Fibromyalgia Syndrome: A Central Role for the Hippocampus—A Theoretical Construct
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Objective: A growing body of evidence implicates the central nervous system as playing a primary role in the diverse phenomena associated with fibromyalgia, including hyperactivity of stress systems and enhanced nociception. The objective of this review is to propose a unifying theory to explain a majority of these.

Findings: Stress exposure causes deleterious changes within the central nervous system, the hippocampus being particularly vulnerable. The hippocampus is perhaps best known for its role in memory and cognition, two functions which are impacted by elevated glucocorticoid levels such as occur in prolonged stress. The hippocampus also provides inhibitory drive to brain centers associated with the stress response, i.e., the hypothalamic paraventricular nucleus, central amygdala, and locus coeruleus. In addition, the hippocampus has been demonstrated to participate in nociception, a function positively correlated with the activity of hippocampal N-methyl-D-aspartate [NMDA] subtype glutamate receptors. A variety of stress-related hormones are known to enhance the activity of hippocampal NMDA receptors, thereby increasing excitatory neuro-transmission within the hippocampus. While the impact of stress-related hormones on hippocampal NMDA receptor function is adaptive in the acute scenario, exposure to chronic stress eventually leads to hippocampal dysfunction and atrophy secondary to excessive excitatory neurotransmission [i.e., excitotoxicity].

Conclusion: Fibromyalgia is characterized by abnormalities that appear to be related to hippocampal dysfunction, including hyperactivity of both corticotropin-releasing hormone neurons and the sympathetic nervous system, impaired declarative memory, and enhanced NMDA receptor-mediated nociception. It is therefore postulated that stress-induced, NMDA receptor-mediated dysfunction within the hippocampus plays a central role in the etiopathogenesis and clinical phenomena of fibromyalgia.