Author's response to reviews

Title: Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome

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Author's response to reviews: see over
Re: Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome by Okada et al.

Dear Editor:

Enclosed is the revised manuscript titled “Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome” by Okada et al. to *BMC Neurology*. We wish to thank the reviewers for their helpful criticisms of our paper, which are reflected in the revised manuscript. We have addressed each of the comments on the attached pages, which were incorporated in the revised manuscript.

The work reported in this paper has not been and is not intended to be published anywhere except in *BMC Neurology*. In addition, all the co-authors have seen and agree with the contents of the manuscript.

We appreciate the opportunity to revise a paper, and hope it is now acceptable for *BMC Neurology*.

Sincerely yours,

Norihiro Sadato, MD, PhD

Enclosures
Response to Reviewer's report

I would suggest not to use CSF as an acronym for chronic fatigue syndrome, since CSF is typically used in neurology for cerebrospinal fluid.

Response:
We now omit the abbreviation in Abstract.

1. Tables 1 and 2 can be omitted. The relevant pieces of information contained in table 1 can be presented in the text using descriptive statistics.

Response:
We would like to preserve the Tables as the definition of performance status and detailed information of each subject and is important for the characterization of the volume reduction of the prefrontal cortex. No change was made.

2. The abstract should contain a section on patients and methods.

Response:
The abstract is now modified as suggested.

3. MS cannot be excluded on the basis of a neurological examination. They should, at least, provide results of conventional MRI scans.

Response:
As the reviewer pointed out, MRI provides very useful adjuncts in evaluation of the patient with suspected MS, however, the clinical findings remain paramount in establishing the diagnosis. Nine out of 16 patients in the present study showed clinical manifestation that is unlikely to indicate the MS, and hence diagnostic MRI was not performed. Other 7 patients underwent clinical MRI which was reported to be negative. Furthermore, main purpose of the present study was to study the mechanisms underlying fatigue sensation, not to depict manifestations specific to CFS. This point is now clarified in the text.
Discretionary Revisions (which the author can choose to ignore)

1. Introduction is very long and somehow repetitive. It can be cut down significantly.

Response:

Introduction is now reduced in length.

2. Were patients consecutively recruited? How many were screened and excluded? For which reasons? How other causes of fatigue were excluded? Please specify.

Response:

The patients were recruited from the outpatients in fatigue clinic in Osaka University Hospital (HK’s special clinic). The CFS patients who met the diagnostic criteria of chronic fatigue syndrome (Fukuda et al., 1994) were more than 430. The patients with other causes were already excluded by the diagnostic criteria. We asked these CFS patients to participate in the present volumetry project. Sixteen of them willingly joined. This point is now added in the text.

3. The amount of frontal lobe atrophy found in patients with chronic fatigue is very high. This would deserve a comment in the discussion.

Response:

This is what we have observed and discussed. No change was made in the text.

4. I believe conventional MRI scans were obtained in these patients. The corresponding data should be presented.

Response:

Referring physicians usually excluded the diagnosis of MS based on detailed neurological examination and the past and present history, with adjuncts of conventional MRI (7/16) which were reported to be negative. This is now clarified in the text.

5. There is an fMRI study of fatigue in MS (Filippi et al., NeuroImage 2002), which should be quoted.
and discussed.

Response:
It is now cited and discussed in the text.

Reviewer #2
General - This is an extremely interesting paper. With implication of the cerebellum, however, it would be of added benefit if the authors had extended their analysis to that part of the brain. However, I would leave the decision of whether or not to do this up to the authors.

Response:
We performed voxel-based morphometry over the whole brain. The prefrontal area was the only region which showed significant atrophy in the CFS compared with the normal control group.
No change was made in the text.

Authors may choose to cite an earlier study in which ventricular enlargement was found in CFS (Lange et al. Applied Neuropsychology, 8:23-30, 2001).

Response:
It is now cited in the text.