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Regulatory mechanism of performance in chronic cognitive fatigue

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ABSTRACT

Chronic cognitive fatigue is characterized by a sensation of long-lasting fatigue that impairs cognitive functions. Facilitation and inhibition systems in the central nervous system play primary roles in determining the output to the peripheral system, that is, performance. Sensory input from the peripheral system to the central nervous system activates the inhibition system to limit performance, whereas motivational input activates the facilitation system to enhance performance. The dysfunction of the facilitation system and central sensitization and classical conditioning of the inhibition system play important roles in the pathophysiology of chronic cognitive fatigue. Because the dorsolateral prefrontal cortex receives input from both the facilitation and inhibition systems to determine performance, metabolic, functional, and structural impairments of the dorsolateral prefrontal cortex induced by repetitive and prolonged overwork, stress, and stress responses contribute to the impaired functioning and cognitive performance that occur in people with chronic cognitive fatigue. This hypothesis of the regulatory mechanism of performance provides a new perspective on the neural mechanisms underlying chronic cognitive fatigue.

Introduction

Fatigue is defined as a condition or phenomenon of declined ability and efficiency of mental and/or physical activities caused by excessive mental or physical activities, or diseases or syndromes, and fatigue is often accompanied by peculiar sense of discomfort, desire to rest, and reduced motivation, which was referred to as fatigue sensation (translated from Japanese into English by M.T.) [1]. Many people complain of chronic fatigue: In Japan, more than one third of the general adult population complains of chronic fatigue [2]. Chronic fatigue impairs activities and contributes to various medical conditions, such as cardiovascular diseases [3], epileptic seizures [4], and death [5]. It would thus be of great value to clarify the mechanisms underlying chronic fatigue, in particular chronic cognitive fatigue that impairs daily cognitive functioning, and develop efficient treatment methods based on the understanding of mechanisms to overcome chronic cognitive fatigue.

Recently, behavioral, neurophysiological, and neuroimaging studies using functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG) have to some extent clarified the neural mechanisms underlying acute fatigue [6]: During acute physical fatigue, sensory input from the peripheral system to the primary motor cortex (M1) produces less motor output (supraspinal fatigue). This is a result of the supraspinal inhibition system increasing inhibitory input to M1 to limit recruitment of the motor unit or slow the motor unit firing rate in M1 [7]. In contrast, as active muscle fibers become fatigued, subjects progressively increase their voluntary effort, which increases motor output from M1 to compensate for physical fatigue until the task requires a maximal effort. This involves the supraspinal facilitation system which increases motor output from M1 to overcome physical fatigue [7–9].

Although the neural mechanisms underlying acute human fatigue have been clarified to some extent, our knowledge about the neural mechanisms underlying chronic human cognitive fatigue was limited. However, neurophysiological and neuroimaging studies in combination with subjective or a newly developed objective evaluation method of chronic fatigue have begun to clarify the mechanisms underlying chronic cognitive fatigue [10]. These suggest the involvement of abnormalities in the central nervous system, and these abnormalities seem to be the primary cause of fatigue sensation and impaired daily activities and performance in people with chronic cognitive fatigue. Because impaired cognitive performance is one of the most important complaints of people with chronic cognitive fatigue, it is of value to identify the central regulatory mechanism of performance in these people. In

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this article, a new conceptual hypothesis of the regulatory mechanism of performance in chronic cognitive fatigue is presented.

Facilitation and inhibition systems

During fatigue-inducing physical trials, as active muscle fibers become fatigued, participants progressively increase voluntary effort and increase the motor output from the primary motor cortex to compensate for physical fatigue [7,9]. Increased activation in the primary motor cortex has been observed in electroencephalography (EEG) [11,12], PET [13,14], and fMRI [15–18] studies, which matched the electromyography (EMG) signals [15] during fatigue-inducing physical tasks. These results indicate the existence of a facilitation system in the central nervous system.

Based on the results of electrophysiological and neuroimaging studies, we proposed a neural pathway or circuit, which represents the facilitation system, to increase the motor output from the primary motor cortex against physical fatigue [6]. The neural circuit or re-entrant loop that interconnects the limbic system, basal ganglia, thalamus, orbitofrontal cortex, prefrontal cortex, anterior cingulate cortex, premotor area, supplementary motor area, and primary motor cortex constitutes the facilitation system, and an increase in the motivational input to the facilitation system, mainly through the dopaminergic drive to the striatal–thalamic–frontal loop, enhances the supplementary motor area and then the primary motor cortex to increase motor output to muscles via the spinal cord during physical fatigue [6].

The facilitation system of mental fatigue has also been described in behavioral, physiological, and neuroimaging studies, during fatigue-inducing mental task trials [18,17,19–26]. A neural pathway or circuit that constitutes the facilitation system and enhances information processing to compensate for the effects of mental fatigue has also been proposed. The neural circuit or re-entrant loop that interconnects the limbic system, basal ganglia, thalamus, orbitofrontal cortex, prefrontal cortex, and anterior cingulate cortex constitutes this mental facilitation system [27]. The mental facilitation system is considered to share common neural substrates with the physical facilitation system [28,29].

Transcranial magnetic stimulation to the primary motor cortex during maximum physical task trials evoked a twitch-like increment in muscle force [8]. This increment indicates that, despite the maximal voluntary effort, the motor output from the primary motor cortex at the time of stimulation is neither maximal nor sufficient to drive the spinal motoneurons to produce the maximal muscle force, suggesting the existence and enhancement of an inhibition system during physical fatigue [9]. The existence and enhancement of the inhibition system during physical fatigue was also suggested in behavioral [30], electrophysiological [31], and neuroimaging [32–37] studies. The neural pathway from the group III and IV muscle afferents to the primary motor cortex that interconnects the spinal cord, thalamus, secondary somatosensory cortex, insular cortex, posterior cingulate cortex, premotor area, supplementary motor area, and primary motor cortex is considered to constitute the inhibition system that limits the descending motor output from the primary motor cortex during fatigue [6]. The existence and enhancement of the inhibition system during mental fatigue has also been suggested in recent behavioral [38,39], EEG [40,41], and MEG [21] studies, and the activated inhibition system causes impaired cognitive task performance [21].

Dysfunction of the facilitation system and central sensitization and classical conditioning of the inhibition system in chronic cognitive fatigue

Enhancement of the facilitation system, caused by psychological, behavioral, or physical triggers, against acute fatigue that improves performance under conditions required to maintain performance may be favorable. However, excessive enhancement of the facilitation system at the expense of functions may cause a dysfunction of this system and lead to further fatigue. Dysfunctions of the facilitation system lead to difficulties in driving the facilitation system. The motivation or voluntary effort enhances the facilitation system, while the further enhanced facilitation system causes further dysfunction of the facilitation system [42–44]. This may induce chronic or accumulated fatigue [10]. Therefore, it was proposed that chronic fatigue occurs due to a failure in the facilitation system [19,20]. In fact, people with chronic fatigue showed dysfunctions of the facilitation system during motor imagery task trials [42] as well as during cognitive task trials [45,46], possible resulting from metabolic, functional, and structural damage to the basal ganglia [19], orbitofrontal cortex [47], prefrontal cortex [47,48], and anterior cingulate cortex [47], all of which are part of the facilitation system.

The enhanced activation of the inhibition system may be centrally sensitized and classically conditioned by repetitive and prolonged overwork and/or stress, because an animal model of fatigue was established using central sensitization, and classical conditioning methods [49] as well as the central sensitization and the classical conditioning of the inhibition system, were successful in humans [50]. It seems that the central sensitization and classical conditioning of the inhibition system play an important role in the development of severe and long-lasting fatigue, in particular chronic cognitive fatigue [10]. This excessive response of the inhibition system seems to be closely associated with the pathophysiology of chronic cognitive fatigue [10].

Dorsolateral prefrontal cortex and performance

The dorsolateral prefrontal cortex (DLPFC) is the brain region associated with the sensory processing [51,52], emotional processing [53–55], attention [56,57], working memory [58–61], planning [62], self-control [63], and decision making [64,65], suggesting that this brain region has a pivotal role in determining cognitive performance.

In addition to having a role in cognitive control and behavior, the DLPFC has a central integrative function in motor control and behavior. This brain area has diverse neuronal connections to several different motor regions such as the premotor cortex, supplementary motor area, cerebellum, and basal ganglia [66–68], and alters motor output from the premotor cortex [69–72]. In addition, the DLPFC contributes to the motor selection decision [73]. Therefore, this brain region also has a crucial role in determining physical performance.

The DLPFC is related to the decisional processes, facilitating anticipatory behavior (facilitation), and preparing behavior by inhibiting unwanted responses (inhibition), depending on the current external environmental and internal circumstances [74,75]. Of note, this brain region has both facilitation and inhibition roles in determining the performance according to the individual's situation. In addition, this brain area is involved in both the facilitation and inhibition systems.

Fatigue and the dorsolateral prefrontal cortex (Fig. 1)

The central compensation mechanism that regulates physical fatigue was examined using an MEG study [74]. In this study, participants performed a fatigue-inducing physical task session in which they performed repetitive grips of the hand at maximal voluntary contraction levels, and before and after the session, imagery of maximum grips was performed for evaluation with MEG. The activation level in the prefrontal area was increased after the