Author's response to reviews

Title: A frequency shift in the anterior default mode network and the salience network in chronic pain disorder

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A frequency shift in the anterior default mode network and the salience network in chronic pain disorder

Dear Prof Gerhard Andersson,
Dear Catherine Olino,

Thank you very much for your letter, dated Sep 07, 2012, and for giving us the opportunity to address the points that require attention.

First, we thank the reviewers for their very helpful comments.

Following the reviewers’ suggestions, we have revised the manuscript (including the title).

We hope that this revised version of the manuscript is now suitable for publication in BMC Psychiatry.

Sincerely,

Michael Noll-Hussong, MD
Reviewer 1 - Report:

Title: Pain disorder leads to a frequency shift in the anterior default mode and the salience network
Version: 4 Date: 9 April 2012
Reviewer: Fredrik Ahs

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.

We re-checked the manuscript and now believe that the language is correct.

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.
We changed the title. The title is now “A frequency shift in the anterior default mode network and the salience network in chronic pain disorder” (see in analogy also [1]).

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.
We changed “suggest” to “indicate”. Causality in fMRI studies is a major problem in the field, and in the end, researchers can only show correlations between human behavior and BOLD signals. Nevertheless, the cited literature and the comparison of matched, non-chronic pain-suffering controls indicate that there is at least some reason to consider that the association between higher network frequencies and chronic pain is more than a random association.

3. Last paragraph: It is not clear from the introduction why the authors hypothesize that patients would exhibit an altered high frequency pattern.
Malinen et al. [1] showed that chronic pain influences the temporal aspect of functional connectivity by changing the frequency of the spontaneous firing of neurons within the FIN from lower levels (below 0.12 Hz) to a higher range, between 0.12 and 0.24 Hz. As Malinen et al. [1] examined chronic pain but did not distinguish between nociceptive and non-nociceptive pain, there is good reason to speculate that non-nociceptive pain would also increase the frequency of spontaneous firing of neurons within resting state networks. This is now more clearly indicated in the introduction.

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?
We thank Reviewer 1 for this important critique. Originally, the networks in our study were identified only by visual inspection. Although this approach was widely used in previous
studies on resting state networks and pain, we agree with Reviewer 1 that the reliability and validity of a study needs to be enhanced. Therefore, we compared the networks found in our study (19 controls and 21 patients) with networks that were calculated from a sample of approximately 600 healthy people in a study previously published by Allen et al. [2]. The aDMN showed the strongest overlap with component 25 from Allen et al. [2], which represents the anterior part of the default mode network (multiple regression value 0.22). The pDMN showed the strongest overlap with component 50 from Allen et al. [2], which represents the posterior part of the default mode network (multiple regression value 0.14). The SMN showed the strongest overlap with component 29 from Allen et al. [2], which represents the somatosensory network (multiple regression value 0.14). The FIN showed the strongest overlap with component 55 from Allen et al. [2], which represents the fronto-insular salience network (multiple regression value 0.22). We revised the manuscript accordingly.

Results

5. Under “Psychometric Measurement”, it is stated that patients showed higher levels of depression and trait-anxiety, but no statistics are given. Following the reviewers’ advice, we added median scores, ranges and p-values to Table 1 (see revised manuscript).

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.
The functional relevance of high-frequency BOLD oscillations is actually quite speculative. Malinen et al. [1] state in their abstract: “The accentuated 0.12- to 0.25-Hz fluctuations in the patient group might be related to altered activity of the autonomic nervous system”, but the nature of this assumed relation is unclear (“However, the exact relationship between local vasomotion and, for example, the ANS drive as a possible synchronization mechanism of arteriolar diameter variations still remains an open question.” [1]). Baliki et al. [3] state: “The neuronal mechanisms linking spontaneous pain processing to high-frequency BOLD fluctuations within the frontal cortex remains unknown and can be attributed to both peripheral and central processes”. These authors then speculate about a broad range of processes that might be involved, termed “peripheral and central processes”. We wish to add a new and more biopsychosocial point of view without reiterating what has been written already by Baliki et al. [3]. We believe that there is good reason to speculate about the clinically relevant and well-known characteristics of somatoform pain patients [4-8] because the readers of BMC Psychiatry are often clinicians.

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.

Our patient population is different from previous samples because there is no convincing nociceptive input that could explain the ongoing pain from which they suffer; in fact, we specifically ruled out such an input (see Methods). In all other samples that have been studied so far, nociceptive input is not ruled out, leading to at least some kind of neural processing of peripheral sensory pain that might influence the DMN. In our patient sample, there is no peripheral nociceptive pain input that was able to explain the pain from which the patients subjectively suffer; therefore, some call it “medically unexplained pain”.

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.”

Our last sentence in the discussion section is speculation that encourages further research. We changed it as follows:

“The resting state of the human brain is thought to serve as a ‘memory of the future’ [9, 10], 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 [11] might provide a useful framework that reflects the behavioral changes that impair the daily lives or interactions with their environment of patients with chronic pain disorder. “

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
Reviewer 2 - report

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

Version: 4 Date: 21 August 2012
Reviewer: Karin Jensen

Reviewer's report:

1. Is the question posed by the authors well defined?

Major revision: Not really, since the distinction between “explained” pain and “unexplained” pain is confusing. It is not true that the pain in previous studies, mentioned in the introduction, have “a convincing organic correlate”. Chronic low back pain, for example, is often idiopathic and not more organic than the pain described by the authors in this manuscript. The point is that previously “unexplained” pain syndromes have become medically explainable due to scientific progress. The cause for pain is often impossible to determine in chronic pain disorders and comorbidity with psychiatric diagnoses is high. High correlation doesn’t mean that there is a given causality where negative affect leads to pain. The authors should have adapted a more dynamic approach to the definition of “unexplained chronic pain” and psychiatric symptoms. How many patients with musculoskeletal pain such as Fibromyalgia, or IBS, would fulfill the inclusion criteria in this study? In spite of the point about “explained” versus “unexplainable” pain in the introduction, the discussion seems to include both types of pain without any mechanistic distinction. Very confusing.

We thank Karin Jensen for this remark, as we personally fully support her point of view. Unfortunately, in previous studies in the field, especially US-based studies, authors have not distinguished between different origins of pain (central versus peripheral), nor have they discussed the inclusion of a few chronic pain patients in their population (for example, patients with CRPS II, cervical spine degeneration and phantom limb pain in the study of Malinen et al. [1]). To our knowledge – and despite unquestionable scientific progress – there is no convincing and accepted neurobiological model that could explain somatoform (pain) disorder. Due to diverse reasons, such as the coexistence of the DSM-IV for the USA and the ICD-10 for the rest of the world, the term “somatoform pain disorder” is generally avoided in the American scientific literature and replaced with terms such as “functional pain” or “medically unexplained pain” [12]. Thus, the “confusion” is also an issue of disease classification and different ideologies or scientific belief systems behind
the diagnosis; perhaps something will change with the introduction of the ICD-11 or DSM-V [13].

However, we tried to be more precise and modified our introduction and discussion accordingly. Our homogenous patient population is well classified as patients with chronic pain disorder (see Methods). Personally, we do not support artificial syndromal concepts such as ‘fibromyalgia’, which echo the parallel [14] classification of human disorders as functional or somatoform disorders in our present official classification systems (e.g., see [15, 16]).

2. Are the methods appropriate and well described?

Major revision: Methods are generally well described but the practical steps around fMRI scanning are poorly described. The multiple comparison correction in the less stringent fMRI analysis (threshold at p=0.005) needs to defined: Was it voxel-wise or cluster-wise? Is there a z-value threshold that the authors can describe in the methods section, instead of p-values? How was the functional connectivity in relation to depression and anxiety scores performed? Dual regression? This needs to be described in the methods section.

The a priori threshold was p = 0.005 uncorrected on the voxel-level and p = 0.05 corrected for multiple comparisons on the cluster level. The uncorrected threshold on the voxel-level was chosen to reduce the risk of false-negative results. Following the reviewer’s advice, we added the corresponding z-value threshold as z > 2.58 following Baliki et al. [3] (see revised manuscript).

The reviewer asked how the functional connectivity analysis was performed in relation to the depression and anxiety scores.

1. To detect significant group-differences in functional connectivity, we performed two-sided unpaired 2-sample t-tests with the depression scores and anxiety scores as covariates of no interest (see revised manuscript).

2. To measure the influence of depression, anxiety, and clinical pain on functional connectivity, we performed a partial correlation analysis between the functional connectivity and the level of depression (controlling for the level of anxiety) in the patient group using SPM5. We also performed a partial correlation analysis between functional connectivity and the level of anxiety (controlling for the level of depression) in the patient
group. Furthermore, we correlated clinical pain with functional connectivity in the patient group (see revised manuscript).

3. Are the data sound?

Major revision: Six minutes of BOLD fMRI for resting state is normal and the analyses used in this study are standard. However, the comparisons of power spectra seem to suffer from a multiple comparison problem. Do the results survive Bonferroni correction?

The threshold was $p < 0.05/6 (=0.0083)$, which represents a Bonferroni correction for 6 frequency bins per network. Therefore, all significant results in the FIN and the aDMN survive Bonferroni correction because they are lower than $p < 0.0083$.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

Minor revision: Yes, but data is not detailed. Only the main results are reported and there could have been more elaborate investigations of data by using plots or looking at functional connectivity that controlled for ongoing clinical pain etc. P-values should be mentioned in the tables.

Following the reviewer’s advice, we added a new table to better describe the relationship between the power spectra and the psychometric measurements (Table S5). Furthermore, we added a table to describe the (non-significant) correlations between psychometric measurements and functional connectivity (Table S4). P-values were added to the tables. Moreover, a table was added to describe the non-significant group differences in functional connectivity (Table S3).

5. Are the discussion and conclusions well balanced and adequately supported by the data?

Major revision: Some points in the discussions are presumptuous, for example the section about “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 discussion should mirror the line of thought used in the introduction, where somatoform disorder is thought to be different from pain syndromes with a clear
etiology. We revised the discussion, keeping the possible clinical-psychiatric (and not “only” neurobiological) implications of our findings in mind.

6. Are limitations of the work clearly stated?
Major revision: Yes. However, the theoretical limitations of this work are not considered. The distinction “medically explained” and “unexplained” needs to be addressed.
See point 1.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes.

8. Do the title and abstract accurately convey what has been found?
Major revision: NO. The title implies causality, which has not been investigated in this study. “Pain disorder leads to…” This has to be changed into a more appropriate title.
The title has been changed. The title is now: “A frequency shift in the anterior default mode network and the salience network in chronic pain disorder”.

9. Is the writing acceptable?
Minor essential revision: Acceptable but needs revision and language check.
Language has been checked and revised.
Level of interest: An article whose findings are important to those with closely related research interests
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
Reviewer 3 - report
Title: Pain disorder leads to a frequency shift in the anterior default mode and the salience network

Version: 4 Date: 17 August 2012
Reviewer: Radi Masri

Reviewer's report:
Dear Dr. Anderson

The research manuscript by Noll-Hussong and colleagues describe significant temporal changes in brain functional connectivity in patients suffering from somatoform pain disorder. In these patients, the authors find increased power in higher frequency bands in cortical networks commonly involved in pain processing. While overall this is an important contribution to the literature, I have several reservations:

**Major Compulsory Revisions:**

1- The authors provide no rationale as to why they decided to use 6 frequency bins. None of the cited studies that perform similar analysis used similar bins. What did the authors do to confirm that the results they find are not just due to the bins they used?

The analysis program we used is well validated and established in the analysis of neural networks (see revised manuscript). From a methodological viewpoint, more bins lead to a higher possibility of obtaining false positive results. Therefore, we used Bonferroni corrections.

2- The conclusions are over stated. The authors demonstrate that the patients suffer not only from somatoform pain, but also from depression and anxiety. All of these conditions are known to affect the networks studied. Why are the changes due to pain and not depression, or anxiety? or the combination of the three?

All group comparisons were corrected for the influence of depression or anxiety (covariates of no interest). Until now, the causal relationship between pain and mental disorders such as anxiety and depression remains unclear. Depression increases the risk for chronic pain disorder, and chronic pain disorder increases the risk for depression; however, a convincing, undisputed causality in either direction has not been proven.
3- The authors provide spatial connectivity maps (Fig. 1) for the two groups combined together (patients and controls). The authors should show these spatial maps separately for each group.

Following the reviewer’s advice, figure 1 was completely revised.

4- In the Results, the authors provide no numbers or statistical figures for the readers to evaluate the magnitude of shifts in the frequencies. The 3D figure shown (Fig. 2) depicts the results poorly. A two dimensional figure showing standard deviations and statistical annotations on the figure would be more helpful. In addition, perhaps show only the results from the networks that had significant changes.

Following the reviewer’s advice, we completely revised this figure. We added error bars and showed the results from networks that had significant alterations (now Figure 3).

Minor Compulsory Revisions:

4- In Table 1 please indicate that these results are the average of the group scores (not a total score). Also, please provide the median scores, range and p values.

Table 1 was revised.

5- When reporting that no correlation existed, please provide the correlation coefficient s and the p values.

We added new tables (Table S4 and Table S5).

6- The authors should be consistent with the terms they use throughout the manuscript, for example: The authors use the term cingulate-insular networks (CIN) in the results while in discussion they refer to the frontal-insular networks (FIN); use the term somatoform pain disorder rather than chronic pain disorder and avoid using the term “nociceptive pain”.

We revised the manuscript. The DSM-IV states: Chronic pain disorder is a somatoform disorder lasting longer than 6 months in which the predominant area of focus is painful bodily complaints in which psychological factors are determined to be central to the onset, severity, exacerbation or maintenance of the complaint [17] (see first sentence of our introduction). Therefore, both terms - “chronic pain disorder” and “somatoform pain
disorder” - equally reflect the international usage of the designation of this clinical entity, keeping both the US- (DSM-IV) and non-US-reader (ICD-10) in mind. Against the background of the most relevant literature in the field (e.g., [1, 3, 18, 19]), we prefer to use the term “chronic pain disorder”, as we want to follow the tradition of published results and maintain consistency in the scientific literature.

7- Spell out abbreviations the first time they are mentioned.
We corrected this issue.

8- In the text, Table S2 is mentioned before Table S1. It is probably more logical for them to be numbered according to when they appear in the text.
We revised the text according to the reviewer’s advice.

9- In Table 2, please replace all commas with a decimal point.
We revised the text according to the reviewer’s advice.

10- In Background, second paragraph, the authors report: “chronic pain influences the temporal aspect of functional connectivity by changing the frequency of spontaneous firing of neurons within the FIN from lower levels (below 0.12 Hz) to a higher range between 0.12 and 0.24 Hz [11].” The study cited did not assess spontaneous firing of neurons, and only studied rhythmic oscillations in BOLD signals.
We thank Reviewer 3 for this important advice. The BOLD-signal is an epiphenomenon (see [20]). Therefore, we revised the text according to the reviewer’s suggestions.

11- There were several grammar mistakes. Those are indicated in the attached file.
We also re-checked the manuscript for language and grammar.

Discretionary Revisions:
It is not clear why the authors focused their study only on the 4 networks described in the results. Somatoform pain, as the authors point out, is atypical and may affect areas other than those altered by neuropathic or diabetic pain, especially when combined with depression and anxiety. It would be helpful to the readers to show whether other networks are changed/or not in this condition.

We focused on published pain- and emotion-related networks to test the hypothesis that somatoform pain is associated with disturbed pain processing. Of course, other networks could be of interest using a more exploratory approach. Our approach, however, was driven by the hypothesis that disturbed affective and sensory-discriminative processing occurs in somatoform pain disorder.

Level of interest: An article whose findings are important to those with closely related research interests
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 have no competing interests
References


