Reviewer's report

Title: Cluster analysis of behavioural and event-related potentials during a contingent negative variation paradigm in remitting-relapsing and benign forms of Multiple Sclerosis

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Reviewer: Pablo Villoslada

Reviewer's report:

In this study authors assessed attentional evoked potentials, using Posner paradigm, for studying patients with MS compared with controls. In addition, they performed a comparison between typical RRMS cases and RRMS with benign course. Finally, they attempt to identify subgroups of patient based in the attentional ERP performance that may be related with different degree or type of brain damage based in cluster analysis. They found that MS group showed impaired responses in terms of amplitude and latencies of ERP compared with controls. When analyzing RRMS subtypes, they found poorer performance by the so-call “being” group compared to the typical RRMS cases. Finally, they were able to identify 4 different clusters, two of them specific for MS cases and with different frequency among RRMS subgroups, suggesting different patterns of brain damage, being more severe in benign MS. The study is well designed and conducted and results reinforce the concept of widespread brain damage in MS, even at early stages of the diseases or in subgroups with low physical disability, challenging the concept of benign MS and even the concept of low disability in RRMS.

Comments:

1. The article is very long. Even if there is not a formal limitation for length in BMC Neurology, it is important to keep in mind the reader. For this reason, it is always very convenient to keep manuscript in a range below 6,000 words. I recommend to short all sections taking in consideration that clinical aspects about MS are well known by readers, methods previously published can be shortened and referred to previous papers, for results, avoid the overlap between text and tables and figures. In general is very easy to grasp the info from tables and figures more than text. Discussion should be focus in what is new and what is challenging this paper. Same for references, select the most important ones; readers are going to appreciate this work.

2. Abstract should provide more details about results, providing some numbers. Specifically, if you say patients have more “important” deficits, illustrate it with some numbers. Also, split background from methods with subheadings. You can add a sentence for background (e.g. ERP may distinguish tissue damage or phenotypes in MS....)

3. The hypothesis is descriptive and not clearly state. They state as the objective
“to investigate the information processing…”. Based in the authors understanding they can formulate a clearer hypothesis at the end of the introduction in order to help reader to know the question this article address (e.g. RRMS patients have significant attentional impairment that do not correlates with physical disability…) 

4. The disease subtypes are not clearly defined. 1) Benign MS is always RRMS: then I suggest describe the cohort as RRMS and divide it between benign MS and "common or typical" RRMS. 2) definition of benign MS is not clear in the literature but there is the consensus that at least should be a EDSS < 3.0 (better < 2.5) after 10-15 years disease duration. EDSS 3.5 is not benign MS and using disease duration of 8 years is less than previous definitions. Because the majority of the benign MS patients in this cohort fulfill these criteria, I suggest to remove the few of them not fitting this criteria and provide a reference for benign MS definition (e.g. Amato et al. J Neurol 2006) 

5. In the introduction, current standard of disease subtypes are based in Lublin criteria (Lublin F Neurology 1996). Please, use this reference and not ref 1,2 that are very general. 

6. A main limitation of the study is the lack of a formal cognitive assessment of patients in addition to the attentional task included. This would be critical in order to correlate with attentional performance and for proving that MS subtypes based in EDSS do not correlated with cognitive ERP, such as in the case of the so call benign MS. Have authors data from BRB-N battery or other neuropsychological tests? Similarly, lack of MRI quantification is another significant limitation. Cognitive performance would be more associated with brain atrophy or lesional load than physical scales used for stratifying patients. You should comment it in limitations of the study 

7. The two disease subtypes differs in disease duration and age, because in order to be define as benign MS it requires longer observation period than for RRMS. This also affects the validity of the control group, because it cannot match with both subgroups at the same time. 

8. Methods: please, state whether patients are the same one or if they differs from the one reported in Gonzalez-Rosa et al. 2006 

9. Methods. Sample size is small (27MS/18 controls) for the many comparisons planned. You should comment it in limitations of the study 

10. Methods: The use of the disease onset definition based in the first visit to neurologist is fine for natural history studies, but in a cross-sectional study it do not provide any value compared to the disease duration variable. 

11. Methods: list the clinical variables collected in all patients: sex, age, EDSS, (BRB?)… 

12. Methods: authors performed many statistical tests and for this reasons it is required to adjust for multiple tests (you ca use FDR because Bonferroni is going to be very exigent at this time). Then, authors must indicated which results survived correction and which are significant but not after correction. 

13. Methods: how to manage outliers is always a problem. By removing then, it is easier to identify patterns that explain most of the data, but at the price of loosing
generalization. Then, validation of the identified patterns would be required by crossvalidation.

14. Avoid priority claims (“the first study….“). They decrease value of the study and have no added value.

15. Results: when authors claim that patients have a slowing of information processing, indicate the parameters used for such statement based in ERP results.

16. The ERP recording method and analysis are right. However, authors highlight many small differences considering the small sample size and lack of correction for multiple testing. Moreover, the most significant differences are between patients and controls and not between patients subgroups.

17. In results, authors use differences in the ERP as proof of cognitive impairment which is not right. In this setting, they can talk about altered cognitive processing, but not claim cognitive impairment because they have not performed a neuropsychological assessment and the relationship between ERP and cognition is not straightforward.

16. Discussion: authors argue about a new reclassification of disease subtypes based in ref 93. But this is mainly focused in progressive MS and it is not really new (1999). I think the issue of benign MS is still pending to be redefined.

17. Limitations of the study should indicate also the issue of small sample size, the lack of patients with progressive MS, the lack of MRI and neuropsychological data.

18. Table 1. Indicate also the sample size (n), sex, age at onset and the use of disease modifying drugs and the p value for comparisons between groups.

19. Tables: it is easier for readers to identify which results are significantly different if you indicate the presence of significant differences by putting the superscript after the numerical value and not in the name of the variable, because it requires a lot of checking the legend and the corresponding subgroup.

20. Figure 1 is the same than in Gonzalez-Rosa et al. 2006. They should decide whether it should be kept or just referred.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests