Author’s response to reviews

Title: Association between fatigue, motivational measures (BIS/BAS) and semi-structured psychosocial interview in hemodialytic treatment

Authors:

Michela Balconi (michela.balconi@unicatt.it)
Laura Angioletti (laura.angioletti@gmail.com)
Daniela De Filippis (daniela.defilippis@unicatt.it)
Maurizio Bossola (maurizibossola@gmail.com)

Version: 2 Date: 04 May 2019

Author’s response to reviews:

Dear professor Harris and Byrne,

Thank you for your answer. We have revised the paper taking into account Reviewer’s suggestions.

We included a response to the Reviewer (6 pages), that reports our answers. Additional changes introduced in the text were underlined in green colour.

Waiting for other requests you may wish to make.

Sincerely,

Angioletti Laura

Department of Psychology
Catholic University of Milan
Largo Gemelli, 1
20123, Milan, Italy
Phone: +39-2-72345929
e-mail: laura.angioletti@gmail.com

Reviewer reports:
Nicole Rascle, Ph.D (Reviewer 1): Corrections requested have been made. The quality of paper is significantly improved.

Haikel A. Lim, MSc (Reviewer 2): Thank you for the opportunity to review this revised manuscript. I appreciate the amount of work the authors have put into revising the manuscript. I have a few suggestions that I think might improve upon the manuscript quality for publication in BMC Psychology.

1. The authors might need to clarify if only central or both physical and central fatigue are related to (mediated by?) inflammation (line 55). It would also be good if the authors could give examples of such clinical/biomarkers associated with fatigue; and on related note I would generally caution the authors against making such a statement given that, at best, these associations are non-causational--ill patients generally have elevated inflammatory markers independent of fatigue.

R: We added the following paragraph in the introduction to clarify this point and to add clinical/biomarkers associated with fatigue.

“Indeed, it has been suggested that essentially central fatigue is related to chronic inflammation in patients with chronic disease [11]. Associations between fatigue and inflammatory markers (primarily Interleukin-6, Tumor Necrosis Factor-alpha (TNFα) and C-reactive protein, an acute phase protein) have been previously documented in various medical conditions, including cancer, chronic inflammatory disease, autoimmunity, neurological diseases, and mood disorders [12–14]. With regard, specifically, to end-stage renal disease an association between fatigue and serum IL-6 levels or tryptophan has been recently demonstrated [1, 15].”

We agree with the reviewer that, although given the cross-sectional design of these studies cause-effect relationships cannot be established, a direct relationship of these two factors can be suggested. The use of correlational analysis supports this interpretation. We stated this also in our conclusions.

2. Given the broad reach of BMC Psychology, it would benefit readers if the authors explicated briefly how "inflammatory processes have...influence[d] the functioning of basal ganglia" (line 59).

R: We added a specific in-text paragraph for explaining this point:

“Stimulation of the immune system or the administration of inflammatory cytokines to laboratory animals and humans results in a repertoire of behavioral changes, many of which overlap with those experienced during medical illness and those that have been classically described in depression. Many of these symptoms are also consistent with disruption of the basal
ganglia and dopamine function, including anhedonia, fatigue, psychomotor disturbance, and changes in sleep [17, 18]. There is also evidence, by structural and functional magnetic resonance imaging, alongside diffusion tensor imaging and functional connectivity studies, of significant brain indicators of fatigue essentially in the frontal lobe, parietal lobe, limbic system and basal ganglia [19]."

Further, I think the line of argument may need to be refined; at present the authors are arguing that: fatigue involves some amount of inflammation, inflammation influences basal ganglia function, basal ganglia and prefrontal cortex structures influence motivation/reward, BIS/BAS has been associated with prefrontal cortex and therefore may influence fatigue. The issue here is that, as the authors argue, the BIS/BAS framework seems to have been only associated with the PFC—if there any evidence to suggest that it might be related to the basal ganglia it would greatly help the line of argument.

R: Thanks for this note. We added an evidence from a previous study in order to relate BIS/BAS framework to also basal ganglia structures.

“Moreover, Angelides and colleagues (2017) have recently demonstrated, using resting-state BOLD, correlations between two basal ganglia (caudate and putamen) and bilateral OFC ROIs, establishing single subject connectivity summary scores. Summary scores were correlated with components of BIS/BAS scores. These results demonstrate a novel correlation between BAS-fun seeking and resting-state connectivity between middle OFC and putamen, implying that spontaneous synchrony between reward-processing regions may play a role in defining personality characteristics related to impulsivity.”

3. While I think the authors are operationally and functionally using the "scale" for BIS/BAS, might I suggest that the authors themselves actually mean to use the theoretical framework of the BIS/BAS for understanding behavioural motivation in patients on HD? Specifically highlighting the tool may bring about significant criticism regarding the psychometric properties of the tool and its interpretation, which I assume is not really the crux of this manuscript—rather, the authors seem to want to lens the BIS/BAS to better understand fatigue in patients on HD, which seems to be a novel contribution to the literature.

R: Thanks for this suggestion, we highlight the theoretical framework of BIS BAS and we elucidated the relationship between Gray’s model, BIS-BAS and fatigue in chronic patients by adding more details in the introduction.

“In order to better understand the relationship between fatigue and reward system in patients on hemodialysis treatment, Behavioural Inhibition System (BIS) and Behavioural Activation System (BAS) Gray’s model [20, 21] may holds potential for exploring behavioral motivational responses that are relevant to approach and withdrawal behavior. Indeed, according to this model two fundamental motivational systems, BIS and BAS, may explain individuals motivation and emotion at four different levels: behavioral, neural (i.e., defining the brain structures and activity related to motivational behaviors), computational and personality level, that is, reflecting individual differences in the functioning of the basic systems of motivation [22].
Going down with the specifics, [...] 

Besides previous studies suggested a possible correlation between behavioral inhibition and activation systems, reflecting motivational dispositions, levels of fatigue and different patients’ experiences of chronic conditions, comparable to hemodialysis treatment [11, 31, 32]. Taken together, these evidences allowed us to suppose that BIS/BAS theoretical framework and related measurement scale could be interesting firstly to measure motivational tendency in HD patients and then to be linked to possible differences in their fatigue severity levels.”

4. I am still having some trouble seeing the value the qualitative component brings to this manuscript (lines 106-111) given that the authors have rightly pointed out other studies that have since been done on fatigue amongst patients on HD (lines 103-105). Perhaps if the qualitative component were to better reinforce or elucidate the findings from an as-yet theoretical conceptualisation of BIS/BAS as mediators/moderators of fatigue, this might be clear to readers and would capitalise on the value of their contribution of this manuscript to the extant literature. It is important for the aims to come across strongly to the readers because the analyses later may come across as confusing.

R: We stressed the relevance of adding the contribution of qualitative components by adding the following paragraphs:

“Thus, we believe that given the theoretical conceptualization of BIS/BAS as possible moderators of fatigue, the added value of including qualitative components could be the reinforcement and elucidation of motivational and fatigue related aspects in this chronic population. So far, to our knowledge, only one previous study investigated the association between BIS/BAS motivational systems, fatigue severity and words belonging to psychosocial topics emerging from interviews applied to hemodialysis patients [32]. This novel preliminary evidence highlighted how HD patients narratives analysis allowed to suggest an association on one side between higher levels of BIS and patients’ tendency to stress more the negative aspects of their daily routine, from the other between patients with high and medium levels of BAS and their use of a vocabulary associated to approach behavior, such as the use of words related to their role in seeking strategies to face chronic conditions.”

5. The hypotheses might need to be clarified; might I suggest the authors present their hypotheses in accordance to their aims? Based on my interpretation of the manuscript, I am assuming that the authors' aims were to (a) identify the influence of BIS/BAS as a theoretical framework to understand fatigue in patients on HD; (b) examine the influence of gender in the relationship between BIS/BAS and fatigue; and (c) explore how patients' lived experiences further reflect and reinforced the relationship between BIS/BAS and fatigue. Therefore, in line with these aims, it seems like the hypotheses are (a1) as the authors rightly described (lines 117-118); (a2) a negative correlation between BAS and fatigue scores (again I am postulating but am not sure if this is what the authors are gunning for); (b1) gender would moderate the relationship between BIS/BAS and fatigue; (c1) the BIS component would be correlated with more
negative(?) themes... ; and (c2) the BAS component would be correlated with more positive(?) themes. This is the assumed hypotheses that I am going on when reviewing the rest of the paper.

R: Thanks, we followed your suggestions and we specified hypothesis in line with aims.

6. It would be helpful for the authors to also use the full phrase for the FSS in page 6 (line 118) as I believe this is where we first encounter the term.

R: Thanks, acronym was specified.

7. It would be helpful for readers if the authors included their sampling frame numbers or the response rate just as a gauge for sample representativeness. It might also be helpful if the authors highlighted that all N=94 participants were interviewed (I am assuming).

R: Thank you, we added this detail.

8. I am assuming the clinical markers are those that may influence disease control/progression/severity and may be related to fatigue (anemia, etc.); but the authors may need to justify their use of the BDI and STAI since these are not mentioned in the hypotheses but are used all throughout the results. It might also be helpful to label Y1 as State and Y2 as Trait.

R: BDI and STAI were used only for excluding related anxiety disorder or depressive symptoms in the sample. We mentioned this point in text.

9. Were the additional medication taken (BB, CCB, ACEi, EPO, etc.) taken into consideration in the analyses given their influence of "fatigue" scores? If so this should be highlighted, and if not, this should be included as a limitation.

R: Thanks for this note, we have added this aspect as a limitation in the conclusion of our discussion, as following: “Future studies may also consider and analyze the additional medication taken by patients as possible factors influencing fatigue levels in this specific population.”.

10. It would be helpful for readers who are not familiar with these scales (FSS BIS/BAS BDI STAI) if the authors provided the Cronbach’s alpha in their sample.

R: Cronbach’s alpha coefficient have been inserted for FSS, STAI, BIS/BAS and BDI.

11. Might the interview questions, especially the closed questions, that were used be available as supplementary material for readers? It would be helpful to also understand which items were
used as dichotomous responses, and which were scored on a Likert-type scale. If one item could be graded both dichotomously and as a Likert-type format this needs to be explained and justified.

R: Yes, this material may be made available on request, not as supplementary file, due to the actual structure of the paper. No transformations were applied to these items: dichotomous items were graded dichotomously and items on Likert-type scale as Likert only.

12. It is also unclear what the authors are describing from lines 220-225. Based on my reading it seems like the closed-ended questions were graded on a dichotomous or Likert-type scale, and the qualitative components were also then given scores. It is not very clear why the qualitative components were given scores, and how these were scored.

We defined the topics based on transcripts analysis. Dichotomous items (e.g. Have you ever asked for psychological support since you started the dialysis?) and Likert scale Type items (e.g., On a scale from 1 to 5 -where 1 is not at all and 5 a lot-, how much do you think support from a mental health specialist could help in hemodialysis?) were related to the qualitative nature of the topic. Within each qualitative topic a main dimension related for example to the utility of the psychological figure within the hemodialysis department was identified and dichotomous variable assess this fact (for example yes/no).

Was each transcript graded on how frequent the topics (1-8) appeared as compared to itself, or to the rest of the 93 transcripts? Given the subjective nature of agreement between judges, the scientific and quantitative rigour applied to the qualitative interviews need to be better explicated.

R: The eight topics were present in all the sample (for each participants). The agreement reliability for raters was Cohen’s kappa=.88.

13. Given the large spread of "dialytic vintage", might the authors suspect that this would influence results? This should be discussed. Further, was this, and other variables, "normal" based on the kurtosis/asymmetry? Given the parametric tests used I am assuming this is the case.

R: we inserted this note at the end of Discussion, as a possible limitation. Asymmetry and kurtosis were checked before the inferential analysis.

14. If the authors are going to compare gender (as alluded to in their hypotheses; Table 3), please also state which test was being used in the statistical analyses portion--no statistical values other than the P value was used so readers are left wondering which tests were employed. If the goal is to investigate the moderating effect of gender, there are many other suitable tests for these aside from just splitting the sample in two.
R: Within the paragraph “Gender differences in fatigue levels and BIS/BAS score”, we specified that we splitted the sample for gender variable and we used independent-groups t test to test potential differences in FSS and BIS/BAS scores. Our sample was a priori balanced for gender in order to compare male and female groups of patients and to apply following correlational analyses.

We limited the data report to this statistical aim. For this reason, some not useful data were eliminated (see revised Table 3).

15. I think the authors using mean BDI and STAI scores are somewhat problematic given the spread of their data. Again, the use of these scores need to be justified, and if it truly is to rule out patients who may have comorbid probable depression/anxiety then perhaps the authors might want to use another approach (exclusion, controlling for these in regression/correlation models, etc.).

R: We applied BDI and STAI for excluding related higher levels of anxiety, anxiety disorders or depressive disorders in this study, for the present sample. We used this criterion for excluding possible confusing effects deriving from higher anxiety levels and depression disorders. However, the possible comorbidity was not denied to priori, but it was not of our interest, and for this reason it was not hypothesized in this study and not controlled with regression or correlation models.

16. I am of course basing this comment on my assumption of what the hypothesis is, but I believe that a regression model or at least a partial correlation model would be more suitable to investigate the BIS/BAS relationship on fatigue (controlling for the effect of depression/anxiety/clinical lab parameters). The hypotheses again need to be clear so that we as readers can follow the line of thought and better appreciate the results.

R: as reported for the point 1 in our response and as suggested by the Reviewer, due to absence of a clear causal relationship between BIS/BAS and fatigue construct suggest a more cautious model of analysis: for this reason, we used the correlational analysis. A successive step of the present research could better explore this relationship, considering also other possible mediators/moderators.