygdala, hippocampal formation, brainstem, thalamus, and entorhinal cortex, including the limbic system [McEwen and Milner, 2007; Osterlund and Hurd, 2001]).
Secondary Changes in Brain Function that Impact Allostatic Load

Reports of cognitive testing in adult migraineurs and controls have yielded inconsistent results, but migraine patients with aura experience more neuropsychological deficits than migraine patients without aura (O’Bryant et al., 2005). Diffusion tensor imaging data shows changes in gray matter suggestive of a possible basis for cognitive dysfunction (Rocca et al., 2006). However, migraine has been reported to be associated with lower cognitive processing and intelligence quotient and verbal intelligence quotient scores (Parisi et al., 2010) in some studies (De Ciantis et al., 2008; Kalaydjian et al., 2007), whereas others reporting on the lifetime diagnosis of migraine show that it is not associated with cognitive deficits in middle age (Gaist et al., 2005).

The brain responds in different ways to different stressors that seems to be age dependent (see Ferriero and Miller, 2010). There are times of major changes in the developing brain during which stress affects adaptation. Early life stressors may program stress circuits, thereby producing alterations in the neuroendocrine phenotype with subsequent maladaptation, resulting in susceptibility to disease or altered responses to treatments (Markham and Koenig, 2011). Migraines affect preadolescent children and become more manifest after puberty (Bigal and Arruda, 2010). Migraine often lasts less than 1 hr in young children. In some children, progression is present (Bigal and Arruda, 2010). Chronic daily headache affects 2%–4% of adolescent females and 0.8%–2% of adolescent males (Cuvellier et al., 2008; Wang et al., 2006). Treatments may also alter cognitive and executive function in childhood (Pandina et al., 2010) and may also be considered as potential modifiers of allostatic load. Predisposing factors to migraine are not well defined. Some data suggest that conditions such as seizures may be linked with migraine later in life (Bianchin et al., 2010). However, a growing body of literature suggests that early life stress may be associated with migraine (Tietjen and Peterlin, 2011) and may be a risk factor for migraine chronication. The long-term consequences of migraine on the developing brain are not known, but even prenatal exposure to stressors and exposure to stressor in childhood may alter the “trajectory of brain development” (Markham and Koenig, 2011). Regions involved in cognitive and affective functions that undergo prolonged postnatal development (frontal regions) and stress (amygdala) are vulnerable targets that may be affected as a result of early life stress (Pechtel and Pizzagalli, 2011).

Brain Regions in Migraine: Targets of Allostatic Load

A central role of the brain in stress and adaptation relates to how specific regions respond and, in doing so, may undergo stress-induced structural and/or functional changes (McEwen, 2007). Although it is now well documented that migraine is associated with structural (May, 2006) and functional (ictal hyperalgesia and allodynia and interictal neural excitation [Marcus, 2003]) changes, recent research has implicated changes in the very regions noted in the general stress response. Stress or cytokine-induced release of glucocorticoids normally produce immunosuppressive and anti-inflammatory changes but may have other effects in the brain (Sorrells et al., 2009). Chronic elevated levels of cortisol impair synaptic plasticity, diminish neurogenesis and spinal density, and may result in dendritic atrophy (McEwen and Magarinos, 2001) and dysregulate glutamate neurotransmission (Iyo et al., 2010). Such changes may contribute to alterations in brain regions such as the hippocampus that may manifest as syndromes associated with migraine, such as depression (Musazzi et al., 2011). Data supporting increases in stress hormones including noradrenaline and cortisol in response to stress in migraineurs have been reported (Leistad et al., 2007), thus providing a basis for specific brain-induced changes in migraine. Migraine is considered to be a hyperexcitable state, and increases in excitatory neurotransmitters during the interictal period may reflect such a state (Prescott et al., 2009).

Of the brain regions studied, the hippocampus, amygdala, hypothalamus, and prefrontal cortex seem to play an important role in this process. Some regions such as the hippocampus and prefrontal cortex are responsive to the repeated action of glucocorticoids, together with excitatory amino acids and other mediators, on the brain region that affect hippocampal function and structure (McEwen, 2007). The hippocampus has been a model for understanding the effects of stress on neuronal plasticity and allostatic load (McEwen, 2001). In stressful conditions, neurogenesis and apoptosis in hippocampus are suppressed (Kubera et al., 2011). Such a situation could be operating every time an individual has a migraine attack. The process may involve other brain regions that have connections with the hippocampus, including the hypothalamus and the amygdala. For example, with unpredictable stress, inhibitory input to neurons involved in the hypothalamus are reportedly suppressed, leading to dysregulation of the axis and potentially overexposure of the brain to glucocorticoids (Joëls et al., 2004) and may result in dendritic atrophy (McEwen and Magarinos, 2001) and dysregulate glutamate neurotransmission. In addition, a putative role for the amygdala in allostatic load, related to anticipatory anxiety, has been suggested (Schulkin et al., 1994). The involvement of the amygdala in migraine has been supported by a number of other reports, including changes related to cortical spreading depression (Dehbandi et al., 2008); chronic migraineurs show decreased amygdala volume (Valfré et al., 2008). Its role in this may relate to the high levels of anxiety or fear in patients with migraine (Casucci et al., 2010), particularly in those suffering from chronic daily migraine (Dodick, 2009).

Given the role of the hypothalamus in autonomic control (viz., neuroendocrine, homeostasis, pain modulation, sleep-wake cycle, food intake), its overall role in the stress response, and its connections with multiple brain regions, the hypothalamus is central to the effects of stress on the brain (Baumann and Turpin, 2010). Measures of altered hormone are reported in chronic migraine patients (including prolactin, cortisol, and melatonin), which is indicative of abnormalities in circadian biology (Peres et al., 2001). Thus, the hypothalamus may control systems that could have many functional implications through such alterations in hormone and autonomic function, impinging on many organ systems, including the brain. One example is that of the association of obesity and migraine (Peterlin et al., 2010). Alterations in hypothalamic control may be manifest and contribute to both syndromes, because
alterations in neurotransmitters and hypothalamic peptides may be abnormal in both conditions.

Uncoupling Allostatic Overload in Migraine: Adaptive Plasticity

Given that there may be multiple stressors that contribute to the allostatic load (Figure 4) and increased disease burden with chronification (Figure 5), ideally, one could evaluate and quantify each and provide a rational approach to devolving, uncoupling, diminishing direct inputs onto systems that modulate the allostatic load and directly impact those systems that have been altered. A new approach to defining and measuring the relative contributions and their cumulative or additive effects would bring opportunities to improve diseases such as migraine where we only have a limited response in terms of preventing the attacks and/or treating chronic migraine. A new approach to defining and measuring the relative contributions and their cumulative or additive effects would bring opportunities to improve diseases such as migraine where we only have a limited response in terms of preventing the attacks and/or treating chronic migraine. Specifically, the following principles would seem to be salient: (1) intervene as early as possible to prevent the negative cascade; (2) top-down interventions (e.g., exercise, social support, stress reduction, diet, etc. [see McEwen and Gianaros, 2011]) to help reestablish systemic and brain “balance,” which may include plastic changes and neuronal connectivity (Castrén, 2005); (3) pharmacotherapy may contribute to the top-down process and may be more efficacious in the context of other modulators of allostatic load. One example in support of interactive effects is the use of antidepressants in the context of a positive therapeutic environment and may diminish this state may be useful in migraine prevention. Currently, topiramate is the only FDA-approved drug for migraine prevention (Silberstein et al., 2007). Evidence for a specific mechanism related to this is suggested to act by a kainate receptor antagonism on brain system, as well as the trigeminovascular system (Andreou and Goadsby, 2011). Magnetic resonance spectroscopy (MRS) studies support this notion, because topiramate may alter GABA levels in the brains of healthy subjects (Moore et al., 2006).

Network Modification

The notion that treatments alter networks through changes in functional and morphological connectivity is not novel. Progressive plasticity of neuronal systems (e.g., spine morphology, dendritic branching, etc.) by medications has been considered in other diseases such as depression. In the latter condition, therapeutic effects may be delayed and should be a focus of evaluation of treatment efficacy throughout the brain (Baudry et al., 2011). Thus, the clinical effects may include inducing altered neurogenesis in specific regions, such as the hippocampus, that may contribute to clinical improvement through blockade of stress signals (Warner-Schmidt and Duman, 2006). Furthermore, alterations in neuronal activity can elicit long-lasting changes in the synaptic strength transmission at excitatory synapses, and drugs or disease may modify dendritic spine density and thus synaptic contacts (Malenka, 2003). Such changes have significant effects on networks that can now be
evaluated using a technique in neuroimaging that measures multiple low-frequency changes in brain systems called resting state networks (RSNs) (De Martino et al., 2011).

Neurohormonal Tempering
Migraine generally improves after menopause or with hormonal therapies (Calhoun and Hutchinson, 2009). Neurohormonal modulation, including gonadal and glucocorticosteroids and insulin, clearly has implications on brain modification. For example, estrogen is known to be excitatory, and glucocorticoids also have excitatory effects throughout the brain (see above). Indeed, modification of repeated migraines induced by menstrual period has been reported to diminish migraine burden (Calhoun and Ford, 2008). Another example relates to the orexin (a neuropeptide released by the posterior lateral hypothalamus) system in augmenting treatment of sleep in migraine (Scammell and Winrow, 2011). However, some hormonal therapies may make migraine worse or add significant risks. For example, combined contraceptives (which have estrogen and progesterone) are contraindicated in migraine with aura and may induce ischemic stroke (Allais et al., 2009). Some migraine conditions improve after pregnancy (e.g., menstrual migraine) (Silberstein, 2001).

Inhibiting Neuronal Gain
Insights into the headache of migraine pain as it progresses from premonitory symptoms to the headache itself and then the persistence of the headache relate to progressive enhancement of neural assemblies from nociceptors in the trigeminal ganglion to the trigeminal nucleus and then thalamic and cortical regions (Burstein et al., 2010). This has been termed central sensitization. Early initiation of treatment seems to halt the migraine attack, whereas delayed treatments may not have any benefit (Burstein et al., 2004), stemming the negative feedforward cascade. In some ways, this is a metaphor for all other aspects of migraine treatments.

Modulating Brain Circuits with Neurostimulation
In recent years, a number of neuromodulation approaches have been used via various neurostimulation techniques in migraine (Dafer, 2010) that may alter neural networks. Most approaches are noninvasive (e.g., transcranial magnetic stimulation [TMS; Lipton and Pearlman, 2010]), whereas some are invasive (e.g., vagal nerve stimulation [Lenaerts et al., 2008] or deep brain stimulation for cluster headaches [Franzini et al., 2010]). Interestingly, some data suggest significant improvement, even in patients who have had migraine for years. It is assumed that TMS techniques alter neural connectivity through alteration in neural excitability.

Taken together, the above issues relate to modulating brain circuits and neuroconnectivity. Top-down strategies that control stress through targeted neurobiological mechanisms may progressively diminish allostatic load with expected improvement of symptoms (Figure 6). Clearly, the latter is dependent on “readjusted” neural networks, because brain function defines behavior.

Allostatic Load and Other Pain Conditions
Although we have focused on migraine as a model brain disease of allostatic load, we would suggest that similar abnormal allostasis may apply to chronic pain. Although a complete description of this is beyond the scope of this review, we provide a summary of processes relating to allostatic load that may be
observed in chronic pain. (1) Stress as an issue in chronic pain disorders is reported in the literature of fibromyalgia (Martinez-Lavin and Vargas, 2009) and pain associated with depression (Hammen, 2005). Fibromyalgia and migraine are common disorders and may have similarly underlying neuroendocrine dysfunction (Valença et al., 2009). Some chronic pain conditions are more likely in those who have had prior stress (e.g., childhood abuse [Schofferman et al., 1993]) or posttraumatic stress disorder (Defrin et al., 2010) or other lifetime traumas (Sledjeski et al., 2008). Some “evoked” stressors common to exacerbating both migraine and chronic pain conditions include environmental factors such as barometric change (Mukamal et al., 2009) or emotional stressors (Hertig et al., 2007). (2) The issue of underlying pathophysiology between chronic pain and migraine may have an overlapping feature in so-called chronic nociceptive pain, as observed in arthritis. Both structural and functional changes have been observed in patients with rheumatoid (Wartolowska et al., 2011) and osteoarthritis (Gwilym et al., 2010). These are progressive disorders that usually start off with pain (that may follow an injury) and then progress to osteoarthritis over years (Thorstensson et al., 2009). Thus, there are some parallels with the migraine model regarding the intermittent pain presentation that may show chronification. Such alterations may manifest both in chronic pain and in migraine as changes in emotional or cognitive processing (Apkarian et al., 2004). The underlying process of chronification from acute injury to chronic pain may have some parallels that include a feedforward process. (3) Chronic pain and migraine both demonstrate central sensitization (Wooff, 2011) and allodynia (Schwedt et al., 2011). In addition, intermittent pain may be common to diseases such as back pain, in which there is an underlying and continuous (albeit fluctuating) spontaneous background or ongoing pain, as well as exacerbations related to evoked stimuli (viz., mechanical, chemical).

Conclusions and Future Opportunities

The allostatic load model expands the stress-disease literature by proposing a temporal cascade of multisystemic physiological dysregulations that contribute to disease trajectories (Juster et al., 2010) in the brain and body. Allostatic load in migraine represents the cumulative effects of the disease, as well as its treatment, on brain systems with effects throughout the body via the neural and endocrine effects upon systemic physiology. As such, a number of important conclusions can be made. First, early interruption of a feedforward vicious cycle that involves not only the brain but also other systems of the body that can cause problems in key brain areas, as well as systemic pathophysiology, is a key component to diminishing allostatic load. Second, although current clinical practice for migraine frequently utilizes multimodal techniques (medication, stress reduction, etc.), these are rarely quantified. The allostatic model in migraine allows the implementation of a bio-psycho-social model that can be systematically measured to define how different systems interact to impact the allostatic load of the disease. Insights based on such research on the role of allostatic load in migraine may provide a foundation to improve health outcomes through methods that manage stress (Ganzel et al., 2010). Fortunately, the brain is a plastic organ, and adaptations can be brought about by treatments that alter allostatic load.

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