PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
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<tr>
<th>TITLE (PROVISIONAL)</th>
<th>The Frontal Assessment Battery for Detecting Executive Dysfunction in Amyotrophic Lateral Sclerosis Without Dementia: A Retrospective Observational Study</th>
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<tr>
<td>AUTHORS</td>
<td>Barulli, Maria; Fontana, Andrea; Panza, Francesco; Copetti, Massimiliano; Bruno, Stefania; Tursi, Marianna; Iurillo, Annalisa; Tortelli, Rosanna; Capozzo, Rosa; Simone, Isabella; Logroscino, Giancarlo</td>
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VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Bjorn Oskarsson</th>
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<tr>
<td></td>
<td>Assistant Professor of Clinical Neurology</td>
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<tr>
<td></td>
<td>University of California, Davis, USA</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>15-Dec-2014</td>
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</tbody>
</table>

GENERAL COMMENTS

It is with pleasure that I read this retrospective analysis by Barulli et al. The FAB is a frequently used measure not only by ALS specialists, but by neurologists in general. This is may be it's main advantage over ALS specific measures such as the ECAS or ALSCBS. This report certainly adds to our knowledge of the FAB in ALS. My specific comments are as follows;

1. The sentence “Tree-based analysis identified three subgroups with older age and low respiratory function as main prognostic variables.” is confusing and should be reworded both in the abstract (and the similar sentence in the paper), so that the three groups are clearly described. The sentence could be removed from the abstract as this division is rather complex to describe and not of the highest relevance.

2. Please list how many patients who were excluded due to 1) Dementia, 2) MMSE <26, 3) Weak hands and dysarthria, 4) Missing neuropsychological tests. This is necessary for the STROBE statement.

3. Personally I'm not familiar with the RECPAM methodology and after a brief review I am unsure about if it adds much to the paper. I'm suggesting a statistical review of the manuscript for clarification.

<table>
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<th>REVIEWER</th>
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<tr>
<td></td>
<td>Faculty of Psychology. Rosario National University Argentina</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>18-Feb-2015</td>
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</table>

GENERAL COMMENTS

The study is well designed, properly written and interesting in terms...
of the need to assess executive dysfunction in ALS, which usually goes unrecognized and is associated with worse prognosis of the illness.

Some minor spelling errors need to be corrected such as those in table 1: possibile (possible), probabile (probable)

Background
Previous studies have assessed frontal executive dysfunction in amyotrophic lateral sclerosis using Frontal Assessment Battery (FAB) (e.g., Oskarsson B, et al. Using the Frontal Assessment Battery to identify executive function impairments in amyotrophic lateral sclerosis: A preliminary experience. Amyotroph Lateral Scler. 2010; 11(1-2):244-7; Terada T et al. Assessing frontal lobe function in patients with amyotrophic lateral sclerosis by frontal assessment battery. Rinsho Shinkeigaku. 2010 Jun; 50(6):379-84) and validity of FAB as a screening tool for executive dysfunction did not correlated with age, disease duration, ALS Functional Rating Scale, spirometry, or blood gas analyses, pretty alike with results exhibited in the present study.

Subjects
- How was sample size estimated?
- It is well known the heterogeneity of ALS’ patient populations especially with regard to their particular disease stage during the time of study, which may affect the results. Some of those conditions include for example sporadic or familial ALS, presence of mutations of several genes such as C9ORF72, MAPT, PGRN, valocin-containing protein, TARDBP, FUS, SOD1, A4V, E21G, G37R, D90A G93C, I113T, etc.; rate of disease progression, or even psychosocial factors such as perceived stress, depression, hopelessness, anger expression, purpose in life and marital status. Of those factors only depression was explored in the present work. It is generally recognized that malnourishment is a relevant determinant of cognitive function in ALS including Body Mass Index (BMI) as independent factor, but again this was not included in the research. It is not clear whether patients were exposed to any treatment during the disease. Another example of this heterogeneity is provided by the authors regarding disease duration, which ranges between 2 months to 12 years.

Study design
- Retrospective design has several pitfalls: 1) it does not allow certain prognostic factors, such as symptoms progression rate to be assessed; 2) it is less accurate with regard to certainty of disease diagnosis, since it is usually based on the retrospective revision of only clinical data; and 3) there is a risk of missing specific subsets of patients not captured by the study design. This should be accomplished as a limitation of the study.
- On page 9 lines 40-42 you wrote “Since EI (executive index) was defined as the mean of 4 standardized random variables, the computed cutoff of 2 SD below the mean was -1” not clear what this means

Statistical methods
- During implementation of the RECPAM algorithm and tree-growing procedure, was clinical and scientific knowledge about ALS integrated into automatic set up of the model?
- Was the population split in any subgroups?
- The algorithm stopped when there were less than
- Authors mention that the algorithm stopped when less than 15% of the total sample was achieved within each terminal node, but doesn’t mention stopping rules for desired minimum leaf size, number of patients for each group, and minimum leaf number of events.
As splitting covariates author’s didn’t mentioned educational level, which has been associated as a confounding factor for EI or FTD (Wilson RS et al, Educational attainment and cognitive decline in old age. Neurology 2009; 72:460–465)

The reviewer also provided a marked copy with detailed comments. Please contact the publisher for full information about it.

**REVIEWER**  
Tatsuhiro Terada  
Laboratory of Human Brain Imaging Research  
Molecular Imaging Frontier Research Center  
Hamamatsu University School of Medicine, Japan

**REVIEW RETURNED**  
23-Feb-2015

**GENERAL COMMENTS**  
This study described that Frontal Assessment Battery (FAB) was a reliable tool for assessing the frontal cognitive impairments in amyotrophic lateral sclerosis (ALS) without apparent dementia. The manuscript is informative in that current study provides a fundamental support to use of FAB as a screening tool with relatively large sample study. However, reviewer would like to suggest some revision on the following point.

Comment 1  
Previous study indicated that the score of the FAB was influenced by language version. Dubois et al first reported the FAB score in the normal subjects (17.3 ± 0.8) (1). Then, as for the Italian version of the FAB, Lavarone et al showed the normative data was 15.29 ± 2.77 (2), and Apporonio et al showed 16.1 ± 1.8 (3). Kenangil et al reported that normative data of the FAB in Turkish was 14.4 ± 3.07 (4). Shutaro et al reported that normative data of Japanese version of the FAB was 16.5 ± 1.0 (5). Therefore, my suggestion is to add the comment what language version of FAB (probably Italian version) did you used in this study at the method paragraph.


Comment 2  
Author described that the FAB score was related to age, these results indicated that the age level has significant effects on
performance of the FAB at the discussion. Therefore, when assessing frontal cognitive impairments by using FAB, the age of the subjects should be taken into consideration when evaluating the results of the FAB. My suggestion is to add some comment on this point.

The reviewer also provided a marked copy with detailed comments. Please contact the publisher for full information about it.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer Name Bjorn Oskarsson, MD  
Institution and Country Assistant Professor of Clinical Neurology  
University of California, Davis, USA  
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below  
It is with pleasure that I read this retrospective analysis by Barulli et al. The FAB is a frequently used measure not only by ALS specialists, but by neurologists in general. This is may be it's main advantage over ALS specific measures such as the ECAS or ALSCBS. This report certainly adds to our knowledge of the FAB in ALS. My specific comments are as follows;

1. The sentence "Tree-based analysis identified three subgroups with older age and low respiratory function as main prognostic variables." is confusing and should be reworded both in the abstract (and the similar sentence in the paper), so that the three groups are clearly described. The sentence could be removed from the abstract as this division is rather complex to describe and not of the highest relevance.
   1. As suggested by this Reviewer, the sentence "Tree-based analysis identified three subgroups with older age and low respiratory function as main prognostic variables" has now been removed from abstract. More details were provided in Statistical analysis and Results sections (pages 8, 9, and 11).

2. Please list how many patients who were excluded due to 1) Dementia, 2) MMSE <26, 3) Weak hands and dysarthria, 4) Missing neuropsychological tests. This is necessary for the STROBE statement.
   2: We thank the Reviewer for this important comment. In this retrospective cohort study, We enrolled a total of 152 consecutive patients with ALS. Four patients were excluded due to the presence of dementia syndrome, 32 patients were further excluded due to MMSE < 26, four patients were excluded due to missing neuropsychological tests, and 17 patients were excluded due to weak hands and dysarthria. Therefore, the final sample was constituted by 95 patients with ALS (62 males and 33 females, range: 33-82 years of age). We included this statement t the beginning of the results section (page 10, lines1-4).

3. Personally I'm not familiar with the RECPAM methodology and after a brief review I am unsure about if it adds much to the paper. I'm suggesting a statistical review of the manuscript for clarification.
   3. When a multivariable linear regression model with main effects is estimated, a linear relationship between included variables and the study outcome is assumed. Most importantly, the presence of possible multiplicative interactions between these variables (often) remains unknown or unclear. In addition, to explore non-linear relationships, a specific functional shape of each continuous variable must be evaluated through suitable transformations of their values (e.g. quadratic, cubic or any polynomial transformation), with the further inclusion of these terms into the model. Commonly, the final model is chosen using some specific goodness of fit criteria (e.g. AIC). With respect to this standard statistical analysis, the most important advantage on the use of any tree-based method, like
RECurse Partition and AMalgamation (RECPAM), is that it allows to better explore possible interactions between demographical and clinical variables, identifying patients’ subgroups with different executive index (EI) means (i.e. the outcome at issue), by means of a recursive partitioning of the whole sample with respect to the most suitable candidate variable (which achieved the highest likelihood ratio statistic). Furthermore, this method was internally validated with a permutation approach, which allowed to obtain a “robust and stable” cut-offs to split patients into the EI classes. Moreover, the final RECPAM tree put in evidence not only a sort of hierarchy of all variables involved in the interaction but also shows at which specific cut-offs groups were consecutive defined. Tree-structured analyses (e.g. Classification And Regression Trees, RECurse Partition and AMalgamation trees and MOdel-Based recursive partitioning) and their graphical representations are very common in medical literature and widely used because of their easy clinical interpretation (please consider the following references [1-5] as an example).


“The Frontal Assessment Battery for Detecting Executive Dysfunction in Amyotrophic Lateral Sclerosis Without Dementia” (Manuscript ID bmjopen-2014-007069)

Reviewer Name Daniel Serrani Azcurra
Institution and Country Faculty of Psychology. Rosario National University Argentina
Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below
Commentary to FAB assessment in ALS
The study is well designed, properly written and interesting in terms of the need to assess executive dysfunction in ALS, which usually goes unrecognized and is associated with worse prognosis of the illness.

Some minor spelling errors need to be corrected such as those in table 1: possibile (possible),
probabile (probable)
We corrected these spelling errors.

Background
1. Previous studies have assessed frontal executive dysfunction in amyotrophic lateral sclerosis using Frontal Assessment Battery (FAB) (e.g., Oskarsson B, et al. Using the Frontal Assessment Battery to identify executive function impairments in amyotrophic lateral sclerosis: A preliminary experience. Amyotroph Lateral Scler. 2010; 11(1-2):244-7; Terada T et al. Assessing frontal lobe function in patients with amyotrophic lateral sclerosis by frontal assessment battery. Rinsho Shinkeigaku. 2010 Jun; 50(6):379-84) and validity of FAB as a screening tool for executive dysfunction did not correlate with age, disease duration, ALS Functional Rating Scale, spirometry, or blood gas analyses, pretty alike with results exhibited in the present study.

1. We included some amount of discussion in the revised version of the manuscript including also the study of Terada and colleagues (reference 30).

Subjects
2. How was sample size estimated?
2. The power calculation has now been included into the revised manuscript. A sample of 36 patients with executive dysfunction and 59 patients without executive dysfunction achieved 90% power to detect an overall discriminatory power (AUC) for FAB (total score) of 0.693, under the null hypothesis of AUC of 0.50, using a two-sided z-test at a significance (alpha) level of 0.05 (page 12 , lines 1-4 ).

3. It is well known the heterogeneity of ALS’ patient populations especially with regard to their particular disease stage during the time of study, which may affect the results. Some of those conditions include for example sporadic or familial ALS, presence of mutations of several genes such as C9ORF72, MAPT, PGRN, valocin-containing protein, TARDBP, FUS, SOD1, A4V, E21G, G37R, D90A G93C, I113T, etc.; rate of disease progression, or even psychosocial factors such as perceived stress, depression, hopelessness, anger expression, purpose in life and marital status. Of those factors only depression was explored in the present work. It is generally recognized that malnourishment is a relevant determinant of cognitive function in ALS including Body Mass Index (BMI) as independent factor, but again this was not included in the research. It is not clear whether patients were exposed to any treatment during the disease. Another example of this heterogeneity is provided by the authors regarding disease duration, which ranges between 2 months to 12 years.
3. We thank Dr Azcurra for these comments. All the patients were taking riluzole when they were interviewed for this study, we included this in the revised manuscript (page 7, lines 13 and 14). In this revised version of the manuscript, we included in the discussion section also the suggested sources of heterogeneity in our ALS’ patient population not addressed in the present study (page 16, lines 2-4).

Study design
4. Retrospective design has several pitfalls: 1) it does not allow certain prognostic factors, such as symptoms progression rate to be assessed; 2) it is less accurate with regard to certainty of disease diagnosis, since it is usually based on the retrospective revision of only clinical data; and 3) there is a risk of missing specific subsets of patients not captured by the study design. This should be accomplished as a limitation of the study.
4. As suggested by Dr Azcurra, we included among limitations in the revised version of the manuscript the pitfalls linked to the design of the study (page 15, last 4 lines).

5. On page 9 lines 40-42 you wrote “Since EI (executive index) was defined as the mean of 4 standardized random variables, the computed cutoff of 2 SD below the mean was -1” not clear what this means
5. Thank Dr Azcurra for this comment. As already mentioned, the EI is defined as the mean of four Z
scores. Each Z score is assumed as an independent standardized normally distributed random variable (i.e. with zero mean and variance equal to one). Consequently, EI is a normally distributed random variable with expected mean of zero (i.e. Mean=(0+0+0+0)/4 = 0) and a variance of 0.25 (i.e. Variance= (1+1+1+1)/16 = 0.25 ) and a standard deviation of 0.5. A patient was defined as impaired if had an EI<-2•SD = -2•0.5= -1, which represents the cut-off which were reported.

Statistical methods
6. During implementation of the RECPAM algorithm and tree-growing procedure, was clinical and scientific knowledge about ALS integrated into automatic set up of the model? 
6. Unfortunately, no clinical and scientific knowledge about ALS could be integrated into the automatic set up of the model. At each partitioning step, the best splitting variable (along with its specific cut-off) is merely chosen when it achieves the highest likelihood ratio statistic, with respect to all the other possible variables splitting. The list of possible candidate splitting variables should be defined a priori by the user.

7. Was the population split in any subgroups? 
7. Possible splits are evaluated for each (subsequent) defined subgroup and were performed until stopping rules are met as reported in the Statistical Analysis section (pages 8 and 9).

8. The algorithm stopped when there were less than 
8. Please see the answer provided below.

9. Authors mention that the algorithm stopped when less than 15% of the total sample was achieved within each terminal node, but doesn’t mention stopping rules for desired minimum leaf size, number of patients for each group, and minimum leaf number of events.
9. The algorithm stopped when there were less than 14 patients (which correspond about 15% of the total sample) within each terminal node. This correspond to the desired minimum leaf size, that is the number of patient for each terminal node. No events are considered since EI (the outcome) is a continuous variable. Please see the revised version of Statistical Analysis section (page 9, lines 6 and 7).

9. As splitting covariates author’s didn’t mentioned educational level, which has been associated as a confounding factor for EI or FTD (Wilson RS et al, Educational attainment and cognitive decline in old age. Neurology 2009; 72:460–465)
9. We really thank Dr Azcurra for this interesting suggestion. We have re-run RECPAM analysis where the educational level has now been considered along with the others candidate splitting variables. We indeed found that such variable was selected (just at the first split) to partition the whole sample in two subsamples: patients with educational level ≤ 8 (N=60, left split, mean EI= -1.75) vs. those with educational level >8 (N=35, right split, mean EI= -0.14).We modified accordingly the Article Summary (page 4), the Results and Discussion sections (pages 11 and 13), Figure 1, the Appendix, and the Supplementary Figure 1.

“The Frontal Assessment Battery for Detecting Executive Dysfunction in Amyotrophic Lateral Sclerosis Without Dementia” (Manuscript ID bmjopen-2014-007069)

Reviewer Name Tatsuhiro Terada, MD, PhD
Institution and Country Laboratory of Human Brain Imaging Research, Molecular Imaging Frontier Research Center, Hamamatsu University School of Medicine, Japan
Please state any competing interests or state 'None declared': none
This study described that Frontal Assessment Battery (FAB) was a reliable tool for assessing the frontal cognitive impairments in amyotrophic lateral sclerosis (ALS) without apparent dementia. The manuscript is informative in that current study provides a fundamental support to use of FAB as a screening tool with relatively large sample study. However, reviewer would like to suggest some revision on the following point.

Comment 1
Previous study indicated that the score of the FAB was influenced by language version. Dubois et al first reported the FAB score in the normal subjects (17.3 ± 0.8) (1). Then, as for the Italian version of the FAB, Lavaroni et al showed the normative data was 15.29 ± 2.77 (2), and Apporonio et al showed 16.1 ± 1.8 (3). Kenangil et al reported that normative data of the FAB in Turkish was 14.4 ± 3.07 (4). Shutaro et al reported that normative data of Japanese version of the FAB was 16.5 ± 1.0 (5). Therefore, my suggestion is to add the comment what language version of FAB (probably Italian version) did you used in this study at the method paragraph.


Comment 1: As correctly suggested by Dr Terada, we included a statement on the Italian version used in the present study (reference 7: Appollonio et al. The Frontal Assessment Battery (FAB): normative values in an Italian population sample. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2005; 26: 108-16) (page7 , lines 18 and 19). Furthermore, following the suggestions of the other Reviewer Dr Azcurra, we included some amount of discussion in the revised version of the manuscript including also the study of Terada and colleagues (reference 30).

Comment 2
Author described that the FAB score was related to age, these results indicated that the age level has significant effects on performance of the FAB at the discussion. Therefore, when assessing frontal cognitive impairments by using FAB, the age of the subjects should be taken into consideration when evaluating the results of the FAB. My suggestion is to add some comment on this point.

Comment 2: As suggested by Dr Terada, we included a comment on age effect on FAB performance in the revised Discussion section of the manuscript (page 13, lines 21-23).

**VERSION 2 – REVIEW**

<table>
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<th>REVIEWER</th>
<th>DANIEL SERRANI AZCURRA</th>
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<td>REVIEW RETURNED</td>
<td>22-May-2015</td>
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previous suggestions were taken into account and subsequently corrected.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name DANIEL SERRANI AZCURRA
Institution and Country FACULTY OF PSYCHOLOGY UNIVERSIDAD NACIONAL DE ROSARIO
Please state any competing interests or state 'None declared': NONE DECLARED

Please leave your comments for the authors below
previous suggestions were taken into account and subsequently corrected.
1) We thank Dr Azcurra for the final comment.
Frontal assessment battery for detecting executive dysfunction in amyotrophic lateral sclerosis without dementia: a retrospective observational study

Maria Rosaria Barulli, Andrea Fontana, Francesco Panza, Massimiliano Copetti, Stefania Bruno, Marianna Tursi, Annalisa Iurillo, Rosanna Tortelli, Rosa Capozzo, Isabella Laura Simone and Giancarlo Logroscino

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