

# Increase in the Regional Cerebral Blood Flow following Waon Therapy in Patients with Chronic Fatigue Syndrome: A Pilot Study

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## Abstract

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**Objective** Chronic fatigue syndrome (CFS) is a complex disorder, with no consensus on therapeutic options. However, Waon therapy has been reported to be an effective treatment. The purpose of this study was to evaluate changes in the cerebral blood flow (CBF) before and after Waon therapy in CFS patients and to investigate the correlation between such changes and the therapeutic efficacy of Waon therapy.

**Methods** Eleven patients (2 men and 9 women, mean age 27 years old) diagnosed with CFS participated in the study. The disease duration was 8-129 months, and the performance status was 5-8 (on a scale of 0-9). All patients underwent CBF scintigraphy using brain single-photon emission computed tomography (SPECT) with technetium-99m ethyl cysteinate dimer (<sup>99m</sup>Tc-ECD) before and after Waon therapy. CBF changes after Waon therapy were evaluated using a statistical analysis of imaging data, which was performed with a statistical parametric mapping software program (SPM5).

**Results** Waon therapy reduced symptoms in all 11 patients. We also observed an increase in the CBF within the prefrontal region, orbitofrontal region, and right temporal lobe. These results indicated that an improvement in clinical symptoms was linked to an increase in the CBF.

**Conclusion** The results indicated abnormalities of the cerebral function in the prefrontal region, orbitofrontal region, and right temporal lobe in CFS patients and that Waon therapy improved the cerebral function and symptoms in CFS patients by increasing the regional CBF. To our knowledge, this is the first report to clarify the CBF changes in CFS patients before and after Waon therapy.

**Key words:** chronic fatigue syndrome, cerebral blood flow, SPECT, Waon therapy, pain, depression

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## Introduction

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Chronic fatigue syndrome (CFS) is characterized by chronic fatigue of unknown cause. The work, school, and home lives of patients with CFS are disrupted because of persistent, long-term, extreme fatigue. CFS patients present with physical symptoms suggestive of inflammation, such as headaches, muscle pain, joint pain, a mild fever, and pharyngitis, as well as psychological and neurological symptoms, such as insomnia, impaired concentration, and depres-

sion. CFS has multiple possible causes, and the endocrine system, immune system, genes, and the environment, among others, have been implicated. The pathology is suggestive of homeostatic imbalance (1), but the precise aetiology of CFS is unknown. Because abnormal cerebral blood flow (CBF) and brain volume loss in CFS patients have been reported, the central nervous system (CNS) may play a critical role in causing chronic fatigue (2).

Psychological, physical, and medical therapies have been attempted, and graded exercise and behaviour therapy have been confirmed to be effective for CFS (3, 4). However, the

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efficacy of these therapies is associated with a progressive increase in the exercise volume, which may not be possible for patients with severe CFS. We developed Waon therapy for CFS patients, which is safe and easy to apply (5). Waon therapy was initially performed in 2 and 11 cases of CFS in separate reports by Masuda et al. (6, 7), in 10 cases by Soejima et al. (8), and in 9 cases by Amano et al. (9). These groups reported that Waon therapy was effective for recovering from fatigue and exertion.

Because abnormalities of the cerebral function seem to be a key factor in the aetiology of CFS, we hypothesized that the mechanism underlying the therapeutic effect of Waon therapy is related to the brain function. To verify this hypothesis, we measured the CBF before and after therapy using single-photon emission computed tomography (SPECT) in CFS patients who underwent Waon therapy. The purpose of this study is to clarify the correlation between CBF and the efficacy of Waon therapy in CFS patients. This is the first report to investigate the CBF changes in CFS patients before and after Waon therapy.

## Materials and Methods

### Patients

Eleven inpatients with CFS who received Waon therapy at Kagoshima University Hospital participated in this study. The efficacy of Waon therapy for 10 patients has already been reported, but the data of the CBF were not analysed (8). A 17-year-old woman was a new inpatient; she did not meet the diagnostic criteria of the Centers for Disease Control and Prevention for CFS, but she did meet the diagnostic criteria for paediatric CFS suggested by Jason et al. (10). Five patients with post-infectious CFS and three with complications associated with depression that developed after the onset of CFS were included (age range, 15-60 years old). The duration between the onset of CFS and admission to our hospital was 8-129 months (median, 29 months). The performance status (PS) rating (on a scale of 0-9) was used to assess the fatigue severity and activities of daily living (11, 12), and the patients scored between 5 and 8 (median, 7). All 11 patients with CFS were right-handed.

### Waon therapy

Waon therapy was reportedly effective in 10 inpatients with CFS. The same protocol used in these 10 inpatients (8) (a 20-session Waon therapy program [once a day for 45 minutes, 5 times a week for 4 weeks]) was used in the 17-year-old woman. In each session, the patient was placed in a supine position for 15 minutes in a Waon therapy room (a far-infrared-ray dry sauna), in which the temperature was evenly maintained at 60°C; a blanket was used to cover the patient's body in order to maintain sufficient warmth for 30 minutes outside the Waon therapy room. Patients did not receive any new medical therapy or psychological treatment during the program.

### Measurements

We asked inpatients about their level of fatigue, which is the main subjective symptom of CFS, three times a day as the primary outcome variable. Fatigue severity scores range from 0 (none) to 10 (most severe) (13). The average fatigue severity scores were calculated from the data obtained the day before the first therapy session (Week 0) and the day after completion of Week 4 of therapy. Pain, mood, and PS as secondary outcome variables were measured at Weeks 0 and 4. The average pain severity scores were calculated from the data obtained at Weeks 0 and 4 using the same method as for fatigue severity (14). The PS rating was used to assess fatigue severity and activities of daily living on a scale of 0-9 (11, 12), and the Profile of Mood States (POMS) test was used to evaluate patients with CFS on a 6-point scale (15).

### Imaging

Eleven patients underwent CBF scintigraphy using brain SPECT with technetium-99m ethyl cysteinate dimer ( $^{99m}\text{Tc}$ -ECD) before and after 20 sessions of Waon therapy. Each patient was placed supine at bed rest. After informed consent was obtained, 720 MBq of  $^{99m}\text{Tc}$ -ECD was intravenously injected as a bolus. The SPECT data were acquired for 20 minutes starting 5 minutes after the injection of  $^{99m}\text{Tc}$ -ECD, using a triple-head rotating gamma camera. This imaging method has been described by Nakabeppu et al. (16).

### Statistical analyses

Brain SPECT was performed in all 11 patients before and after 20 sessions of Waon therapy, and the CBF changes were evaluated using a statistical analysis of the imaging data, which was performed with a statistical parametric mapping software program (SPM5 [Wellcome Department of Cognitive Neurology, London]). The SPECT data were transformed into a standard stereotactic space, and comparisons before and after 20 sessions of Waon therapy were performed on a voxel-by-voxel basis. The subset of voxels exceeding a threshold of  $p < 0.05$  in omnibus comparisons and a cluster size exceeding 100 was displayed as a volume image rendered in three orthogonal projections. Correlations between variations in fatigue and depression scores in the POMS test and CBF after 20 sessions of Waon therapy were determined by a statistical analysis of imaging data using SPM5. Correlations were also determined before and after Waon therapy between variations in fatigue and depression scores and blood flow in voxels for each patient. A voxel is a volume unit in a virtually divided brain in three dimensions. Every voxel showing a significant negative correlation was mapped as a colour on the brain image. We used the analysis method reported by Nakabeppu et al. in part for our analyses (16).

### Informed consent

Approval for this study was obtained from the clinical research ethics committee at Kagoshima University Hospital.

**Table 1.** Clinical Data of Patients with Chronic Fatigue Syndrome.

| patient number | gender | age (years) | BMI (kg/m <sup>2</sup> ) | BP (mmHg) | lipid (mg/dL) |    |     | FBG (mg/dL)  | CRP (mg/dL) | renal function (mg/dL) |     | Na/K (mEq/L) | smoking history | medications                                                                                                                                             |
|----------------|--------|-------------|--------------------------|-----------|---------------|----|-----|--------------|-------------|------------------------|-----|--------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
|                |        |             |                          |           | T-Chol        | TG | LDL |              |             | BUN                    | Cr  |              |                 |                                                                                                                                                         |
| 1              | male   | 60          | 20.1                     | 114 / 70  | 202           | 48 | 111 | 91           | <0.05       | 16.5                   | 0.6 | 139/4.1      | none            | fluvoxamine 75 mg<br>hochuekkito 7.5 g<br>loflazepate 1 mg                                                                                              |
| 2              | female | 34          | 16.3                     | 100 / 70  | 181           | 37 | 92  | 71           | <0.02       | 13.9                   | 0.8 | 137/3.9      | none            | milnacipran 75 mg<br>brotizolam 0.25 mg                                                                                                                 |
| 3              | female | 44          | 17.4                     | 110 / 70  | 180           | 51 | 104 | 77           | <0.02       | 15.8                   | 0.6 | 140/4.0      | none            | tandospirone 30 mg<br>zolpidem 5 mg                                                                                                                     |
| 4              | female | 17          | 16.9                     | 110 / 70  | not examined  |    |     | 76           | <0.02       | 13.9                   | 0.6 | 139/3.9      | none            | vitamin complex 1.0 g<br>bifidobacterium 3.0 g                                                                                                          |
| 5              | female | 15          | 21.0                     | 108 / 66  | 170           | 65 | 98  | 81           | 0.03        | 11.6                   | 0.5 | 140/3.7      | none            | setipiline 1mg,<br>brotizolam 0.25 mg<br>hochuekkito 7.5 g                                                                                              |
| 6              | male   | 35          | 19.6                     | 117 / 81  | not examined  |    |     | 96           | 0.02        | 12.1                   | 0.6 | 141/4.0      | none            | ascorbic acid 1,500 mg<br>amoxapine 50 mg,<br>milnacipran 75 mg<br>tandospirone 30 mg,<br>zolpidem 10 mg<br>ascorbic acid 200 mg,<br>juzentaihoto 7.5 g |
| 7              | female | 15          | 16.0                     | 102 / 68  | 155           | 50 | 80  | 87           | 0.02        | 10.8                   | 0.7 | 140/3.7      | none            | no medication                                                                                                                                           |
| 8              | female | 23          | 19.9                     | 106 / 60  | 171           | 72 | 92  | 90           | <0.02       | 12.0                   | 0.5 | 143/4.0      | none            | lorazepam 1.5 mg<br>sertraline 25 mg                                                                                                                    |
| 9              | female | 16          | 21.3                     | 88 / 53   | 156           | 59 | 71  | not examined | 0.02        | 10.7                   | 0.5 | 142/3.7      | none            | neurotropin® 4 u                                                                                                                                        |
| 10             | female | 19          | 19.9                     | 92 / 62   | 162           | 99 | 106 | not examined | <0.02       | 10.5                   | 0.5 | 142/4.5      | none            | hochuekkito 7.5 g<br>ascorbic acid 600 mg                                                                                                               |
| 11             | female | 17          | 16.0                     | 98 / 65   | 208           | 61 | 132 | 80           | <0.02       | 15.9                   | 0.5 | 140/3.6      | none            | fluvoxamine 25 mg<br>bromazepam 2 mg                                                                                                                    |

BMI: body mass index, BP: blood pressure, T-CHO: total cholesterol, TG: triglyceride, FBG: fasting blood glucose, LDL: low density lipoprotein cholesterol, BUN: blood urea nitrogen, Cr: creatinine, BMI:  $18.6 \pm 2.1$  (average  $\pm$  standard deviation), BP:  $104 \pm 9 / 67 \pm 7$ , T-Cho:  $176.1 \pm 18.8$ , TG:  $60.2 \pm 17.8$ , LDL:  $98.4 \pm 17.8$ , FBG:  $83.2 \pm 8.2$ , BUN:  $13.1 \pm 2.2$ , Cr:  $0.6 \pm 0.1$ , Na:  $140.3 \pm 1.7$ , K:  $3.9 \pm 0.3$

The purpose, significance, methods, and safety of this study were explained to all of the patients in written form, and informed consent for research participation and publication was obtained from the patients. In patients under the age of 20 years old, informed consent was obtained from both the patient and their guardian.

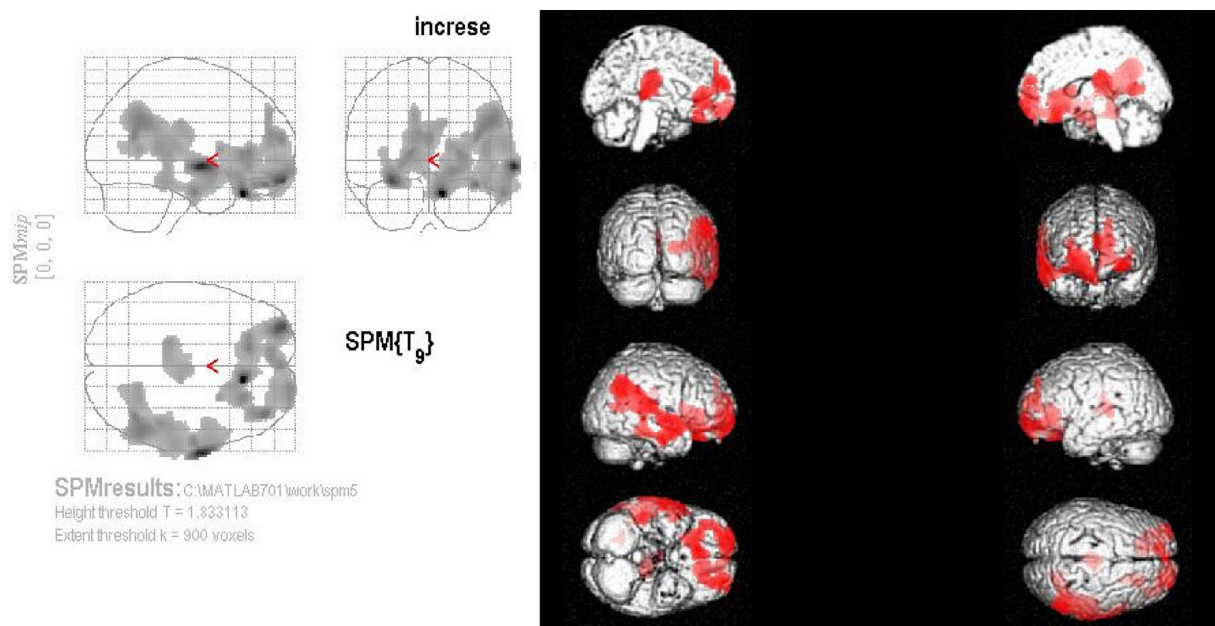
## Results

Table 1 shows fasting blood glucose levels. Although the fasting blood glucose was not determined in two cases, the urine sugar was negative, and the patients did not have overt symptoms of diabetes, such as dry mouth and excessive uri-

**Table 2.** Comparison of Values for Primary and Secondary Outcome Variables before and after Waon Therapy over Four Weeks in 11 CFS Patients.

| Variables                       | Waon Therapy                           |                                       | p values* |
|---------------------------------|----------------------------------------|---------------------------------------|-----------|
|                                 | Before Median<br>(Interquartile range) | After Median<br>(Interquartile range) |           |
| Primary outcome                 |                                        |                                       |           |
| Self-rating Scale <sup>1</sup>  |                                        |                                       |           |
| fatigue                         | 7.1 (6.0 - 8.2)                        | 5.6 (3.9 - 7.3)                       | 0.0095    |
| Secondary outcome               |                                        |                                       |           |
| Self-rating Scale <sup>1</sup>  |                                        |                                       |           |
| pain                            | 4.6 (2.4 - 6.9)                        | 3.1 (1.1 - 5.1)                       | 0.0460    |
| POMS <sup>2</sup>               |                                        |                                       |           |
| Anxiety                         | 49.4 (44.6 - 54.1)                     | 42.6 (37.4 - 47.9)                    | 0.0092    |
| Depression                      | 55.2 (46.9 - 63.5)                     | 48.6 (42.4 - 54.9)                    | 0.0064    |
| Fatigue                         | 59.6 (52.5 - 66.7)                     | 51.7 (44.5 - 59.0)                    | 0.0089    |
| Vigor                           | 37.5 (32.2 - 42.9)                     | 42.2 (35.9 - 48.5)                    | 0.0695    |
| Performance status <sup>3</sup> | 6.5 (5.8 - 7.1)                        | 3.9 (2.7 - 5.9)                       | 0.0002    |

\*Paired t - test

<sup>1</sup>Numerical rating scale(0 - 10) with higher scores indicating greater severity.<sup>2</sup>Higher scores for anxiety, depression, and fatigue indicate greater disturbance of mood; higher scores for vigor indicate a more vigorous mood.<sup>3</sup>Likert-type scale(0 – 9) with higher scores indicative of a worse performance status.**Figure 1.** Increased regional CBF (red) at Week 4 (after 20 sessions of Waon therapy) compared with Week 0 (before Waon therapy) (paired t-test,  $p < 0.05$ , Extent=900). An increase in the CBF was found in the prefrontal region, orbitofrontal region, and right temporal lobe.

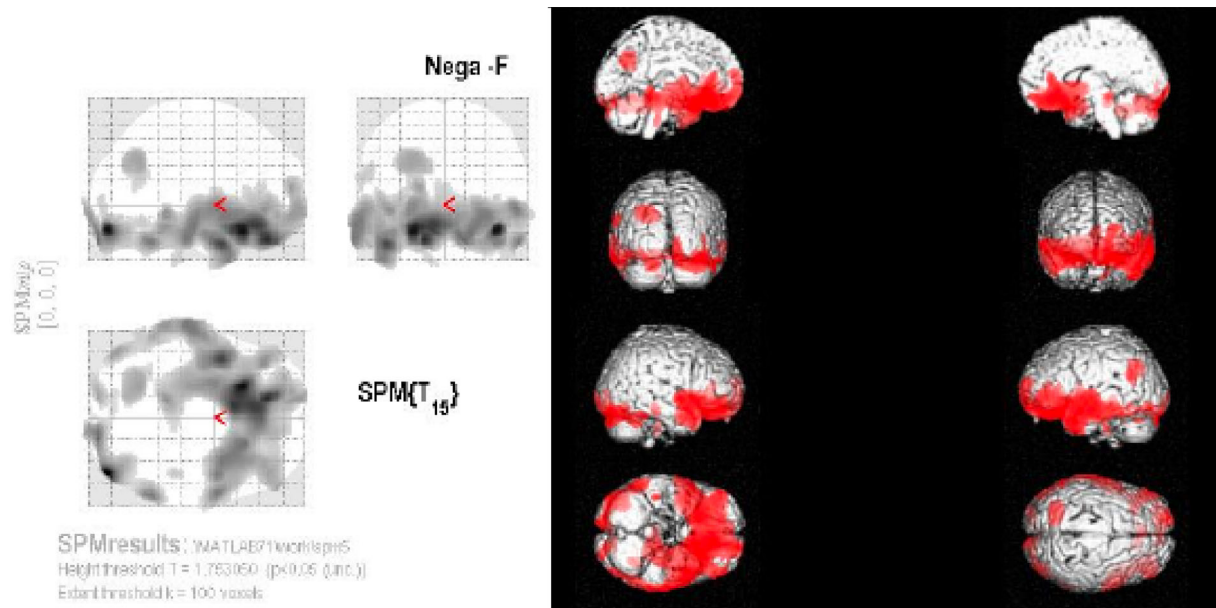
nation, obesity, or a family history of diabetes. In all but two cases, we measured the total cholesterol, neutral fat, and low-density lipoprotein cholesterol levels. We also determined the C-reactive protein, blood urea nitrogen, and creatinine levels. While hospitalized, the patients did not receive changes in their usual medications until Waon therapy was completed. These medications included serotonin-specific reuptake inhibitors, anxiolytic drugs, hypnotics, vitamins, and traditional Chinese medicines. The clinical data

in Table 1 did not show abnormalities suggestive of other diseases.

Table 2 shows that the variables of self-rating scales for fatigue and pain, POMS (anxiety, depression, fatigue, and vigor), and PS were significantly improved as a result of the Waon therapy in all 11 patients, thus confirming the therapeutic efficacy.

The brain images showing increased regional CBF after Waon therapy are presented in Fig. 1. Areas of increased





**Figure 2.** There was a negative correlation between variations in the POMS fatigue scores and the CBF in patients with CFS after Waon therapy (paired t-test,  $p < 0.05$ , Extent=900). We determined the correlations between variations in the POMS fatigue scores (F-scores) and the CBF of cerebral voxels in CFS patients after Waon therapy. The F-scores showed differences before and after Waon therapy. Every voxel with a significant negative correlation was mapped and colored red in the brain image. Sites colored red were seen in the prefrontal, orbitofrontal, and occipital regions. In these regions, the CBF increased with decreasing F-score (i.e. with improvement in fatigue). This analysis was performed using SPM5. Voxel: volume unit of virtually divided cerebrum, CFS: chronic fatigue syndrome, CBF: cerebral blood flow, SPM5: statistical parametric mapping software, version 5

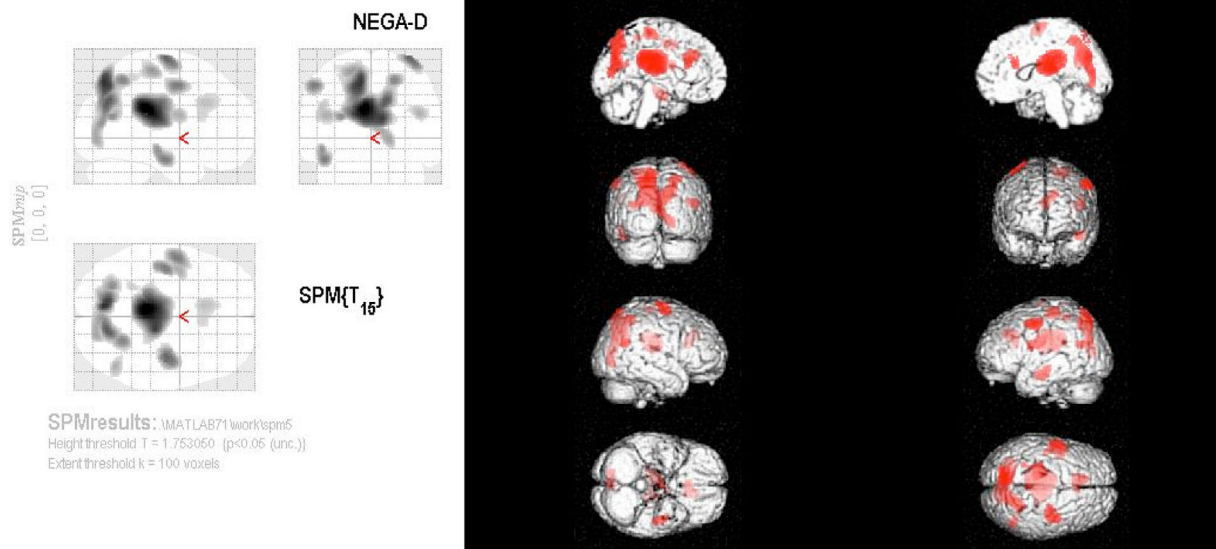
CBF are shown in red. Increases in CBF were found in the prefrontal region, orbitofrontal region, and right temporal lobe. Fig. 2 shows the correlation between the changes in the POMS fatigue score and changes in the CBF after Waon therapy. Variations in the POMS fatigue score were negatively correlated with variations in the CBF in the prefrontal region, orbitofrontal region, temporal lobe, and occipital lobe (increases shown in red). Fig. 3 shows the correlation between changes in the POMS depression score and CBF after Waon therapy. Variations in the POMS depression score were negatively correlated with variations in the CBF in part of the cingulate gyrus, as well as in the parietal lobe and part of the occipital lobe along the longitudinal cerebral fissure (increases shown in red).

## Discussion

Many reports have described overall decreases in the CBF in CFS patients. Two reports used SPECT imaging (17, 18), one performed neuroimaging using arterial spin labeling (19), one reported a decrease in the CBF in the brainstem using SPECT imaging (20), one reported a decrease in the CBF in the anterior cingulate gyrus using SPECT imaging (21), and one reported a decrease in the absolute CBF in the distribution of the left and right middle cerebral arteries using SPECT imaging (22). However, some reports have indicated no changes in the CBF (23-25). Another stated that

the metabolism is decreased in the medial right frontal lobe and brainstem (26), and another showed brain volume abnormalities using magnetic resonance imaging (MRI). Various reports have also indicated increased T2 signals in the white matter as well as sulcal and ventricular enlargement in CFS patients (27), a reduction in global grey matter volume (28), and grey matter volume contraction in the right and left prefrontal cortices (29). Furthermore, Brooks et al. (30) used proton nuclear magnetic resonance spectroscopy to demonstrate decreased levels of *N*-acetylaspartate, a marker of nerve fibre density, in the right hippocampus, although there was no difference in the hippocampal volume between CFS patients and healthy individuals. A recent study showed no abnormalities of the CBF, cerebrospinal fluid, or brain volume in CFS patients, in contrast with the findings of other studies that used functional MRI (31). As noted above, studies using various techniques have reported variable findings concerning the cerebral function in CFS patients, and some have indicated that the CNS plays an important role in the aetiology of CFS, but the results are inconclusive. The above studies reported the results of brain function measurements in CFS patients for a specific time period but did not investigate changes before and after therapy.

We previously demonstrated that Waon therapy improves symptoms in CFS patients. Given these results, we assessed the CBF changes before and after therapy using SPECT in



**Figure 3.** There was a negative correlation between variations in the POMS depression scores (D-scores) and the CBF in patients with CFS after Waon therapy (paired t-test,  $p < 0.05$ , Extent=900). We determined the correlations between variations in the POMS depression scores (F-score) and the CBF of cerebral voxels in CFS patients after Waon therapy. The variations in the D-scores indicated differences before and after Waon therapy. Every voxel with a significant negative correlation was mapped and colored red in the brain image. Sites colored red were seen in the cingulate gyrus and the parietal and occipital lobes along the longitudinal cerebral fissure. In these regions, the CBF increased with decreasing D-scores (i.e. with improvement in depressed mood). This analysis was performed using SPM5. Voxel: volume unit of virtually divided cerebrum, CFS: chronic fatigue syndrome, CBF: cerebral blood flow, SPM5: statistical parametric mapping software, version 5

order to identify the mechanism underlying the effect of Waon therapy in CFS patients. We detected an increase in the CBF in the prefrontal region, orbitofrontal region, and right temporal lobe after Waon therapy, which indicates a correlation between these regions and symptom development. Although our data do not support all of the results of previous studies, the increase in the CBF in the prefrontal region noted in our study is partially confirmatory (21, 22, 29). Therefore, our study seems to be at the forefront of research in this field, by assessing CBF changes before and after Waon therapy. According to a Swedish group, the prefrontal cortex volume has recovered and symptoms have improved in CFS patients who underwent cognitive behavioural therapy (32). Therefore, our finding of an increased regional CBF agreed with their finding of increased regional brain volume in the prefrontal region. Whether or not increases in the CBF and brain volume have the same meaning is debatable, but these increases may at least indicate an improvement in the brain function. The involvement of at least the prefrontal region is also suggestive of the aetiology of CFS.

After Waon therapy, a negative correlation was observed between the POMS fatigue score and changes in the CBF in the prefrontal region, orbitofrontal region, and occipital lobe (Fig. 2). This suggests that the greater the improvement in fatigue severity, the greater the increase in the CBF in the prefrontal region, orbitofrontal region, and occipital lobe.

This also suggests that functional abnormalities in these regions may be associated with protracted fatigue. Previous studies have indicated that grey matter volume reduction in the right prefrontal cortex is related to fatigue severity (29), and mental exhaustion is linked to cortical activities in the parietal lobe, cingulate gyrus, inferior frontal lobe, and superior temporal lobe, as well as to cerebellar and cerebellar vermis activities (33). One study reported that a decrease in plasma acetylcarnitine levels was correlated with fatigue severity and a decreased uptake of acetylcarnitine in the anterior cingulate gyrus, orbitofrontal region, left temporal lobe, and cerebellum in CFS patients (34). This is in agreement with a study which reported that fatigue correlates with involvement of the prefrontal or orbital region. An impairment of the prefrontal region or the orbitofrontal region seems to be closely related to fatigue, which is a basic symptom of CFS. These regions are involved in intention, emotion, motivation, learning, and the cognitive function and may be associated with the cause of chronic fatigue.

A negative correlation between changes in the POMS depression scores and changes in the CBF was also found in part of the cingulate gyrus as well as in the parietal lobe and part of the occipital lobe along the longitudinal cerebral fissure (Fig. 3). When POMS depression scores decreased (that is, when depression improved), we found that the CBF increased more significantly in these regions. Brain functional impairment that causes fatigue is likely to be different

from that which causes depression, indicating that depression and CFS are different disorders. Previous studies also indicate that brain functional abnormalities in CFS and depression are different (25, 26), which also supports our study results.

Therefore, improvement of chronic fatigue may require the improvement of brain function or CBF recovery, primarily in the frontal lobe; this suggests a basis for the effectiveness of Waon therapy in CBF recovery. A relaxation effect may be one mechanism for the therapeutic effect (35), but Waon therapy induces an increase in the cardiac output through systemic arterial and venous vasodilation (36), enhancement of blood flow to all organs, and improvement in brain functional abnormalities through an increase in the CBF. Waon therapy provides gentle and warmly enveloping treatment and can be performed safely in all CFS patients. Thus, Waon therapy is an extremely promising option for the future of CFS treatment.

### Limitations

Our study was conducted in a small group of 11 patients, and there was no control group. Thus, the results suggesting that the CBF changes observed in our study are unique to CFS patients may not be convincing. In order to generalize the results, we need to increase the sample size and prospectively compare control and treatment groups, which will be a challenge for the future. However, we should bear in mind that patients with migraine should be carefully managed, as Waon therapy has vasodilator effects.

### Conclusion

We demonstrated an increase in the CBF in the prefrontal and orbitofrontal regions and the temporal lobe in CFS patients who showed symptom improvement after Waon therapy, indicating a possible relationship between an abnormality in these regions and chronic fatigue. In particular, the prefrontal and orbital regions may play a major role in this correlation. By improving the CBF in these regions, Waon therapy is expected to induce therapeutic effects in CFS patients.

**The authors state that they have no Conflict of Interest (COI).**

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### References

- Dietert RR, Dietert JM. Possible role for early-life immune insult including developmental immunotoxicity in chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME). *Toxicology* **247**: 61-72, 2008.
- Tang LW, Zheng H, Chen L, et al. Gray matter volumes in patients with chronic fatigue syndrome. *Evid Based Complement Alternat Med* 2015 (Epub ahead of print).
- Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. *Lancet* **367**: 346-355, 2006.
- Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramirez G. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. *JAMA* **286**: 1360-1368, 2001.
- Tei C. Waon therapy: soothing warmth therapy. *J Cardiol* **49**: 301-304, 2007.
- Masuda A, Kihara T, Fukudome T, Shinsato T, Minagoe S, Tei C. The effects of repeated thermal therapy for two patients with chronic fatigue syndrome. *J Psychosom Res* **58**: 383-387, 2005.
- Masuda A, Munemoto T, Tei C. A new treatment: thermal therapy for chronic fatigue syndrome. *Nihon Rinsho* **65**: 1093-1098, 2007 (in Japanese, Abstract in English).
- Soejima Y, Munemoto T, Masuda A, Uwatoko Y, Miyata M, Tei C. Effects of Waon therapy on chronic fatigue syndrome: a pilot study. *Intern Med* **54**: 333-338, 2015.
- Amano K, Yanagihori R, Tei C. Waon Therapy is Effective as the Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *J Jpn Soc Balneol Climatol Phys Med* **78**: 285-302, 2015.
- Jason LA, Jordan K, Miike T, et al. A pediatric case definition for myalgic encephalomyelitis and chronic fatigue syndrome. *J CFS* **13**: 1-44, 2006.
- Kitani T, Kuratsune H, Yamaguchi K. Diagnostic criteria for chronic fatigue syndrome by the CFS Study Group in Japan. *Nihon Rinsho* **50**: 2600-2605, 1992 (in Japanese, Abstract in English).
- Iwakami E, Arashima Y, Kato K, et al. Treatment of chronic fatigue syndrome with antibiotics: pilot study assessing the involvement of *Coxiella burnetii* infection. *Intern Med* **44**: 1258-1263, 2005.
- Pouchot J, Kherani RB, Brant R, et al. Determination of the minimal clinically important difference for seven fatigue measures in rheumatoid arthritis. *J Clin Epidemiol* **61**: 705-713, 2008.
- Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* **9**: 105-121, 2008.
- McNair DM, Lorr M, Droppleman LF. Revised manual for the profile of mood states. In: Educational and Industrial Testing Services. San Diego, CA, 1992.
- Nakabeppu Y, Nakajo M, Gushiken T, et al. Decreased perfusion of the bilateral thalami in patients with chronic pain detected by Tc-99m-ECD SPECT with statistical parametric mapping. *Ann Nucl Med* **15**: 459-463, 2001.
- Ichise M, Salit IE, Abbey SE, et al. Assessment of regional cerebral perfusion by 99Tcm-HMPAO SPECT in chronic fatigue syndrome. *Nucl Med Commun* **13**: 767-772, 1992.
- Schwartz RB, Garada BM, Komaroff AL, et al. Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. *AJR Am J Roentgenol* **162**: 935-941, 1994.
- Biswal B, Kunwar P, Natelson BH. Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. *J Neurol Sci* **301**: 9-11, 2011.
- Costa DC, Tannock C, Brostoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM* **88**: 767-773, 1995.
- Schmaling KB, Lewis DH, Fiedelak JJ, et al. Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. *Psychosom Med* **65**: 129-136, 2003.
- Yoshiuchi K, Farkas J, Natelson BH. Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. *Clin Physiol Funct Imaging* **26**: 83-86, 2006.
- Lewis DH, Mayberg HS, Fischer ME, et al. Monozygotic twins discordant for chronic fatigue syndrome; regional cerebral blood flow SPECT. *Radiology* **219**: 766-773, 2001.
- Peterson PK, Sirr SA, Grammish FC, et al. Effects of mild exer-

- cise on cytokines and cerebral blood flow in chronic fatigue syndrome patients. *Clin Diagn Lab Immunol* **1**: 222-226, 1994.
25. Fischler B, D'Haenen H, Cluydts R, et al. Comparison of 99mTc HMPAO SPECT scan between chronic fatigue syndrome, major depression and healthy controls: An exploratory study of clinical correlates of regional cerebral blood flow. *Neuropsychobiology* **34**: 175-183, 1996.
  26. Tirelli U, Chierichetti F, Tavio M, et al. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *Am J Med* **105**: 54S-58S, 1998.
  27. Natelson BH, Cohen JM, Brassloff I, Lee HJ. A controlled study of brain magnetic resonance imaging in patients with the chronic fatigue syndrome. *J Neurol Sci* **120**: 213-217, 1993.
  28. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* **26**: 777-781, 2005.
  29. Okada T, Tanaka M, Kuratsune H, Sadato N. Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurol* **4**: 14, 2004.
  30. Brooks JC, Roberts N, Whitehouse G, Majeed T. Proton magnetic resonance spectroscopy and morphometry of the hippocampus in chronic fatigue syndrome. *Br J Radiol* **73**: 1206-1208, 2000.
  31. Perrin R, Embleton K, Pentreath VW, Jackson A. Longitudinal MRI shows no cerebral abnormality in chronic fatigue syndrome. *Br J Radiol* **83**: 419-423, 2010.
  32. de Lange FP, Koers A, Kalkman JS, et al. Increase in prefrontal cortical volume following cognitive behavioral therapy in patients with chronic fatigue syndrome. *Brain* **131**: 2172-2180, 2008.
  33. Cook DB, O'Connor PJ, Lange G, Steffner J. Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. *Neuroimage* **36**: 108-122, 2007.
  34. Kuratsune H, Yamaguti K, Lindh G, et al. Brain regions involved in fatigue sensation: reduced acetylcarnitine uptake into the brain. *Neuroimage* **17**: 1256-1265, 2002.
  35. Masuda A, Nakazato M, Kihara T, Minagoe S, Tei C. Repeated thermal therapy diminishes appetite loss and subjective complaints in mildly depressed patients. *Psychosom Med* **67**: 643-647, 2005.
  36. Tei C, Horikiri Y, Park JC, Jeong JW, Chang KS, Toyama Y, et al. Acute hemodynamic improvement by thermal vasodilation in congestive heart failure. *Circulation* **91**: 2582-2590, 1995.

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