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THE NEURAL SUBSTRATES OF PHYSICAL FATIGUE SENSATION TO EVALUATE OURSELVES: A MAGNETOENCEPHALOGRAPHY STUDY

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Abstract—It is important to clarify the neural mechanisms underlying fatigue sensation. There have been several studies which identified brain regions in which the level of the neural activities was correlated with the subjective level of fatigue. However, the neural activity evoked when we evaluate our level of fatigue may not be related to the subjective level of fatigue. Thus, we tried to identify the neural activities caused by the evaluation of the level of fatigue, which may not be related to the subjective level of fatigue. We used magnetoencephalography (MEG) to measure neural activity in 10 healthy participants enrolled in our study. During MEG recordings, participants were asked to evaluate the level of physical fatigue in their right hand in time with execution cues (evaluation session) or to direct attention to their right hand in time with execution cues (control session). Equivalent current dipole (ECD) analysis was performed to localize the neural activity limited to the evaluation session. In the evaluation session, ECDs with mean latencies of approximately 380 ms were observed in nine of 10 participants. These were localized in the posterior cingulate cortex (PCC), while in the control session, the ECDs in the same brain region were observed in only two of 10 participants. The proportion of participants in whom ECDs were observed in the PCC in the evaluation session was significantly higher than that in the control session (McNemar test). In addition, the intensities of the ECDs were positively associated with the extent to which the participants successfully evaluated the fatigue in their right hand in the evaluation session. These data suggest that the PCC is involved in the neural substrates associated with self-evaluation of physical fatigue.

Key words: fatigue sensation, physical fatigue, magnetoencephalography (MEG), equivalent current dipole (ECD), posterior cingulate cortex (PCC).

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Abbreviations: ANOVA, analysis of variance; ECD, equivalent current dipole; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GOF, goodness of fit; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PCC, posterior cingulate cortex; PET, positron emission tomography; VAS, visual analog scale.

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INTRODUCTION

Fatigue is a common problem, and more than half of the adult population in Japan complains of fatigue (Watanabe, 2007). Fatigue can be defined as difficulty initiating or sustaining voluntary activity (Chaudhuri and Behan, 2004). Fatigue sensation plays an important role as a biological alarm and urges us to take rest to avoid upsetting homeostasis. In contrast, over-activation of fatigue sensation is considered to be involved in the pathophysiology of fatigue-related diseases, such as chronic fatigue syndrome (CFS) (Tanaka and Watanabe, 2010). Therefore, it is important to clarify the neural mechanisms underlying fatigue sensation.

There have been several investigations of the neural substrates of the fatigue sensation. These studies have focused on identifying brain regions with neural activity correlated to the subjective level of fatigue. The regional blood flow in the medial orbitofrontal cortex measured using $H_2{}^{15}O$ positron emission tomography (PET) was correlated with the level of the fatigue sensation induced by performing prolonged cognitive test trials (Tajima et al., 2010). Another study that used functional magnetic resonance imaging (fMRI) showed that activations in the posterior cingulate cortex (PCC) and other several brain regions were related to the level of the fatigue sensation induced by attention test trials (Cook et al., 2007). During verbal fluency task trials, the concentration of oxygenated hemoglobin was measured using near-infrared spectroscopy (NIRS) in the bilateral channels over the regions from the ventrolateral part of the frontal lobe to the upper part of the temporal lobe and were negatively associated with the subjective level of fatigue (Suda et al., 2009). In these studies, neural activity and the subjective level of fatigue were assessed separately. It is of note that our knowledge of the neural mechanism of fatigue sensation induced by physical fatigue is still more limited: The involvements of the insular and sensorimotor cortices in the sensory information processing related to physical fatigue have been suggested in fMRI and an electroencephalography (EEG) studies (Liu et al., 2003; Hilty et al., 2011a,b), and it has been reported that the EEG changes during exercise were linearly correlated to the perceived exertion (Rasmussen et al., 2004).

Fatigue is usually perceived spontaneously when we are engaging in demanding physical or mental work. However, if we are asked to rate the subjective level of fatigue, we can assess the level of fatigue sensation even when we do not perceive fatigue sensation spontaneously at the time. Because we can assess the subjective level of fatigue even when we do not experience fatigue sensation, the neural activity that is evoked when we evaluate our level of fatigue may not be related to the level of fatigue sensation. In addition, neural activity while participants evaluate the level of fatigue sensation should be assessed to clarify the neural mechanism related to fatigue evaluation. Thus, it seems that the neural activity related to the evaluation of the level of fatigue was not properly assessed in previous studies: These studies aimed to investigate brain regions in which the level of the neural activities were correlated with the subjective level of fatigue sensation and, in addition, the neural activities and the subjective levels of fatigue were assessed separately in these studies. There have been no studies examining the neural mechanisms of fatigue sensation in relation to the evaluation of fatigue. Therefore, identifying the neural substrates of self-evaluation of fatigue sensation is an important approach to clarify the neural mechanisms of fatigue sensation.

The present study is designed to identify neural mechanisms underlying self-evaluation of levels of physical fatigue. We assessed the neural activity evoked when participants evaluated the subjective level of fatigue in their right hand. To control for attentional demand, we also assessed the neural activity that occurs when participants direct their attention to their right hand, and compared the neural responses between the two conditions. The neural substrates of fatigue evaluation may include several brain regions and the temporal sequences among these brain regions may provide important clues to clarify the neural mechanisms of fatigue sensation. Therefore, we used magnetoencephalography (MEG) with high temporal resolution to measure neural activities related to self-evaluation of the level of fatigue.

EXPERIMENTAL PROCEDURES

Participants

Ten healthy male volunteers (23.1 ± 3.6 years of age [mean ± SD]) participated in this study. All the participants were right-handed according to the Edinburgh Handedness Inventory (Olsdfields, 1971). Current smokers, participants with a history of mental or brain disorder, and those taking chronic medications that affect the central nervous system were excluded. The Ethics Committee of Osaka City University approved the study protocol. Participants provided written informed consent for participation in this study in accordance with the principles of the Declaration of Helsinki.

Experimental design

The experiment in this study consisted of two MEG recording sessions: an evaluation session and a control session. Each participant was randomly assigned to either Group 1 to begin with the evaluation session or Group 2 to begin with the control session in a two-crossover fashion. Participants lay on a bed in a magnetically shielded room in the supine position with their eyes closed and were asked to listen to the audio cue sounds played on a personal computer. Each trial consisted of two pacing cues and one execution cue, and each session consisted of 144 trials (Fig. 1). In the evaluation session, participants were instructed to lightly flex the fingers of their right hand and then to extend them to the original position (i.e., shut and open their hand) each time the pacing cue was played back. They were asked to direct attention to sensory aspects of their right hand and evaluate their subjective level of physical fatigue of their right hand in time with the execution cue. We chose to have participants flex and extend their fingers for the experiment because it was easier to evaluate the level of fatigue of the hand with some kind of finger movement than without. After the evaluation session, they were asked to assess the level of subjective feeling that they could direct attention to their right hands successfully and the level of subjective feeling that they could evaluate the level of fatigue of their right hand successfully on a visual analog scale (VAS) from 0 (minimum) to 100 (maximum). In the control session, similar to the evaluation session, participants were instructed to lightly flex the fingers of their right hand and then to extend them to the original position each time the pacing cue was played back. They were instructed not to evaluate the level of fatigue but only to direct attention to their right hand in time with execution cue. After the control session, they were asked to assess the level of subjective feeling that they could direct attention to their right hand successfully and the level of subjective feeling that they evaluated the fatigue in their right hand by mistake on the VAS. Before and after each session, they were asked to rate their subjective levels of fatigue in their right hand on the VAS.

Cue sounds

The pacing and execution cues were created using a freeware program (Metronome10a; http://www.vector.co.jp/soft/dl/win95/art/se358427.html). The temporal duration of the pacing and execution cues was 50 and 150 ms, respectively.

MEG recordings

MEG recordings were performed using a 160-channel whole-head type MEG system (MEG vision; Yokogawa Electric Corporation, Tokyo, Japan) with a magnetic field resolution of 4 $fT/Hz^{1/2}$ in the white-noise region. The sensor and reference coils were gradiometers 15.5 mm in diameter and 50 mm in baseline, and each pair of sensor coils was separated at a distance of 23 mm. The sampling rate was 1000 Hz with a 0.3-Hz high-pass filter.

MEG analyses

Before processing the MEG data, the magnetic noise that originated from outside the magnetically shielded room was eliminated by subtracting the data obtained from reference coils using specialized software (MEG 160; Yokogawa Electric Corporation). The MEG signal data