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

Version: 2 Date: 12 January 2011

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Reviewer's report:

This study is aimed to provide direct evidence about a possible reduction of information processing speed (IPS) in MS patients with different phenotypes. This is an interesting work since recent studies have observed that disturbances in IPS could be a primary cognitive deficit in MS related to the decline of other cognitive functions, such as attention and memory (this premise has been formalized by Deluca et al., 2004 in their Relative Consequence Model). Other positive aspects of this study include the appropriate methodological approach taken. Thus, event-related potentials (ERPs) might be a very appropriate tool to study IPS alterations. Further, the Posner visual-spatial cueing paradigm is a sensitive task to study selective attention deficits in MS patients; finally, cluster statistical analysis might be a useful multivariate statistical approach to classify MS patients in different subgroups according to their scores in different cognitive variables. On the negative side, some parts of this study are confusing and, to my opinion, need to be amended before recommending its publication in a journal such as BMC Neurology. I hope that the following suggestions will be helpful to improve a corrected version of this interesting study.

Major compulsory revisions

A general comment refers to the language use and style throughout this manuscript. More specifically, the text is sometimes confusing and it is difficult to understand what the authors are trying to say in some paragraphs. In addition, authors inconsistently use labels to refer to the different groups involved in the present study (i.e. the labels “control”, “healthy participants” and “healthy controls” are used in different occasions to refer the same subjects’ group). Similarly, not proper attention was paid when trying to standardize some layout/style details (i.e. commas and dots were indistinctly used to separate decimal numbers see Table 4).

Introduction

Overall, this section is well written, although some minor changes should be introduced. Indeed, I have only a few suggestions in two paragraphs

1)“These results have been interpreted, supported by neuropsychological and neuroimaging evidence, as a general objective index of cognitive impairment in MS patients, characterized by slow information processing, as a results of
“disconnections between cortical-subcortical structures”. Recent Studies (Au Duong et al., 2005; see also Leocani et al., 2010) have suggested that a reduction of IPS in MS patients is not only caused by disconnections between cortical and subcortical structures but also by disconnections within cortical structures (e.g. within structures of fronto-parietal networks). Further, the results of the present study also point out to a relevant role of this kind of disruptions at networks interconnecting different cortical structures.

2) “It is likely that the deterioration of different cognitive mechanisms is masked in both the early form of RRMS and the late form of BMS despite physical disability being same”. Is this a hypothesis of the authors? If so, it should properly noted and not presented as a proven fact. Moreover, RRMS patients participating in this study should not be described as “early” (disease duration ranged from 1 to 18 years in this group!).

Methodology
Participants

1) When specifying the MS patients’ selection criteria, the authors state: “Lastly, we must highlight that overall MS patients included in this study had no immunomodulation record before beginning our study” Do the authors mean that none MS (including RRMS) patients had not received any treatment? If so, since the authors highlight this as a highly relevant variable, how it may affect for the interpretation of their results?

2) The educational level and the Intelligence Quotient (IQ) are important variables to be considered in any study assessing cognitive performance of MS patients (as well as of healthy subjects). In this way, and as stressed by the “cognitive reserve” hypothesis, educational level and IQ affect cognitive decline associated to MS and other neurological diseases (see Sumowski et al., 2010). Therefore, it seems crucial to assess, or at least to obtain a validated estimator of, the sample’s IQ (i.e. by using the matrix subtest of the WAIS battery). None of these measures were included, a fact that might be especially problematic given the specific aims of this study. Therefore, since it seems unfeasible to incorporate IQ measurements at this time point, I propose that at least educational level of the sample should be considered.

ERP measures:

1) Authors say in: “For the measurement of CNV, two areas of interest were defined and their amplitudes were calculated with respect to a baseline 100 ms prior to the cue stimulus”. Which two areas? Were two or three the areas of interest used?. In fact, authors seem to specify three areas/ variables: eCNV on parietal, cCNV on fronto-central and finally tCNV on occipital scalp locations.

Statistical analysis

1) Statistical analysis is correct and accurate. Only one suggestion: is it possible to use the educational level as a co-variable in the between subjects ANOVA?. 
2) Another important co-variable to be introduced in the ANOVA might be the years of the disease evolution. This will be of major interest since, as stated by the authors themselves at the introduction section, it is one of the most important variables to understand cognitive impairment in MS patients. Indeed, this idea is further reinforced at the discussion section when referring to the BMS phenotype ("The increase of abnormalities such as delays in information processing, orienting, and behavioural accuracy for BMS patients, may be explained by a higher number of years of disease duration for this form of MS and by a silent but continuous progression of impairment in this disease").

Cluster analysis

1) Please, specify the variables included in the cluster analysis at the following sentence: "The variables introduced in the cluster analysis were those which most clearly discriminated between groups in terms of statistical significance (p < 0.035)" Why authors did write the p<0.035 in the cluster analysis and no p<0.05? I suppose that is in reference to the ANOVA results but is not clear for the reader.

Results

Behavioral data

1) Table 1: EMRR and EMB are not English acronyms.
2) Table 2: It would be clearer for the reader if authors would specify F and P values as additional columns in the table.

CNV period and ERP amplitude

1) The same comment applies for Table 3 as well

Cluster analysis

Table 4 is not readily comprehensible and it actually confuses more than clarifies the obtained pattern of results. Accordingly, this table (as well as the paragraph reproduced below) should be re-elaborated in a form that allows its comprehension by readers not familiarized with some of the statistics described here. Also to facilitate comprehension, please specify all the acronyms in all the legends.

"New values after k-means cluster solution and statistical results of a new ANOVA, performed with demographic as within-subject factor and the different cluster now as between-subject factor, are displayed for different clusters. Outlier cases are shown but they were not included in the new ANOVA. Percentage of cases and the contribution of each different "experimental group (CON = Control, RR = RRMS, and B = BMS) to cluster solutions are also shown. New demographic values (mean and SD) for age, disease duration and EDSS scale are also shown for each cluster and for outlier cluster. Differences between clusters for demographic values were not found. Mean standardized scores of new clusters are reported for Behavioural (RT and %CRs) and ERP parameters (latency and amplitude). Different statistical differences were found between
clusters as following:"

On the other hand, the fact that all subjects identified as “outliers” belong to BMS patients deserves a comment, specially, when considering that the number of subjects falling in this category is rather high (20% of BMS patients were considered as outliers).

Discussion

Behavioral performance

1) In this part of the discussion section, authors said that, in general, MS patients are slower than healthy controls. However, to my personal opinion, such a conclusion cannot be really extracted from the subjects’ behavioral performance but from the ERPs-based results. In this regard, one might argue that BMS had a higher number of errors due to “missed” errors but, without further information, “missed” errors cannot be considered as due to a reduction of information processing speed. Further, this would apply only to the BMS group and would not be applicable for “all MS patients”

2) In this paragraph: “The findings of our study suggest that subtypes of MS disease may be associated with a moderate/severe attentional impairment and with information processing deficits. BMS patients were, compared to RRMS patients, slower and less accurate, which suggests that BMS patients also show a deterioration in visual-motor processing which is potentially greater than other subtypes of MS (such as RRMS) despite an apparent milder physical disability”. I do not agree with this conclusion, specially regarding the last sentence. First, it is true that BMS patients showed reduced accuracy (higher number of “missed” errors) and that this could be related with a reduction of IPS. However, this is not necessarily a consequence of “visual-motor processing deterioration […] despite an apparent milder physical disability”. This seems incompatible with the fact that, according to what is said at the methods section, patients without visual or motor impairment were selected as well as with the fact that BMS patients exhibit lower EDSS scores. Alternatively, it should be considered that IPS is a trait underlying several cognitive processes (i.e. attention, working memory, learning) rather than a cognitive function per se. Therefore, the reduction of IPS could be affecting the attentional functions (and not “visual-motor deficits”). This alternative interpretation seems more compatible with three interesting and specific results of the present study: First, using and attentional paradigm, reduced IPS in MS patients compared to control group was observed. Second, BMS patients showed a higher degree of IPS impairment than RRMS patients. Third, these cognitive differences seem to be related to a disruption between frontal and parietal areas (recruited during the Posner paradigm). Therefore, IPS reduction might be affecting a controlled process (attentional process) rather than a consequence of visual-motor processing deficits (which is an automatic process). In conclusion, the observed deficits might be due to disruptions in the fronto-parietal network necessary to execute and attention spatial task rather than in visual or motor pathways.
A similar comment deserves MSRR results. Thus, although authors state “However, both MS groups appear to have the amplitude of the final period of CNV intact, which is traditionally related to sensory preparation for the imperative stimulus as well as to preparation for the motor act”, it seems that deficits observed in MSRR patients could be related to attentional problems derived of IPS reductions rather than an affection of the pathways carrying the sensorial input/ the output responses

3) I do not agree with the authors’ interpretation of the Mainero et al., 2006 study (“On the other hand, MS patients may have functional cortical changes when performing cognitive tasks because of damage strategic to white matter structures, limiting the adverse clinical consequences of structural brain damage and improving behavioural performance”). In this sentence authors seem to introduce the existence of compensatory mechanisms. However, the study of Mainero et al., 2006 might not be the best one to support such a possibility. Indeed, the MS patients recruited in Mainero et al. 2006 show a worse performance in the PASAT task than healthy controls and, therefore, one should conclude that the activation of additional areas in these patients did not were “compensating” their behavioral deficits. Thus, I would suggest citing other studies that do actually show that additional activations in MS patients might actually have a “compensatory role” as they are observed in the absence of differences in cognitive performance (see Audoin et al., 2003; Forn et al., 2006; 2007).

ERP latency.

1) To my personal opinion, because authors did not include an appropriate a neuropsychological assessment of BMS patients they are not really legitimated to conclude: “Increased ERP latencies in BMS as well as RRMS led us to suggest that ERPs may indicate subtle degrees of cognitive dysfunction that are not always detected by more traditional clinical measures”. If this evaluation would had been performed (i.e. using Rao’s Battery) perhaps these deficits would had been identified. Further, the conclusion that BMS patients do not show cognitive impairments is in contradiction to those of the Amato et al., (2008) and Rovaris et al., (2008) who observed cognitive dysfunctions in this clinical population.

Cluster analysis

1) Which parameters do have greater weight to separate healthy controls and MS patients in regards to cognitive impairment? It seems clear that they must include some ERP components but it is unclear which ones of them have higher significance.

2) In several occasions authors refer to age as an important variable (i.e. Did the authors use the age as a variable of interest in the cluster analysis?), why exactly? Did the authors use the age as a variable of interest in the cluster analysis? Could the effects of age be separated from disease progression?, In this way authors refers the age in two times: “Cluster analysis revealed two more
interesting findings: firstly, two control groups could be created based on their younger age…” “Cluster 1 were relatively younger than healthy control of cluster 2…”

Figure 1.

Experimental paradigm.

In this legend a short description of the Posner task might facilitate the comprehension of the study for the readers. Indeed, I suggest to include this description here and, if needed, to remove it from text.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

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