Reviewer's report

Title: Pain disorder leads to a frequency shift in the anterior default mode and the salience network

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Reviewer: Fredrik Ahs

Reviewer's report:

The present study aims at describing differences in resting state networks between patients with unexplained chronic pain and healthy controls. Although I find that the present study has merits, the manuscript suffers from several problems. In general, I find that the authors' interpretation of the results not always are supported by their observations, that there are several instances of awkward language throughout the paper, and that the authors could do a better job in explaining the significance of their findings.

Throughout the paper, poor language often obscures what the authors are trying to communicate. A few examples:

p.4, last paragraph: “The present study aims to elucidate whether chronic somatoform pain, that is, pain that is not the result of a clear organic etiology or is out of proportion to the intensity of physical findings but caused by a well-classified (ICD-10: F45.40, DSM-IV: 307.80) mental disorder [1, 13] characterized predominantly by chronic ongoing pain, shows similar alterations in frequency and functional connectivity within the brain’s functional architecture.”

p. 13, first paragraph: “Moreover, both there is a general trend towards the 0.20-0.24 kHz frequency bin in patients vs. control subjects, and significant changes in the spatial dimension of functional connectivity could not be detected.”

I would suggest that the authors carefully go through the manuscript to correct the language.

Title

1. The title implies that pain causes the described alteration in the default mode network in the patients. The patients’ default network could however have been altered already before they experienced any pain.

Abstract

2. The conclusion is misleading. It is not clear why the present results suggest that chronic pain is a “self-sustaining and putatively endogenous mental process decoupled from nociceptive input”. Also, the association between higher frequencies and chronic pain might not be causal.
Introduction
3. Last paragraph: It is not clear from the introduction why the authors hypothesize that patients would exhibit an altered high frequency pattern.

Methods
4. The procedure used to identify the pain-related networks has to be described with enough detail for other research groups to be able to replicate it. Now, some references are given to other papers that have described the same networks, but exactly how did the authors know that their networks overlapped with the previously described ones?

Results
5. Under “Psychometric Measurement”, it is stated that patients showed higher levels of depression and trait-anxiety, but no statistics are given.

Discussion
6. On p. 14, first paragraph, the authors conclude that: “Given these data, one might speculate that our findings reflect one neurobiological facet of the strong clinical impression that patients who suffer from pain disorder often show reduced subjective emotional awareness and impaired social understanding”. The authors, however, have no data to support that their patients show reduced subjective emotional awareness. Therefore I find this conclusion too speculative. There might be many reasons to the observed difference between patients and controls. I think it would be more valuable to better describe what the functional relevance of high-frequency BOLD oscillations is. See for example Baliki et al. (2011) for a discussion.

7. Were there any systematic differences that could explain the negative results regarding the default network in this study and previous studies that did find differences in the DMN between pain patients and controls? Now the authors discuss the negative findings in terms of the patient population being different from previous samples, which is a possibility

8. I find that the following section on p. 15, first paragraph, is not supported by the results in this study: “The resting state of the human brain is thought to serve as a ‘memory of the future’ [48, 67], which stores behavioral algorithms to allow a person to adequately cope with upcoming environmental events. Therefore, our research on resting state connectivity as a special form of neuronal oscillations in cortical networks [68] might provide a useful and intriguing framework to synoptically explain the behavioral changes that cause impaired daily life interactions for patients with persistent pain.”

References
Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests