Reviewer's report

Title: Decision-making is impaired in multiple sclerosis: impact of subcortical atrophy and disease disability

Version: 2
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Reviewer: Quinten van van Geest

Reviewer's report:

This study investigated the relationship between ventricular width (i.e., as a measure of (subcortical) atrophy) and decision-making in multiple sclerosis (MS). As the authors already mention in their introduction, decision-making in MS has not been investigated extensively. Hence, studies aiming to better understand (impaired) decision-making, combined with magnetic resonance imaging (MRI), are quite interesting. The authors observed impaired decision-making in MS compared to healthy controls (HCs), but also differences in decision-making between MS subgroups and HCs. Additionally, MS patients showed atrophy relative to non-MS patients. Although a correlation was found between decision-making and information processing speed in MS patients, atrophy independently predicted both worse decision-making and slowed information processing speed. Although this study is interesting, I do have some comments for the authors concerning the study design, methods, and interpretation of data.

Major compulsory revisions

1. Various ‘simple’ MRI measures are used to measure (subcortical) atrophy. I understand that it is impossible to run more advanced imaging analysis methods on conventional (2D) clinical MRI data, but I would like to ask the authors to mention results (i.e., correlation coefficients) of previous studies that correlated for example ventricular width to whole brain volume (or subcortical volumes). This way, the authors can better justify the use of ventricular width as a measure for atrophy. If previous studies have not shown that ventricular width perfectly correlates with subcortical volume, I would like to ask the authors to change the term ‘subcortical atrophy’ in something more suitable (e.g., ventricular width) in the text and title.

2. The aim of this paper is to investigate whether “problems with decision-making under explicit risk in the GDT are linked to increasing disability and loss of brain volume in the course of MS.” Firstly, I would like to ask the authors to define the term ‘disability’. Secondly, in my opinion, increasing disability and loss of brain volume are not two independent measures. That is, atrophy is a relatively good predictor for physical and cognitive problems in MS; patients with severe atrophy will probably also experience (severe) clinical disability. Perhaps the authors could be more specific concerning their research question.

3. Could the authors please explain why they divided the MS group into subgroups based on EDSS score and MS type, and how they have determined
the cut-off values? Please note that correlating EDSS with ventricular width/Game of Dice Task (GDT) in all three subgroups is somewhat circular in terms of reasoning. I would suggest the authors to omit these correlation analyses.

4. Imaging data is acquired on different MRI scans. Could the authors please explicitly mention how many different MRI scanners and protocols were used (including the number of patients/HCs per scanner)? Is there a possibility to correct for the type of scanner?

5. Frontal Horn Width (FHW), Intercaudate Distance (ICD), and Third Ventricle Width are absolute measures, thereby making it difficult to interpret the differences between groups. Is there a possibility to normalize these values for head size?

6. No data is shown concerning lesion volumes of MS patients. I assume the MRI scans are suitable to measure (T1 and/or T2) lesion volumes. Could the authors please add these measures to the results, as it might influence decision-making and information processing speed?

7. The authors used published norm scores for all individual neuropsychological tests to calculate z-scores. However, the HCs in this sample also underwent neuropsychological testing, and in my opinion it would be more informative to calculate the z-scores relative to the HCs (instead of using norm scores).

Minor essential revisions

General
1. Please change ‘neurocognitive’ in ‘cognitive’.

Abstract
2. See the comment above concerning the term ‘subcortical atrophy’
3. Please mention which groups were compared
4. Please omit the statement concerning fronto-striatal signalling, as this has not been investigated in the present study.

Introduction
5. See comment above concerning the correlation between ventricular width and (subcortical) brain volumes
6. Page 4, line 1-3: could the authors please rephrase this sentence? Additionally, the term ‘neurodegenerative’ already implies ‘brain changes’.
7. Page 4, line 4: could the authors please clarify the relevance between the gambling task and ‘blunted physiological reactivity’ in the context of the present study?
8. Page 4, line 7-9: which tracts were measures using diffusion tensor imaging?
9. Please explicitly mention the research question in the final paragraph before stating the hypothesis.

Methods
10. Were patients relapse and corticosteroid treatment free at least four weeks prior to investigation?

11. Page 6, line 9: how did the authors actually validate ventricular width measures? Could they please elaborate on this matter?

12. Page 9, line 17-19: please move this paragraph to the beginning of the methods section

13. Please omit all analyses in which ventricular width is correlated to EDSS in MS subgroups (i.e., circular reasoning; see Major points for revision).

14. Could the authors please mention how subjects performed the GDT (e.g., on a computer)?

15. Could the authors please reconsider the cognitive domains and neuropsychological tests that were used to assess these domains? For example, the Digit Span forward is not a test for psychomotor processing speed, but for short-term memory. Additionally, please explicitly mention which tests were used for each composite z-score.

16. See comment above concerning z-scores of neuropsychological tests.

17. Could the authors please indicate whether they have corrected their p-values for multiple comparisons? A large amount of correlations analyses are performed.

Results

18. Could the authors please be consistent with the methods section in the order in which they present the results?

19. Please move any interpretation of data to the discussion (e.g., page 11, line 7-8).

20. Could the authors please provide the actual p-values?

21. Page 12: the authors performed additional analyses to see whether education and premorbid IQ could influence GDT score. Perhaps a part of this paragraph could be moved to the methods section (statistical analysis).

Discussion

22. Perhaps it would be convenient if the authors would start their discussion with stating their research aim, and subsequently report their main findings.

23. On page 17 the authors speculate on the possible changes in brain circuits that might underlie decision-making problems. I think this is very interesting and important, and I would like to challenge the authors to provide additional information concerning this matter. Perhaps the authors can include other neurological diseases that have used more advanced MRI techniques to better understand problems in decision-making.

24. I would like to ask the authors to mention the strengths and limitations of the present study.

Conclusion
25. Page 17, line 21: please weaken the statement concerning “…subcortical atrophy involving the thalamus and striatum”. The measures that were used in this study do not reflect atrophy of the thalamus and striatum (see Major points for revision).

26. Page 17, line 21: please omit the statement that subcortical atrophy may contribute to disturbances in fronto-striatal signalling related to impaired decision-making, as this cannot be concluded based on the present results.

27. Page 18, line 1: based on the present results, I do not believe that decision-making can be a reliable biomarker for atrophy. Especially considering that atrophy can be measured relatively easy and very accurate with MRI.

Figures
28. Please display in figure 1b the relationship between EDSS score and GDT score for all MS patients (and not for subgroups separately, because of circular reasoning).

Tables
29. Please provide actual p-values (perhaps instead of test statistics)
30. Please do not highlight ‘trends’. These results are not statistically significant and cannot be used to draw any conclusions.
31. Table 2: it would be informative if the authors could display and test the raw neuropsychological data.

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