PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Imaging predictors of post-stroke depression: Methodological factors in voxel based analysis
AUTHORS	Gozzi, Sophia; Wood, Amanda; chen, jian; Vaddadi, Krishnarao; Phan, Thanh

VERSION 1 - REVIEW

REVIEWER	Sibon, Igor CHU Bordeaux
REVIEW RETURNED	14-Mar-2014

GENERAL COMMENTS	In the present manuscript Gozzo et al, explore the relationship between lesion location and post-stroke depression (PSD) using statistical parametric mapping in a population of 55 stroke patients. The authors failed to identify significant association between lesion location and the risk of PSD. Thus, they discuss different points that could explain this negative result in order to improve the design of future studies on this topic. The manuscript is well written and the main objective is of significant interest. However the paper has several limitations: Introduction: This part of the manuscript is very clear and deserves only minor comments. -Overall, the authors look at a specific lesion cortical location that could be associated to an increased susceptibility to PSD. However they do not take into account the potential influence of lesions affecting a larger brain network involved in the regulation of mood. This methodology can have limited the ability of the authors in identifying an association between lesion location and risk of PSD. -PSD is one of the affective disorders that can occur after stroke and probably the most frequent. However the term “affective disorder” encompasses other manifestations than depression. Therefore the definition should be modified in consequence. -The hypothesis on an independent role of lesion location in the risk of PSD is interesting but should always be evaluated in light of the already well known clinical factors that have been associated to an increased risk of PSD. A short listing of these factors, i.e severity of disability or a recent history of depression, should be given in the introduction. Methods: The total number of patients admitted in the stroke unit during the period of the study should be provided in order to appreciate the method of selection of the patients.

	Patients were excluded if they had a history of depression at admission. However some personality traits such as neuroticism and history of depression have been reported as potential risk factors for PSD. Could the authors give some information about any history of psychiatric disorders in their patients? Based on the results of the FLAME study a lot of stroke patients are treated by antidepressant in the early post-stroke phase. Does this parameter was recorded in the present study and used as a confounding factor in statistical analysis? Depression was evaluated at one month post-stroke which is very early. Usually PSD is evaluated between 3 and 6 months post-stroke because in the early post-stroke phase it remains difficult to differentiate the symptoms related to anxiety and those related to depression. The authors should explain why they choose this period of evaluation and discuss this point in the discussion section. A cut-off of 11 was used to select patients with potential PSD on HADS. Did the authors evaluate the anxiety and depression subscales? This could allow identifying patients with high depression scores and low anxiety score which is sometimes observed in apathetic depression, with a total score below 11 while depressive symptoms are present. Infarcts were manually segmented on the native T 2 -weighted images performed within large range of time after stroke (0-85 days). How did the authors manage the presence of brain oedema that is present in the days after stroke and that increases the volume and the number of voxels affected by the lesion but do not allow a perfect delination of the final stroke volume and location? Patients with brain hematoma were also included in the study. The method of intracerebral hemorrhage volume should be provided as well as the sequence on which this lesion was measured. Results: 16 of the 71 patients were lost at follow-up, which is quite important while the evaluation was performed only one month after stroke. The authors should give more detailed about the reason s of exclusion of these patients. 47 patients had a cerebral infarct and 6 an intracerebral haemorrhage which means that 2 patients had no lesion. Why these patients were included in the analysis which was designed to evaluate the association between lesion location and the risk of PSD? Moreover in table 2 it is mentioned that 2 patients in the depressed group and 3 patients in the non-depressed group had no infarct on MRI scan…this is confusing and the results should be more clearly presented Similarly, some data are missing in the tables, i.e stroke laterality is given for 54 patients (29 +20 +5), what about the last patient? The mean volume of intracerebral haemorrhage should be provided as well as the location of these lesions. Altogether the presentation of the results should be clarified to improve the understanding of the analysis. Discussion: The discussion is well written and emphasizes the main limitations of imaging studies performed in the purpose of identifying brain imaging parameters that could be used as potential biomarkers in the prediction of patients at risk of PSD. The authors indicate that lesion in the mood network should be evaluated rather than specific cortical lesion but they should also discuss the potential role of preexisting stroke lesions such as leucoencephalopathy,

	microbleeds, small deep infarcts or previous cortical lesions that have been recently reported to be major predictors of the risk of PSD.

REVIEWER	Davide Quaranta Catholic University of the Sacred Heart - Rome Italy
REVIEW RETURNED	04-Apr-2014

GENERAL COMMENTS	Authors diagnosed depression accoridng to the DSM-IV criteria for minor or major depression; It would be more suitable to apply the criteria for "Mood disorder associated to a medical condition" that is the standard diagnosis for post-stroke depression. Most of the depressed subjects are affected by major depression; this is quite unusual and Authors should clarify this finding. The paper is the first one to investigate a VBM analysis of lesions in PSD. It is well written and provide evidence about the limitations of neuroanatomical correlation study in this field, even when more fine-grained methods are used. I have some observations about the patients selection: - Authors diagnosed depression accoridng to the DSM-IV criteria for minor or major depression; It would be more suitable to apply the criteria for "Mood disorder associated to a medical condition" that is the standard diagnosis for post-stroke depression; - most of the depressed subjects are affected by major depression; this is quite unusual and Authors should clarify this finding; - in the results section the Authors reported the results of a multiple variables regression analysis; they reported that cognitive functioning was entered as a confounder, but they did not report which scales they used to assess it.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Igor Sibon, Institution and Country CHU Bordeaux

1-Introduction: They do not take into account the potential influence of lesions affecting a larger brain network involved in the regulation of mood. This methodology can have limited the ability of the authors in identifying an association between lesion location and risk of PSD.

We are in full agreement that it would be advantageous to identify the influence of lesions affecting larger brain networks involved in the regulation of mood. Unfortunately, this type of analysis cannot be performed when there is sparse data due to minimal overlap of infarcted regions across scans. This is the same challenge that was encountered when performing a voxel based analysis. The text in ‘future directions’ has been revised for clarity and discusses the benefit of analysing the influence of lesions to networks of neural structures involved in mood regulation in future research.

2- Introduction: PSD is one of the affective disorders that can occur after stroke and probably the

most frequent. However the term “affective disorder” encompasses other manifestations than depression. Therefore the definition should be modified in consequence.

The term ‘affective disorder’ has been removed.

3- Introduction: The hypothesis on an independent role of lesion location in the risk of PSD is interesting but should always be evaluated in light of the already well known clinical factors that have been associated to an increased risk of PSD. A short listing of these factors, i.e severity of disability or a recent history of depression, should be given in the introduction.

Cognitive impairment, stroke severity and physical disability and handicap have been listed in the introduction as established risk factors.

4- Methods: The total number of patients admitted in the stroke unit during the period of the study should be provided in order to appreciate the method of selection of the patients.

This information has been added to the methods under ‘Participants’.

5- Methods: Patients were excluded if they had a history of depression at admission. However some personality traits such as neuroticism and history of depression have been reported as potential risk factors for PSD. Could the authors give some information about any history of psychiatric disorders in their patients?

Added a sentence about a personal history of depression under ‘Measures’ and in the Results under ‘Clinical characteristics’.

6- Methods: Based on the results of the FLAME study a lot of stroke patients are treated by antidepressant in the early post-stroke phase. Does this parameter was recorded in the present study and used as a confounding factor in statistical analysis?

A sentence was added in the results section outlining that three patients were taking antidepressants during the study. This parameter was not used as a confounding factor due to the small number of cases affected.

7- Methods: Depression was evaluated at one month post-stroke which is very early. Usually PSD is evaluated between 3 and 6 months post-stroke because in the early post-stroke phase it remains difficult to differentiate the symptoms related to anxiety and those related to depression. The authors should explain why they choose this period of evaluation and discuss this point in the discussion section.

One month post-stroke was chosen as it was considered advantageous to detect the presence of depression as soon as possible due to the negative influence of depression on recovery and outcomes post-stroke. If patients at risk of developing depression in the early post-stroke period could be identified, this information could be used to help guide preventative interventions. The importance of early detection has been added under ‘future directions’.

8- Methods: A cut-off of 11 was used to select patients with potential PSD on HADS. Did the authors evaluate the anxiety and depression subscales? This could allow identifying patients with high depression scores and low anxiety score which is sometimes observed in apathetic depression, with a total score below 11 while depressive symptoms are present.

A cut-off of 11 for the total HADS score was chosen to optimise sensitivity however, a sentence was

added in the discussion, indicating that it is possible that some patients were not detected as depressed if they had high scores on the depression scale and low scores on the anxiety scale.

9- Methods: Infarcts were manually segmented on the native T 2 -weighted images performed within large range of time after stroke (0-85 days). How did the authors manage the presence of brain oedema that is present in the days after stroke and that increases the volume and the number of voxels affected by the lesion but do not allow a perfect delination of the final stroke volume and location?
Patients with brain hematoma were also included in the study.

As segmentations were based on MRI scans acquired at an average of 20.8 ± 23.7 days of stroke (0-85 days), the issue of oedema confounding segmentation of infarcts was not considered to be a significant issue at three weeks post-stroke.

10- The method of intracerebral hemorrhage volume should be provided as well as the sequence on which this lesion was measured.

Infarcts and haemorrhage were manually segmented on FLAIR images using interactive Display, mouse driven software and standardised intensity windows. Lesion volume was determined using a voxel counting algorithm. This information is outlined in the methods section.

11- Results: 16 of the 71 patients were lost at follow-up, which is quite important while the evaluation was performed only one month after stroke. The authors should give more detailed about the reasons of exclusion of these patients.

A sentence was added to the results section indicating that five patients did not undergo an MRI scan.

12- Results: 47 patients had a cerebral infarct and 6 an intracerebral haemorrhage which means that 2 patients had no lesion.

Whether the stroke was an infarct or haemorrhage was obtained from patient medical records. There were two cases where this information was missing and therefore not documented. The format of the footnotes for Table 1 has been revised for clarity.

13- Results: Why these patients were included in the analysis which was designed to evaluate the association between lesion location and the risk of PSD?

The analysis was repeated excluding patients with no identifiable lesion on MRI scans and results remained unchanged. This information has been added to the results section.

14- Results: Moreover in table 2 it is mentioned that 2 patients in the depressed group and 3 patients in the non-depressed group had no infarct on MRI scan…this is confusing and the results should be more clearly presented

Numbers have been checked and corrected.

15- Results: Similarly, some data are missing in the tables, i.e stroke laterality is given for 54 patients (29 +20 +5), what about the last patient?

The footnotes highlighting the missing data in Table 1 has been reformatted for clarity.

16- Results: The mean volume of intracerebral haemorrhage should be provided as well as the

location of these lesions.

This data has been added in the results section under ‘Image analysis’.

17- Results: Altogether the presentation of the results should be clarified to improve the understanding of the analysis.

We hope that the alterations listed above have fulfilled this request.

Discussion:
18- Discussion: The authors indicate that lesion in the mood network should be evaluated rather than specific cortical lesion but they should also discuss the potential role of preexisting stroke lesions such as leucoencephalopathy, microbleeds, small deep infarcts or previous cortical lesions that have been recently reported to be major predictors of the risk of PSD.

A sentence has been added in the discussion, mentioning the potential role of previous infarcts as a predictor of PSD.

Reviewer: 2
Davide Quaranta, Institution and Country Catholic University of the Sacred Heart - Rome
Italy

1- Authors diagnosed depression accoridng to the DSM-IV criteria for minor or major depression; It would be more suitable to apply the criteria for "Mood disorder associated to a medical condition" that is the standard diagnosis for post-stroke depression.

The diagnosis has been changed as recommended in the Methods section.

2- Most of the depressed subjects are affected by major depression; this is quite unusual and Authors should clarify this finding.

Although there is a small difference in cases between groups (n=9 and n=6 for major and minor depression respectively), statistical analyses were not performed to determine whether this was a significant difference due to the small number in each group. Patients with major and minor depression were combined to form the depressed group for the image analyses.

3- In the results section the Authors reported the results of a multiple variables regression analysis; they reported that cognitive functioning was entered as a confounder, but they did not report which scales they used to assess it.

Added a sentence on page 12 to clarify that the ACE-R was used.

VERSION 2 – REVIEW

REVIEWER	Sibon Igor CHU Bordeaux
REVIEW RETURNED	28-May-2014

GENERAL COMMENTS	The authors answered the main questions and modified their manuscript. I have no more comments