Author's response to reviews

Title: Evaluation of emotion processing in HIV-infected patients and correlation with cognitive performance

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Author's response to reviews: see over
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The Biomed Central Editorial Team
Object: MS: 7697420078046057 - Evaluation of emotion processing in HIV-infected patients and correlation with cognitive performance. Dr Eleonora Baldonero et al.

Thank you for consideration of our manuscript for publication in your journal.
We have reviewed the above manuscript according to yours and reviewer’s comments.

Editor's comment:
Dear Dr. Baldonero
Your manuscript has been reviewed both by myself and an expert in the field. We both thought the paper timely and interesting and I would like to invite you to submit a revision of the paper taking into account the points made in the reviews.
Can you please outline how you have addressed each point.
Can you please especially attend to: a) the recent paper by Lane and colleagues (mentioned by both reviewers)

Now we have mentioned and discussed the recent paper by Lane and colleagues (2012) as suggested by both reviewers.

*Ethics Statement*
Research involving human subjects (including human material or human data) that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html). A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

Now we added this information in Section: Methods, paragraph: Standard protocol approvals, registrations, and patient consents. “The research design and protocol received ethical approval from University of Sacred Heart-Rome Ethics Committee. Informed consent was obtained from all participants according to the Helsinki Declaration.” Pag. 6.
Reviewer: Uraina Clark  
**Reviewer’s report:**  
This interesting manuscript reports on facial emotion recognition impairments in HIV patients – a newly emerging, but still understudied, area of research. As such, this study has the potential to make a valuable contribution to the literature. Yet, there are several methodological issues that need to be addresses, as well as some issues relating to content, described below.

**Major Compulsory Revisions**

1. In the Introduction and Discussion sections, please consider integrating results from a recent paper relevant to this topic: Lane et al 2012 (*Neuropsychology, 26*(6):713-22). Now we have added the sentences: “HIV infected patients, compared to an healthy population of subjects, performed worse on emotion recognition tasks, as described in a recent paper [22]” in section: Introduction, pag. 5; the reference [22] in the sentence “Similar to previous studies [22,23], we found that HIV-infected patients performed worse than HC in recognizing the facial emotion of fear” in section: Discussion, pag. 11; the sentence: “...in agreement with a recent study [22] demonstrating that the ability to discriminate between levels of happiness intensity on facial expression was specifically altered in HIV patients with impaired neurocognitive performance” in section: Discussion, pag. 13

2. Are the HIV and HC groups matched on IQ? If there are group differences in IQ, have the authors assessed whether their main findings are driven by this difference? It is pointed out on Pg 18 in the Discussion that previous studies have “reported a relationship between facial emotion recognition and level of intellectual functioning [47, 48].” Were IQ measures obtained in the current study? If the issue of potential group differences in IQ cannot be addressed, please discuss this as a possible limitation. In the current study we did not assess IQ, neither for patients or controls. Now we have discussed this issue as a possible limitation; we added the sentence “Furthermore, we cannot exclude a possible confounding effect of different IQ on emotion recognition, although there is no reason to assume a different distribution of IQ value in patients and controls” in section: Discussion, pag. 14.

3. Several analyses are conducted (e.g., Pearson correlations) but no corrections are made for multiple comparisons. It seems to me that one way to reduce the number of comparisons would be to restrict correlations to those emotions and/or neuropsychological measures on which HIV patients are found to be impaired compared to HC. Please also consider correcting for multiple comparisons. We agree with the reviewer to restrict the correlation analysis to those emotions that we found to be impaired in HIV infected patients compared to HC (fear). We have changed the paragraph title and text in section Results, pag 10-11: Correlation between Fear Facial Emotion Recognition score and performance on neuropsychological tests: “For HIV-infected patients, we conducted a correlation analysis between their Fear Facial Emotion Recognition score and scores obtained on each test of the neuropsychological battery (see Table 3). Fear facial emotion recognition was directly correlated with Immediate recall of Rey Words”. The Bonferroni’s correction for multiple comparisons set the p value at ≤0.004; the significant correlation between Fear recognition accuracy and Immediate Rey recall was confirmed. We added the sentence: “To control for the probability of committing a type I error in multiple comparisons, the Bonferroni correction was adopted by setting the p value at ≤0.004” in section: Methods, paragraph: Data Analysis, pag. 8.
We have also corrected the Table 3, removing data about correlations between Neuropsychological performance and the other emotions. Moreover, we have removed the sentence “When specific cognitive domains were considered, an indirect correlation also emerged between the facial emotion recognition global score and performance on memory, executive and mental processing tasks. Performance on the executive and speed of mental processing tasks was also correlated with performance in recognizing most of the emotions” in section Discussion, pag. 13

4. Page 8, is it common to use a p-value of 0.1 to determine significance? The p value of 0.100 was not used to determine significance but to select variables (those showing a trend to significance) to be analyzed in multiple regression analyses.

5. The variables included in the regression analyses are somewhat unclear, as is the specific number of regression analyses conducted. This raises 2 potential concerns: 1) The possibility that regression analyses may include too many predictors for the sample size. It’s often recommended that one includes a minimum of 10 cases per IV. If this is not possible, could the authors consider applying a method for data reduction? 2) Multiple comparisons resulting in possible Type 1 errors. IV and DV included in the regression analysis are:
   IV: age, gender, education, HIV transmission risk factor, HCV coinfection, years on cART, CD4 cells count, CD4 cells count at nadir, AIDS events, HIV-RNA, CPE rank, number of pathological score at neuropsychological battery, depression level.  
   DV: Facial emotion recognition global score, each emotion score. We conducted a univariate regression analysis for all the IV on each DV. For the multiple regression analysis, we consider all IV that showed a p value <0.1 associated with the DV in the univariate analysis. The IV included in multiple regression analysis never were more than 5 in each multiple regression.

6. Can additional justification be provided for the use of covariates in the regression analyses (e.g., age, education, depression levels, etc.)? Now we added this sentence to clarify this issue (section: Methods, data analysis, pag 8): “Several studies showed that age [37] and depression levels [38] have an impact on emotion recognition abilities; according to these studies, we included this demographic and clinical variables as covariates in multivariate analysis.” We removed education as a covariate according to Discretionary Revisions, point 2.

7. Some analyses appear to examine the relation between past AIDS-defining events and emotion recognition, but this group seems to be relatively small. Is it correct that the number of patients with AIDS-defining events is 9? How could this affect the authors’ interpretation of their results? HIV patients with past AIDS-events are 9: it is correct. Although “9 past AIDS event” subjects is not a large number of observations we could obtain a significant p in the regression analysis. Moreover comparing happiness accuracy of patients with previous AIDS events, with patients without previous AIDS events, we observe a significant difference between the two groups (previous AIDS mean (ds) = 9.11(1.8), NoPrevious AIDS mean (ds) = 9.82(0.4), p= 0.029). This last statistic however is not reported in the manuscript.

8. Did the HIV and HC groups perform similarly on neuropsychological measures? Unfortunately, we did not assess the neuropsychological performance of control population, so it is not possible to determine if the two groups performed
similarly on neuropsychological battery. However, to determine the normality/pathology of patients’ score, we used normative data available for Italian population and not direct comparisons with control population.

9. Could the authors refine the arguments presented on Pg 12 in the paragraph beginning, “In agreement with the results of cross-cultural studies…”? I found this section to be a little confusing. Also please consider that, without the use of a non-emotional control task, the possibility remains that HIV patients in this sample could be impaired on fear recognition simply because this is the most difficult emotion to recognize. 

We agree with the reviewer that our results do not allow us to say if fear recognition is sensitive to the HIV pathology, compared with other emotions. Now we discuss this issue in section: discussion, pag. 12.

10. Pg 12, what is the justification for the statement that, “fear recognition should be considered an early marker of cognitive impairment”? A similar statement is made on pg 13. It is possible that I have misunderstood, but it seems to me that these statements are not well supported currently. Beyond performance on verbal memory tests, there were no correlations between general cognitive ability and fear recognition. In addition, the HIV patients with ANI did not demonstrate significantly greater fear recognition difficulties than those without ANI. Could the authors clarify these statements a bit more, or perhaps provide additional support for these assertions?

We agree that our results do not support the hypothesis that fear recognition should be an early marker of cognitive impairment. Now we talk about this issue in section Discussion, pag. 13.

Moreover we have removed the sentence: “Our findings support the hypothesis that recognizing fear might require the integrity of neural networks specifically damaged by HIV infection, also in the early stages of central nervous system involvement. Although the effect of task difficulty cannot be excluded, the difficulty of recognizing this emotion, even in cases of minimal brain damage, makes it a possible marker for early identification of cognitive disorders in HIV-infected patients.” In section: Conclusions, pag 13.

11. Pg 13, I found the following phrase to be a little confusing, “…accounts for the observation that happiness is easier to recognize than other emotions.” Can this be clarified?

We now have changed the sentence in section: Discussion, pag. 13: “The association between recognition of happiness and general neurocognitive impairment as well as past AIDS-defining events, could lead us to hypothesize that a deficit in recognizing this emotion might emerge only in subjects in more severe stages of HIV pathology in agreement with a recent study [22] demonstrating that the ability to discriminate between levels of happiness intensity on facial expression was specifically altered in HIV patients with impaired neurocognitive performance.”

Moreover, we have removed the sentence: “AIDS-defining events depend on CD4 cells, and a decrease in CD4 cell counts has been associated with gray matter atrophy in the frontal lobe [45]. We found an association between past AIDS-defining events and low scores on recognition of happiness. There may be an indirect relation between CD4 cell counts and the development of abnormalities in emotion recognition, primarily happiness.”

12. Pg 14, Can the authors clarify what is meant by the following: “This could explain the indirect relationship between CD4 cell counts and the
development of abnormalities in emotion recognition, primarily happiness?”? Perhaps I missed something, but I did not find these results reported in the manuscript.

We agree with the reviewer about the speculative nature of this issue, so we decided to remove the sentence: “This could explain an indirect relationship between CD4 cell counts and the development of abnormalities in emotion recognition, primarily happiness.”, section: Discussion, pag 14.

Minor Essential Revisions

1. Page 7 what “cut-off” is used to define ANI status (e.g., 1 SD below the mean of demographically adjusted normative data)?

To define ANI status we use the guidelines explained in Antinori et al., 2007; in their article, ANI was defined as an acquired impairment in cognitive function, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. We corrected the sentence”. Patients were diagnosed with Asymptomatic Neurocognitive Impairment (ANI) if they scored 1SD below the normative cut-off in two or more domains according to standard criteria [33]”, Section: Methods, Neuropsychological examination, pag 7.

2. Please add data for the IADL scale to Table 2.

Now we have added the sentence “IADL score was at ceiling for all patients (8/8)” section: Results, pag 9. We did not add IADL data in the Table because the score was at ceiling for all patients.

3. Page 7, how long were participants allowed to view facial stimuli before responding (e.g., unlimited time, 3 sec)?

Participants could view the facial stimuli until they gave the response. Now we have added the sentence “Participants could view the facial stimuli until they gave the response with no time limitations.” In section: Methods, paragraph: Neuropsychological examination, pag 7.

4. The results from the ANOVA do not include df information for the residuals of the model. Is this standard practice for this journal? Also, is the df reported correctly for the main effect of emotion (Pg 9)?

We now have added df information for the residuals of the model, for the ANOVA (section: results, paragraph: Performance on the Facial Emotion Recognition Test, pag. 9).

There was a typo in the text for df reported for the main effect of emotion; we now have corrected df (5) for the main effect of emotion (section: Results, paragraph: Performance on the Facial Emotion Recognition Test, pag. 9).

5. Pg 13 & 14, Can the authors test their hypothesis that, “a deficit in recognizing happiness might occur only in subjects with more severe brain damage and clinical evidence of a cognitive deficit”? Could a comparison between HIV patients with and without ANI speak to this possibility?

We agree with the reviewer about the possibility to compare HIV with ANI to HIV without a cognitive impairment, to account for the hypothesis of a deficit in recognizing happiness linked to a neurocognitive impairment. However, a comparison between HIV patients with and without ANI did not lead to a confirmation of the data: in fact the mean for happiness accuracy is 9.6 for ANI patients, and 9.8 for patients with no cognitive impairment. Since the maximum
score is 10, both groups show a ceiling effect in this task. We hypothesized that with the evolution of disease, this difference could increase. Now we have added a sentence in section: Conclusion, pag. 13, to clarify this issue: “The association between recognition of happiness and general neurocognitive impairment as well the association between recognition of happiness and past AIDS-defining events, could lead us to hypothesize that a deficit in recognizing this emotion might emerge only in subjects in more severe stages of HIV pathology in agreement with a recent study....”.

6. Table 1, there is no information about depression levels, prior drug use, HCV-status, or sexual orientation of the HC group. Can these data be provided? Do the HIV and HC groups differ on these variables? Unfortunately we did not have information about sexual orientation for control group. HC subjects were not prior drug abusers, HCV infected nor had clinical or anamnestic evidences of depression. We now added a sentence “They had no history for HCV infection and were not past injecting drug users. Moreover, they had no clinical or anamnestic evidences of depression.” in section: Method, pag6, to explain this issue.

Discretionary Revisions

1. Pg 11, it’s not clear to me what is meant by the sentence “Nevertheless, it cannot be held that the subjective experience and behavioural expression of fear depend only on task difficulty and have no dedicated neural substrates.” What is the connection between “behavioural expression of fear” and emotion recognition as measured in the current study? We agree that this sentence is not clear: now we have changed the sentence “On the other hand, there are considerable evidence that the correct recognition of facial expression of fear depend on specific neural structures that have a critical role in mediating the autonomic and behavioural responses associated with this emotion [1,42].” section: Discussion, pag 12.

2. Pg 13, it is possible that the authors, in referencing these particular papers, might be conflating education and IQ in this statement: “We observed an association with education, in agreement with previous studies that reported a relationship between facial emotion recognition and level of intellectual functioning [47, 48].” Relaying on the present review, we have removed the sentence.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
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.
Minor essential revisions

1. I would like to see the Effect sizes for each face emotion and other comparisons.
   We now have added the column “Effect Size” on Table 2.

2. The effect for fear is exceptionally large (especially compared to the others and therefore really quite striking) But the variability (SD) for fear in the HIV group (compared to controls and for HIV on other emotions) suggests there may be a cluster of very low performing individuals.
   Analyzing frequency distribution of scores obtained by patients and controls on fear recognition accuracy, we observed that there is not a cluster of very low performing individuals in the HIV group. In fact, in a 0–10 scale, 57.1% of HIV-patients obtained a score ≥6. Only 16.3% (8 patients) obtain a very low score (i.e. ≤3). In control group, 100% of subjects obtained a score ≥6. We believe that the large effect of fear is due to the distribution of scores described above.

3. Although ns, a moderate effect size of 0.49 for surprise suggests some possible power issues - moreover, the controls identified fewer surprised faces than the HIV group.
   In agreement with the reviewer, we have calculated the effect size for all emotion, as described above. For the emotion “surprise” we calculated an effect size of 0.052. Since the difference between HIV and HC scores was not significant, and the effect size was very small, we have not considered the data attributing it to a randomness. Anyway we acknowledge the power issues arising from the small effect size as suggested by the reviewer.

4. I would like to see the global score (for all 6 emotions) included in Table 2 (with analysis)
   Now we added the global score with analysis in Table 2.

5. Lane et al (2012) Facial Emotional Processing in HIV Infection: Relation to Neurocognitive and Neuropsychiatric Status. Neuropsychology Vol. 26, No. 6, 713–722 - needs to be referenced They showed that the speed of processing fear emotion is affected in HIV+ individuals; and that recognition of the fear expression is not impaired when all HIV individuals are concerned, but is found to be impaired in neurocognitively impaired HIV persons
   Now we have added the sentences: “HIV infected patients, compared to an healthy population of subjects, performed worse on emotion recognition tasks, as described in a recent paper [22]” in section: Introduction, pag. 5; the reference [22] in the sentence “Similar to previous studies [22,23], we found that HIV-infected patients performed worse than HC in recognizing the facial emotion of fear” in section: Discussion, pag. 11; the sentence “...in agreement with a recent study [22] demonstrating that the ability to discriminate between levels of happiness intensity on facial expression was specifically altered in HIV patients with impaired neurocognitive performance” in section: Discussion, pag. 13

6. Please complete df fully in stats
   We now have added df information for the ANOVA (section: Results, paragraph: Performance on the Facial Emotion Recognition Test, pag. 9).
7. p.8 states "Overall, 23.2% of the patients showed an ANI, as assessed by the neuropsychological battery; the others 86.8% showed no cognitive impairment" - These figures cannot be correct
   Yes, we are sorry, there was a typo: the correct percentage is now written in the text.

8. More detail about the regression analyses is required - e.g. what does HIV infection mean? How is it composed?
   To clarify this issue, we correct the sentence “Moreover, HIV infected patients \( \beta=-2.37, \) 95% confidence interval (CI) -3.42 to -1.32, \( p<0.001 \) confirmed to have a worse performance on fear recognition after adjusting for age and education in a multivariate linear regression model”, results, pag 9.

9. Figures - all figures with bar charts need to indicate what the bar charts are measuring (e.g. SD, SE, 95% CI)
   Now we have added “vertical bars denote 0.95 confidence intervals” on bottom of the figure 1.

10. It is unfortunate that the Zung depression scale was not administered to the controls - can the authors eliminate the possibility that depression is an issue?; also it is clear from the mean and SD that the depression scores are heavily skewed i.e. a subgroup would seem much more depressed – does this impact performance?
   Unfortunately, we cannot eliminate the possibility that depression is an important issue, even if controls had not clinical or anamnestic evidences of a depression. However, splitting HIV patients in depressed and non depressed patients, as assessed by Zung Depression Scale, we did not found a significant difference on fear recognition accuracy between the two groups \([T-test \text{ depressed vs non depressed patients(mean and sd): 5.00 (2.0) vs 5.68 (2.4), } p= 0.55]\)

11. It seems quite feasible that a lack of correlations for happiness (the only emotion to not correlate with anything) almost certainly reflects the ceiling level performance obtained and should be discussed
   We agree with the hypothesis that a lack of correlations for happiness reflects the ceiling level performance obtained by the subjects. Now we have removed correlation data about the single emotions, except for the emotion “fear” that is the only emotion we found to be impaired in HIV group compared to HC.

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**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'