Reviewer's report

**Title:** Stable cognitive performance in relapsing remitting multiple sclerosis patients during 2 years treatment with intramuscular interferon-beta-1a: an observational study in daily practice

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**Reviewer:** Emilio Portaccio

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In this paper, the Authors assess the evolution of cognitive functioning in a group of 43 relapsing-remitting (RR) multiple sclerosis (MS) patients treated with intramuscular (IM) interferon beta 1a (IFN). Neuropsychological dysfunction is assessed using the Digit Symbol Substitution Test (DSST), the Paced Auditory Serial Addition Test (PASAT) and the Cognitive Drug Research computerized cognitive test battery (CRD). The Authors find that cognitive functioning remains substantially stable over a 2-year follow-up period.

The study topic is of some interest, given the limited information on the efficacy of disease modifying therapies on cognition in MS

I found a few issues

- The main limitation of the study is the lack of a control group (untreated patients). In this condition is not possible to evaluate the real effect of IFN on cognitive functions. For instance, the stability observed in the study may actually embody a worsening when an improvement due to practice effect may be expected. Indeed, in this study the practice effects are only partially controlled by repeated administration in the first four months. This limitation should be at least commented in the Discussion
- The neuropsychological test battery used in this study is not widely applied in MS population and may be not fully tailored for the profile of cognitive dysfunction in MS. The Authors provide some psychometric properties of this battery in a sort of validation of the battery. However, the validation of the battery is beyond the objectives of the study and cannot be performed in this relatively small sample size. Moreover, a validation study should include as reference criterion the presence of cognitive impairment assessed through neuropsychological tests validated for MS (for instance the Rao’s Brief Repeatable Battery). The correlation with PASAT scores alone is not sufficient.
- There is no information on the cognitive functioning at the individual level. Moreover, there is no definition of overall cognitive impairment (failure on how may domains?). It has been documented that cognitive functioning in MS can remain stable and tends to progress over time particularly in subjects with a cognitive impairment at baseline (see for instance Amato MP et al Arch Neurol 1995, Amato MP et al Arch Neurol 2001). This information should be retrieved. In
particular, it should be of interest to know the proportion of impaired patients at baseline and the evolution of cognitive functioning over time in this subgroup of subjects. Furthermore, baseline cognitive functioning should be presented before the follow-up data.

- Changes over time have been assessed including only age as a covariate. The analysis should be performed including other demographic and clinical variables, such as gender, education, disease duration and disability levels on the EDSS. At this regards, there is no information on depression and fatigue, that are widely recognised as possible confounders of cognitive functioning in MS. Also this variables should be included as covariates in the model.

**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