

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Decision-making impairment in patients with multiple sclerosis: a case-control study
AUTHORS	Farez, Mauricio; Crivelli, Lucía; Leiguarda, Ramón; Correale, Jorge

VERSION 1 - REVIEW

REVIEWER	Jeannie Lengenfelder Kessler Foundation, USA
REVIEW RETURNED	28-Mar-2014

GENERAL COMMENTS	<p>The manuscript was an interesting investigation into decision-making in MS. Twenty-seven individuals with MS and matched HC were administered the two decision-making measures as well as additional neuropsychological measures. Overall, the paper was well-written, hypotheses and analyses appropriate and discussion sound. Some points to strengthen the manuscript are primarily in the Introduction.</p> <p>I think the authors can do a better job of identifying their intent to test explicit vs. ambiguous risk conditions, defining each clarifying the risk conditions. The connection of the risk conditions to executive /memory abilities is weak and also needs to be expanded and clarified.</p> <p>I also think the authors do not do an adequate job in describing in IGT in the same way they do for the GDT. Since there are studies of the IGT in MS these deserve more expansion for the reader.</p> <p>Minor point: Labeling GDT in each y axis for Figures 1 A and B similar to the way the authors do for IGT in Figure 2 would be helpful.</p>
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REVIEWER	Nils Muhlert Cardiff University UK
REVIEW RETURNED	16-Apr-2014

GENERAL COMMENTS	<p>In this study the authors compare decision making performance in people with recently diagnosed multiple sclerosis and healthy controls. Decision making is assessed using the Game of Dice Task (GDT) and the Iowa Gambling Task (IGT), providing a means for separating feedback processing and decision making under differing levels of ambiguity. Using these tests the authors demonstrate that people with MS perform worse on both the GDT and the later blocks of the IGT.</p>
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	<p>In my view, there are two major points to this study. First, there was no difference in the proportion of patients and controls that modify decisions following negative feedback. This indicates that decision making impairments in MS are not underpinned by deficiencies in feedback processing. Second, decision making difficulties are seen despite the low levels of physical impairment (EDSS less than 2) in those with MS, demonstrating changes even at this early stage of the disease (in line with Nagy et al., 2006, JINS).</p> <p>I feel that this study is interesting but that the manuscript needs further work to improve how it reads and to emphasise the main findings. In addition, it would be useful to note whether some of the correlations were hypothesis driven or carried out post-hoc.</p> <p>1. Large portions of the results should be in other sections. This is either because they are speculating on possible explanations, which should be reserved for the discussion, or introducing new models for analysing their data, which should be listed in the statistical analysis section. For instance:</p> <p>a. Page 12, paragraph 2: “These deficits could be caused by... To assess whether this was the case, a subject-specific, random-intercept proportional odds model...”</p> <p>b. Page 13, paragraph 2: “Since feedback processing deficit was not the reason... The MCST was used to assess whether deficits in categorisation...”</p> <p>c. Page 14, paragraph 2: “It has been argued that IGT actually assesses... We then built a mixed-effects regression model to assess...”</p> <p>d. Page 15, paragraph 3: “Thus, deficits in DM making (sic) observed in MS patients seem to be caused mainly by...”</p> <p>2. I see why the authors have examined the correlations with other aspects of cognition in their MS cohort, but find the association with visuo-spatial learning surprising. The patients don't show impairment in their visuo-spatial (or verbal) learning, only in their delayed visuo-spatial memory. In addition, whilst the links between decision making and working memory (or executive function) have a clear rationale, I think further evidence is needed to explain why this would be expected with visuo-spatial learning. If this is a post-hoc analysis, then it may be worth mentioning this and being more cautious in interpreting this finding.</p> <p>3. In the discussion (page 17, paragraph 2) the authors state that “our results highlight the fact that memory deficits are not only important per se, but can also affect other equally or even more important areas, such as DM.” However they later rightly note that correlation is not causation and that other factors could influence both memory and decision making. The authors could use a mediational analysis to assess whether decision making deficits are mediated by memory deficits.</p> <p>4. Did the authors assess whether participants were aware of the risk associated with different decks on the IGT? If so, then there's a stronger argument for difficulties with 'explicit' risk. If not, it should be noted that this can only be assumed.</p> <p>Minor points</p> <p>5. Page 5 paragraph 1 reports a low frequency of impaired executive function in people with MS. This frequency is likely to depend on the</p>
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	<p>tests used (as shown by Foong et al., 1997, Brain), and higher estimates of 24% (van der Hiele et al., 2013) and above have been reported. This should be acknowledged.</p> <p>6. Page 5 paragraph 2 starting “DM can be assessed using...” Much of this information should be in the methods rather than the introduction.</p> <p>7. Page 6 hypotheses: the authors state that decision making will be impaired BECAUSE OF executive and/ or memory impairment. I don't think this is supported by the data, but could be tested using a mediational analysis.</p> <p>8. Page 8 “The subjects were aware of the duration of the test.” This seems out of place, perhaps this can be expanded to explain its relevance.</p> <p>9. Table 3: the MS group have much greater variability in performance on the GDT task. Is there a normal distribution in scores, or would it be worth separating those performing normally from those that are impaired?</p>
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VERSION 1 – AUTHOR RESPONSE

REVIEWER NAME JEANNIE LENGENFELDER

The manuscript was an interesting investigation into decision-making in MS. Twenty-seven individuals with MS and matched HC were administered the two decision-making measures as well as additional neuropsychological measures. Overall, the paper was well-written, hypotheses and analyses appropriate and discussion sound.

1. Some points to strengthen the manuscript are primarily in the Introduction. I think the authors can do a better job of identifying their intent to test explicit vs. ambiguous risk conditions, defining each clarifying the risk conditions. The connection of the risk conditions to executive /memory abilities is weak and also needs to be expanded and clarified.

The introduction has been expanded and clarified and all changes are highlighted in the text.

2. I also think the authors do not do an adequate job in describing in IGT in the same way they do for the GDT. Since there are studies of the IGT in MS these deserve more expansion for the reader. We have added in paragraph 5 of the Introduction a brief description of the IGT and we have expanded paragraph 6 of the introduction with specific mentions to previous reports of IGT evaluation in MS patients. IGT full description is also in the methods section.

3. Minor point: Labeling GDT in each y axis for Figures 1 A and B similar to the way the authors do for IGT in Figure 2 would be helpful.

GDT was added to y axis of Figures 1A and 1B.

REVIEWER NAME NILS MUHLERT

In this study the authors compare decision making performance in people with recently diagnosed multiple sclerosis and healthy controls. Decision making is assessed using the Game of Dice Task (GDT) and the Iowa Gambling Task (IGT), providing a means for separating feedback processing and decision making under differing levels of ambiguity. Using these tests the authors demonstrate that people with MS perform worse on both the GDT and the later blocks of the IGT. In my view, there are

two major points to this study. First, there was no difference in the proportion of patients and controls that modify decisions following negative feedback. This indicates that decision making impairments in MS are not underpinned by deficiencies in feedback processing. Second, decision making difficulties are seen despite the low levels of physical impairment (EDSS less than 2) in those with MS, demonstrating changes even at this early stage of the disease (in line with Nagy et al., 2006, JINS).

I feel that this study is interesting but that the manuscript needs further work to improve how it reads and to emphasise the main findings. In addition, it would be useful to note whether some of the correlations were hypothesis driven or carried out post-hoc.

The correlations investigated in our manuscript were hypothesis driven. This is now stated in the last paragraph of the introduction (highlighted in the text).

1. Large portions of the results should be in other sections. This is either because they are speculating on possible explanations, which should be reserved for the discussion, or introducing new models for analysing their data, which should be listed in the statistical analysis section. For instance:
 - a. Page 12, paragraph 2: "These deficits could be caused by... To assess whether this was the case, a subject-specific, random-intercept proportional odds model..."
 - b. Page 13, paragraph 2: "Since feedback processing deficit was not the reason... The MCST was used to assess whether deficits in categorisation..."
 - c. Page 14, paragraph 2: "It has been argued that IGT actually assesses... We then built a mixed-effects regression model to assess..."
 - d. Page 15, paragraph 3: "Thus, deficits in DM making (sic) observed in MS patients seem to be caused mainly by..."

We have now rewritten the results section and moved or deleted paragraphs or sentences to other sections of the manuscript. All changes are highlighted in the manuscript.

2. I see why the authors have examined the correlations with other aspects of cognition in their MS cohort, but find the association with visuo-spatial learning surprising. The patients don't show impairment in their visuo-spatial (or verbal) learning, only in their delayed visuo-spatial memory. In addition, whilst the links between decision making and working memory (or executive function) have a clear rationale, I think further evidence is needed to explain why this would be expected with visuo-spatial learning. If this is a post-hoc analysis, then it may be worth mentioning this and being more cautious in interpreting this finding.

We shared the surprise with the reviewer about the correlation between visuo-spatial memory and DM. We have now emphasized in the manuscript that this findings should be interpreted with caution and that further studies are required (highlighted in the discussion). We provide a few potential explanations on why we think such correlation was found, the most plausible is that visuo-spatial memory has an impact on DM through its effect on working memory, but this also need to be tested in future studies.

3. In the discussion (page 17, paragraph 2) the authors state that "our results highlight the fact that memory deficits are not only important per se, but can also affect other equally or even more important areas, such as DM." However they later rightly note that correlation is not causation and that other factors could influence both memory and decision making. The authors could use a mediational analysis to assess whether decision making deficits are mediated by memory deficits. We agree with the reviewer that mediational analysis is an appropriate approach for this question. We have made preliminary attempts to assess the effect of working memory and / or visuo-spatial memory on DM using the Sobel-Goodman mediation tests and we found that the mediation effect of working memory was statistically significant with approximately 30% of the effect (of visuo-spatial memory on decision making) being mediated. However, mediational analysis has several assumptions (no unmeasured exposure-outcome confounding, no unmeasured exposure-mediator confounding, no unmeasured mediator-outcome confounding) that unfortunately were not fulfilled by

our study and that we think should be addressed in future studies (Holland et al 1998, McDonald et al 1997).

4. Did the authors assess whether participants were aware of the risk associated with different decks on the IGT? If so, then there's a stronger argument for difficulties with 'explicit' risk. If not, it should be noted that this can only be assumed.

We did not assessed if the participants were aware of the risk, it was assumed based on the literature. This is now clarified in the results section (highlighted)

Minor points

5. Page 5 paragraph 1 reports a low frequency of impaired executive function in people with MS. This frequency is likely to depend on the tests used (as shown by Foong et al., 1997, Brain), and higher estimates of 24% (van der Hiele et al., 2013) and above have been reported. This should be acknowledged.

We have rephrased this sentence to reflect the fact that the prevalence of executive dysfunction seems to be lower than other cognitive domains. (highlighted in the text)

6. Page 5 paragraph 2 starting "DM can be assessed using..." Much of this information should be in the methods rather than the introduction.

We have included brief description of the tests in the introduction (according also to reviewer's #1 suggestion) for clarity purposes. We also provide full details of the tests in the methods section

7. Page 6 hypotheses: the authors state that decision making will be impaired BECAUSE OF executive and/ or memory impairment. I don't think this is supported by the data, but could be tested using a mediational analysis.

We changed "because" for the term "in relationship with" in order to clarify that only association can be inferred by our data and that to infer causation, beyond the theoretical plausibility, further studies are needed, such as the mediational analysis suggested by the reviewer.

8. Page 8 "The subjects were aware of the duration of the test." This seems out of place, perhaps this can be expanded to explain its relevance.

We modified the sentence as follows: "The subjects were aware of the duration of the test, affording the application of long-term strategy to increase the outcome" (highlighted also in the text)

9. Table 3: the MS group have much greater variability in performance on the GDT task. Is there a normal distribution in scores, or would it be worth separating those performing normally from those that are impaired?

The reviewer is correct in that the money balance on the GDT does not follow a normal distribution and thus median and standard deviation is provided as a summary measure and the Mann-Whitney test was used. We agree with the reviewer in that separating two populations is an interesting approach to analyze our data, but due to the small size of our cohort and the small differences between scores, that would have greatly diminished our statistical power to detect any possible difference between healthy controls and patients and thus we preferred to analyze the complete set of patients.

VERSION 2 – REVIEW

REVIEWER	Nils Muhlert Cardiff University, UK
REVIEW RETURNED	22-May-2014

GENERAL COMMENTS	<p>The revised manuscript is substantially improved.</p> <p>I think the authors should be able to carry out a mediational analysis using bootstrapping - which does not have the same assumptions as the Sobel-Goodman method. This can be carried out using the method described and made available by Andrew Hayes (see 'MEDIATE' for SPSS: http://www.afhayes.com/spss-sas-and-mplus-macros-and-code.html). This could further strengthen the manuscript, by testing whether worse decision-making in people with MS is indeed mediated by working memory/ visuospatial memory, but I leave it to the authors discretion whether to add it at this stage.</p>
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VERSION 2 – AUTHOR RESPONSE

Following reviewer's suggestion, we performed a mediational analysis using the Preacher and Hayes bootstrapped test of mediation. We assessed whether the effect of visual memory on DM is mediated by working memory and we found that the relationship between visual memory and DM was partially mediated by working memory (27%) and that the direct effect remained significant ($P=0.01$). We have added this to the revised version of the manuscript (highlighted in the text).