

# Chapter 23

## Integrated Imaging on Fatigue and Chronic Fatigue



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### 23.1 Introduction

Fatigue is defined as a condition or phenomenon of decreased ability and efficiency of mental and/or physical activities, caused by excessive mental or physical activities, diseases, or syndromes. It is often accompanied by a peculiar sense of

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discomfort, a desire to rest, and reduced motivation, referred to as fatigue sensation. Acute fatigue is a normal condition or phenomenon that disappears after a period of rest; in contrast, chronic fatigue, lasting at least 6 months, does not disappear after ordinary rest. Chronic fatigue impairs activities and contributes to various medical conditions, such as cardiovascular disease, epileptic seizures, and death. In addition, many people complain of chronic fatigue. For example, in Japan, more than one third of the general adult population complains of chronic fatigue. It would thus be of great value to clarify the mechanisms underlying chronic fatigue and to develop efficient treatment methods to overcome it.

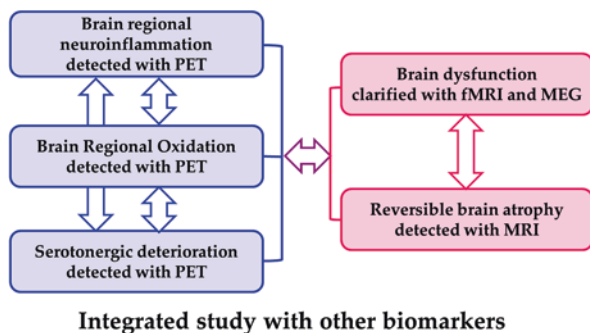
Here, we review the data obtained from molecular imaging and neuroimaging studies related to neural dysfunction as well as autonomic nervous system, sleep, and circadian rhythm disorders in fatigue (Watanabe et al. 2008; Tanaka et al. 2015). These data provide new perspectives on the mechanisms underlying chronic fatigue and on overcoming it.

### 23.2 Integrated Imaging Studies

Integrated multi-modal imaging technologies with Omics analyses and precise biomarker analyses give us the chance to create Precision Medicine and Precision Health. Especially, PET technologies open up a new era of 4-dimensional analyses of molecular events in human body. In combination with functional and anatomical imaging with MRI and MEG, total understanding of human dysfunction such as fatigue and chronic fatigue could be obtained.

We focused on the multi-modal imaging studies on fatigue and chronic fatigue, even on the patho-physiology of the patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). As shown in Fig. 23.1, we especially focused on the correlation studies between neuro-inflammation and serotonergic deterioration maybe intermediated through biological oxidation, and also among autonomic dysfunction (Mizuno et al. 2011; Tanaka et al. 2011), such molecular changes in neurotransmitter systems and cytokine systems, and functional deterioration in the brain.

**Fig. 23.1** Integrated multi-modal imaging studies on fatigue and chronic fatigue (interactions are the main issues of this chapter supported by The Uehara Memorial Foundation)



### 23.3 PET Studies

Previously, we found the decrease of the density of serotonin reuptake sites (5-HT transporters) in the rostral subdivision of the anterior cingulate cortex of the patients with ME/CFS by using [ $^{11}\text{C}$ ](+)McN5652 as compared with that in normal volunteers (Yamamoto et al. 2004). This subdivision is different from that in the dorsal anterior cingulate in which binding potential values of individual patient showed a weak negative correlation with self-reported pain score of the patients. Therefore, we thought that an alteration of serotonergic system in the rostral anterior cingulate plays a key role in pathophysiology of ME/CFS. The deterioration of the serotonergic tone in this brain region is related to the autonomic nerve dysfunction, since the autonomic center is close to the region. We recently found with [ $^{11}\text{C}$ ](R)-PK11195 and PET that neuro-inflammation is present in widespread brain areas (in the cingulate cortex, hippocampus, amygdala, thalamus, midbrain, and pons) in ME/CFS patients and was associated with the severity of neuro-psychologic symptoms (Nakatomi et al. 2014). In ME/CFS patients, the BP(ND) values of [ $^{11}\text{C}$ ](R)-PK11195 in the amygdala, thalamus, and midbrain positively correlated with cognitive impairment score, the BP(ND) values in the cingulate cortex and thalamus positively correlated with pain score, and the BP(ND) value in the hippocampus positively correlated with depression score. Evaluation of neuro-inflammation in CFS/ME patients may be essential for understanding the core pathophysiology and for developing objective diagnostic criteria and effective medical treatments.

In the present study, we performed the combination study of autonomic nerve function and other fatigue biomarkers such as biological oxidation (Fukuda et al. 2016), less repair energy (decrease of initial members of TCA cycle) (Yamano et al. 2016), and inflammation biomarkers (highly sensitive CRP etc.), with PET study using [ $^{11}\text{C}$ ]DASB instead of [ $^{11}\text{C}$ ]McN5652 for serotonin transporter density and [ $^{11}\text{C}$ ](R)-PK11195 for extent of neuro-inflammation. So far with 10 ME/CFS patients, we could preliminarily show a positive correlation between autonomic dysfunction and serotonergic tone in the anterior cingulate cortex, and also negative correlation between serotonin transporter density and extent of neuro-inflammation. We are still recruiting more numbers of patients for this study.

For biological oxidation PET study, we developed the novel  $^{11}\text{C}$ -labeled PET probe, but this probe is rather rapidly metabolized in chronic fatigue model rats. We are now improving the structure of the probe.

### 23.4 MRI Morphometry

Previously we found regional gray matter volume reduction in the dorsolateral prefrontal cortices in both hemispheres in the patients with ME/CFS as compared with those of healthy age-matched subjects (Okada et al. 2004). Especially, the extent of volume reduction of right prefrontal cortex was correlated with the severity score of

their fatigue. This finding was confirmed by de Lange et al. (2008), and de Lange et al. demonstrated this tentative atrophy recovered in the responders of Cognitive Behavioral Therapy. Then, in the present study, Mizuno et al. tried to see such volume reduction under the subacute-chronic fatigue state, and could demonstrate almost the same results even in the young adult population.

### 23.5 fMRI Study

In 2006, we reported the over-defense mechanisms of fatigue in ME/CFS patients (Tanaka et al. 2006). Namely, they performed visual tasks resulting in the decrease of visual cortical activity afterward. The healthy volunteers showed almost similar decline in the visual activity, but only the patients with ME/CFS showed the decline of auditory cortical activity, even they just did visual tasks. We hypothesized that the control tower in the brain (might be the prefrontal cortex) is watching the lowered local brain activities and then the control tower ordered the rest in the other brain regions in the case of ME/CFS patients, since the patients should not go into much severer state otherwise could not be recovered. This phenomenon could be confirmed by another angle with resting state fMRI in the subacute-chronic fatigue. Sasaki et al. recently demonstrated particular brain region(s) specific for prolonged fatigue sensation.

### 23.6 MEG Study

The mechanisms of fatigue sensation were analyzed mostly with MEG. An MEG study related to the mirror system of fatigue sensation has been reported by our group (de Lange et al. 2008). Twelve healthy male volunteers participated in this study and viewed 80 pictures with fatigued facial expressions and those with neutral facial expressions in a randomized order. Since there have been several reports showing that seeing emotional changes in others activates the brain regions involved in experiencing similar emotions, it is hypothesized that the brain regions activated when they viewed the fatigued facial expressions may be candid brain regions related to the neural mechanisms of fatigue sensation. In fact, the equivalent current dipole (ECD) in the posterior cingulate cortex (PCC) was observed in 9 of 12 participants, and the ECD in the insular cortex (IC) was observed in 3 of 12 participants only when they viewed the fatigued facial expressions, suggesting that the PCC and IC are the candid brain regions related to the neural mechanisms of fatigue sensation (Ishii et al. 2012).

Since it has been reported that the PCC is involved in self-reflection or self-monitoring, the neural substrates related to self-evaluation of the level of physical and mental fatigue were examined using MEG. Ten healthy male volunteers participated in a study that examined the neural substrates related to self-evaluation of the

level of physical fatigue. When they self-evaluated the level of fatigue of their right hand, the ECD in the PCC was observed in 9 of 10 participants. On the other hand, when they directed their attention to their right hand as a control condition, the ECD in the PCC was observed in 2 of 10 participants. In addition, the intensity of the ECD in the PCC observed in relation to the self-evaluation of the level of physical fatigue was positively associated with the extent to which fatigue of the right hand was successfully evaluated. These results suggest that the activation in the PCC was related to the self-evaluation of the level of physical fatigue (Ishii et al. 2014a).

In the next study, the neural substrates related to self-evaluation of the level of mental fatigue were examined. Fourteen healthy male volunteers participated in this study. They performed 90 evaluation trials and 90 control trials in a randomized order. In the evaluation trials, they were asked to self-evaluate the level of their mental fatigue. The control trials were resting trials in which they were asked to do nothing. The ECD in the PCC was observed in 7 of 14 participants when they self-evaluated the level of their mental fatigue, although it was observed in only 1 of 14 participants when they performed the control trials, suggesting that the activation in the PCC was also related to self-evaluation of the level of mental fatigue (Ishii et al. 2014b). It has been shown that the PCC is not only involved in the neural mechanisms of fatigue sensation but is also involved in the neural mechanisms of making decisions in the presence of fatigue (Ishii et al. 2014c). If individuals do not rest, despite the signs of fatigue, they may experience overwork, which may be a starting point of chronic fatigue as discussed later. Therefore, the decision of whether or not to rest based on the level of fatigue is important. Fifteen healthy male volunteers participated in this study. They performed 1200 reverse Stroop test trials and were intermittently asked whether to take a rest or not to maintain task performance; neural activities related to making decisions to rest were assessed. When they made decisions to rest, a decreased 4–8 Hz band power was observed in the PCC, and this decreased 4–8 Hz band power in the PCC was positively associated with the subjective level of fatigue caused by performing the experiment. As for the IC, it has been reported that the IC is involved in mental effort evaluation in an fMRI study in which the participants rated their mental effort investment required for performing 1-, 2-, and 3-back tests. These findings suggest that the PCC and IC are involved in the neural mechanisms of fatigue sensation to self-evaluate the level of fatigue, and that the PCC plays an important role in making decisions to take a rest in the presence of fatigue.

More recently, we performed the MEG study (Ishii et al. 2018) to examine whether thinking positively about the fatigue sensation would increase motivation to accomplish the workload. Fourteen healthy male volunteers participated in this study and performed a two-back test for 30 min to induce mental fatigue sensation. After their subjective level of fatigue had recovered to the baseline level, they re-experienced the fatigue sensation experienced in the two-back test positively, negatively, and without any modification (i.e., re-experienced the fatigue sensation as it was). The level of motivation to perform another two-back test they felt during the re-experiencing was assessed. The neural activity related to the re-experiencing was recorded using magnetoencephalography. The level of the motivation to perform

another two-back test was increased by positively re-experiencing the fatigue sensation. The increase in delta band power in Brodmann area 7 was positively associated with the increase in motivation. These results show that positive thinking about fatigue sensation can enhance motivation and suggest that this enhanced motivation may have some effects on visual attention system.

Finally, we have tried to reveal whether the neural activation level is altered in the patients with ME/CFS. Actually, the subtraction between the resting state with open eyes and that with closed eyes gave a great difference between healthy subjects and the patients with ME/CFS (Tanaka M et al., on-going study).

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