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Migraine: Maladaptive Brain Responses to Stress

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Abstract

Migraine offers a unique model to understand the consequences of repeated stressors on the brain. Repeated stressors can alter the normal response of physiological systems and this concept has been termed 'allostatic load'. In the case of the brain, the effects of repeated stress may lead to alteration in brain networks both functionally and structurally. As a result the brain responds abnormally to environmental conditions (psychological or physiological). Here we present an alternative perspective on migraine disease and propose that changes in brain states may occur as a result of repeated migraine attacks through maladaptive coping mechanisms. The cascade of these effects can lead to further deterioration of adaptation and thus lead to transformation or chronification of the disease.

Introduction

Migraine is a disabling primary headache disorder affecting millions of individuals, by some estimates 45 million Americans [1]. As a condition it is complex and may be considered in a continuum not only in terms of the peri-headache changes in episodic migraine but also the progression to high frequency and chronic daily headache. Thus it is a major perturbator of the brain systems in a number of ways. These include behavioral and/or physiologic responses such as pain [2], cardiovascular changes [3], immunological changes [4].

The responses to a migraine attack (e.g, pain, stress hormones, affective changes, nausea/vomiting etc) are mediated through increased activity of mediators that are in excess of normal adaptive processes [5, 6]. Over time these stressors could lead to an altered brain state characterized by increased cortical excitability [7], changes in brain morphology and changes in behavior [8–11]. Such stressors are typically repeated periodically in both episodic migraine and chronic daily headache. As a result the brain will responds abnormally to environmental conditions (psychological or physiological). If viewed in this context, pathophysiological changes in brain structure and function in migraine may contribute to an improved understanding of the condition that frequently affects individuals for a significant portion (>15 years [12]) of their lives.

Stress and Migraine

Stress as a trigger for migraine attackes is present in nearly 70% of individuals [13]. High levels of stress are reported in migraine patients, particularly in those suffering from chronic daily migraine [14]. Both endogenous (e.g., hormone) and exogenous (e.g., physical stressors (e.g., light) or psychological stressors stressors add to the burden of the disease. Emotional or physical trauma (e.g., abuse, particularly in childhood), socioeconomic or social stress [15] are examples of psychological stressors. Stressors could also be of physiological origin such as menstrual period in women. Some women experience menstrual migraines or their

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migraines around menstrual period could be more intense or even last longer. In addition, migraine is comorbid with numerous brain diseases that are associated with stress and a potential contributing factor (e.g., anxiety, depression [16]). Even in the pediatric population, stress plays and important role. Children with migraine have increased pulse rate, higher diastolic blood pressure and higher low-frequency/high-frequency ratio after a 5-min recovery from an emotional stressor [17]. When the frequency or severity of these stressors escalate, the protective adaptive responses (allostatic responses) that maintain a stable state for the brain become overused and dysregulated. As a result there is wear and tear on the brain ("allostatic load") which may alter brain networks both functionally and structurally. As a result the brain responds abnormally to stressors and reaches an altered state, in which both behavior and systemic physiology are altered in ways that can lead to further allostatic load, Figure 1.

Effects of Repeated Migraines on the Brain

Are there any biological consequences in the brain as a result of migraine attacks? While there is no clear answer to this question yet, there are multiple lines of evidence that suggest that the migraine brain is different compared to normal brain [18–21]. The migraine brain is hyperexcitable during the migraine-free periods between the attacks (interictal phase) [22–2425]. During the attacks the brain's response to some stimuli is abnormal. For example, in many patients light, smell or noise could exacerbate the migraine pain when they are experiencing an attack. Hyperexcitablity of the brain [7] could be due to a decrease in inhibitory neurotransmitters (e.g., GABA), or an increase in excitatory neuortransmitters (e.g., glutamate) in the cortical regions. Impaired or diminished habituatation to stimuli in the interictal period in migraineurs [26, 27] is another characteristic of migraine, which also supports maladaptive brain changes. Increasingly, evidence suggests abnormal inhibitory control of pain with migraine that may result from deficiencies in inhibition or increased facilitation [28]. A variety of stressful stimuli have been shown to affect pain sensitivity suggesting altered higher centers have a significant influence on pain modulation. Neural substrates mediating active versus passive emotional coping have been identified within distinct, longitudinal neuronal columns of the midbrain periaqueductal gray (PAG) region [29]. In addition to pain modulation [30]., the PAG has been implicated in responses to defensive and autonomic regulation [31].

The basal ganglia have also been implicated in migraine. In general, the basal ganglia play an important role in pain processing (reviewed in [32]). Migraineurs with more advanced forms of the disease, reduced response to noxious thermal stimulation in the caudate, putamen and pallidum associated with larger volume in caudate [8]. These may be explained by ongoing inflammation, enhanced iron accumulation or increased dendritic complexity. Hypometabolism in the caudate has been reported for familial hemiplegic migraine [33].

Decreased grey matter in anterior cingulate cortex [9, 10, 34] and insula [9, 10] in migraine patients has been reported. These changes correlate with the frequency of migraine attacks or duration of the disease [9, 10]. Decreased cortical gray matter volume in the cingulate cortex is reported in patients with depression [35] too. Interestingly, migraine is also associated with an increased rate of affective illness including depression [36] with patients who have higher frequency headaches as in daily chronic headache [37] at an increasing higher risk of depression.

Impairment of stress response adaptation has been associated with inactivation of the medial prefrontal cortex activity in rats [38]. Evidence of altered function in this area has been supported by fMRI studies of migraine patients stimulated with a painful heat stimulus showing increased activation in the perigenual cortex vs. healthy controls [39]. A connection

between stress and medial prefrontal cortical regions has also been reported in resting state functional connectivity studies of adolescents undergoing social stress: cortisol responsivity was shown to be correlated with "salience" network that includes the anterior insula and medial prefrontal cortex [40]. The region is involved in processing negative emotion including anxiety.

Conclusion

Migraine is considered a brain disease with widespread alterations in a number of distributed functions that include both cortical and subcortical systems. Multiple brain changes are reflective of alterations in the migraine brain that may be a result of the repetitive nature of the disease state, a predisposition in these patients, genetic factors or a combination of all of these. There is evidence for co-localized morphometric and functional cortical differences as a function of the number of to repeated migraine attacks [11] specifically in the response patterns in the sensory vs. affective processing regions in the brain. While response to acute stressors is mostly protective but chronic stressors do produce damage [41] and thus a model disease of allostatic load [42].

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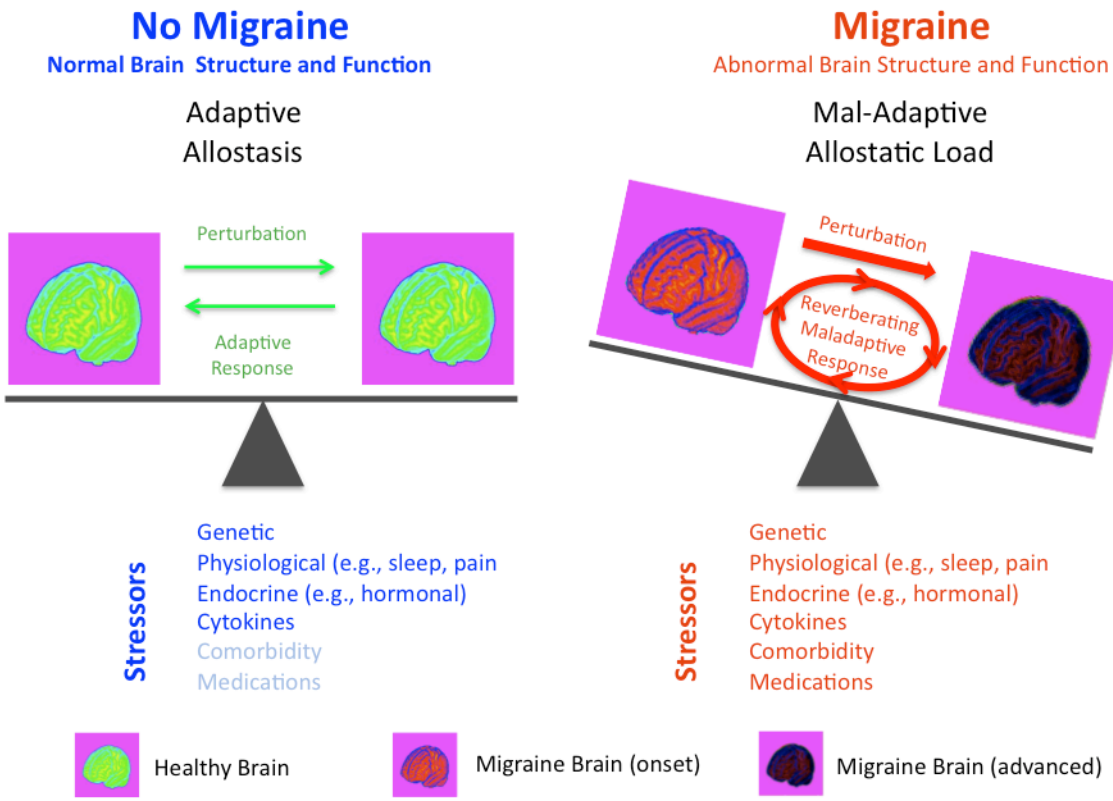

Figure 1.

Brain in the normal state responds adaptively (adaptive allostasis) to stressors ranging from physiologic to genetic in order to maintain the same brain state. In migraine the effect of stressors may be additive or cumulative and the brain's response to the same stressors becomes maladaptive and thus changes to the brain may happen changing state of the brain to a new state.