

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Are there sleep-specific phenotypes in patients with Chronic Fatigue Syndrome? A cross-sectional polysomnography analysis
AUTHORS	Ellis, Jason; Gotts, Zoe; Deary, Vincent; Newton, Julia; van der Dussen, Donna; de Roy, Pierre

VERSION 1 - REVIEW

REVIEWER	Simon Collin, Research Fellow, University of Bristol, UK No conflicts of interest
REVIEW RETURNED	10-Apr-2013

THE STUDY	The hierarchical cluster analysis method is introduced first in the Results section. This method needs to be described, with appropriate reference(s), in full in the Methods section. Ditto correlation matrix and Euclidean squared distance measure of similarity!
GENERAL COMMENTS	<p>In this paper, the authors investigate heterogeneity in sleep phenotypes among patients diagnosed with CFS. The paper is generally well-written (although none of the statistical methods are described in the Methods section) with a good introduction and thorough discussion placing the study and its results in context. The authors' findings make an important contribution to specialist understanding of sleep disorders in CFS, and the authors also translate their findings into terms which can be understood by the non-specialist.</p> <ol style="list-style-type: none">1. Statistical methods are not described in the Methods section of the paper.2. Figure 1: legend to abbreviations is needed3. Results: sufficient to report P-values and not F-statistics4. Table 2: what do letters a, b, c signify?5. Table 2: sufficient to report P-values and not F-statistics6. I don't understand the authors' statement that the 'significantly' higher ratio of males to females 'is likely to be artefact'. What was the strength of evidence that the apparent difference was not due to chance?7. Did the patients sleep at the clinic? If so, is this likely to affect the results in some way?

REVIEWER	Jo Nijs Associate Professor Vrije Universiteit Brussel Belgium I have no competing interests.
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GENERAL COMMENTS

Patients with CFS suffer from a severe condition, which often includes severe sleeping difficulties. Hence, this is an important area of research. I applaud the efforts done by this international group of CFS experts to study this complex problem. The authors clearly have the expertise to conduct and report such a study. Below you will find my suggestions for improving the quality of the paper.

- I have an issue with the use of 'otherwise healthy' patients with CFS wording. I know this is sometimes used in the CFS literature, but I would advise against it. It diminishes the importance of the diagnosis CFS, and it fuels the controversy surrounding the illness. Please omit it from the paper.
- The use of only one night, without a familiarization night, might be a methodological issue.
- Abstract: please spell out all abbreviations in full (including REM) when first used.
- The large number of patients included supports the submission to a top-ranked journal like BMJ. This is unique for this disorder, especially given the highly specialized and time-consuming nature of the examinations reported here.
- In addition, the findings are compelling, and have wide applicability for GP's. This is important work.
- I think the first paragraph informs the readers about our current understanding of CFS. Nice work! However, one issue is lacking: the role of central nervous system hyperexcitability (central sensitization). Please add to make the picture complete, as it might relate to the topic of interest here (sleep in CFS).
- I have no issues with the remaining part of the introduction, which is very well written.
- The reporting of the methods, applied statistical analyses and reporting of the study findings (results) is fine, I have no issues.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

The heirarchical cluster analysis method is introduced first in the Results section. This method needs to be described, with appropriate reference(s), in full in the Methods section. Ditto correlation matrix and Euclidean squared distance measure of similarity!

Response: This was an oversight on our part and we have now included an analysis section to the manuscript (Page 9, Paragraph 1, Lines 1-9).

Details of ethical approval not given

Response: We have now included details of the ethical approval (Page 8, Paragraph 1, Lines 1-2).

1. Statistical methods are not described in the Methods section of the paper.

Response: This was an oversight on our part and we have now included an analysis section to the manuscript (Page 9, Paragraph 1, Lines 1-9).

2. Figure 1: legend to abbreviations is needed

Response: We have now added a legend to the figure (Figure 1).

3. Results: sufficient to report P-values and not F-statistics

Response: We have removed the F statistics from the text and retained the P-values (Page 10, Paragraph 3, Line 3).

4. Table 2: what do letters a, b, c signify?

Response: We have added a legend to the table to describe what the letters signify.

5. Table 2: sufficient to report P-values and not F-statistics

Response: We feel that it is important for readers to be able to determine the strength of the overall differences from the ANOVA in the results section. As such we would respectfully like to report the F Statistics in Table 2.

6. I don't understand the authors' statement that the 'significantly' higher ratio of males to females 'is likely to be artefact'. What was the strength of evidence that the apparent difference was not due to chance?

Response: We have amended this section as technically a Chi Square analysis was not appropriate as there were two groups with less than 5 males in each group (Page 10, Paragraph 3, Lines 4-5). We have also included the sex distributions by group in Table 2 to add clarity.

7. Did the patients sleep at the clinic? If so, is this likely to affect the results in some way?

Response: Patients did sleep at the clinic. We have made this explicit in the text (Page 8, Paragraph 2, Line 7 & Page 16, Paragraph 1, Line 1) and discussed how this may have affected the results (Page 15, Paragraph 2, Lines 7-9) as a lead into the discussion about the first-night-effect in CFS (Page 15, Paragraph 2, Line 6 – Page 16, Paragraph 1, Line 9).

Reviewer 2:

1. I have an issue with the use of 'otherwise healthy' patients with CFS wording. I know this is sometimes used in the CFS literature, but I would advise against it. It diminishes the importance of the diagnosis CFS, and it fuels the controversy surrounding the illness. Please omit it from the paper.

Response: We have removed the term 'otherwise healthy' from the manuscript (Abstract: Page 2, Paragraph 4)

2. The use of only one night, without a familiarization night, might be a methodological issue.

Response: We agree that a single night study may be an issue due to a lack of familiarisation. We have provided an explanation of this 'first-night-effect' and have made this more explicit in the text and how this may have affected the results (Page 8, Paragraph 2, Line 7 & Page 16, Paragraph 1, Line 1) and (Page 15, Paragraph 2, Lines 7-9) as a lead into the discussion about the first-night-effect (Page 15, Paragraph 2, Line 6 – Page 16, Paragraph 1, Line 9).

3. Abstract: please spell out all abbreviations in full (including REM) when first used.

Response: We have amended the abstract to spell out the abbreviation for REM (Abstract: Page 2, Paragraph 6, Line 5) and checked the rest of the manuscript for this oversight.

4. The large number of patients included supports the submission to a top-ranked journal like BMJ. This is unique for this disorder, especially given the highly specialized and time-consuming nature of the examinations reported here.

Response: We thank the reviewer for their kind comments

5. In addition, the findings are compelling, and have wide applicability for GP's. This is important work.

I think the first paragraph informs the readers about our current understanding of CFS. Nice work! However, one issue is lacking: the role of central nervous system hyperexcitability (central sensitization). Please add to make the picture complete, as it might relate to the topic of interest here (sleep in CFS).

Response: We have included CNS hyperexcitability to the list of physiological factors involved in CFS (Page 5, Paragraph 1, Lines 12-13). We have also added two references here and added them to the reference list (Page 18, References 13 & 14).

6. I have no issues with the remaining part of the introduction, which is very well written.

The reporting of the methods, applied statistical analyses and reporting of the study findings (results) is fine, I have no issues.

Response: Again, we thank the reviewer for their kind comments.