

Peer Review History

BMJ Open-2010-000007

Magnetic Resonance Spectroscopy in the prediction of early conversion from amnestic Mild Cognitive Impairment to dementia.

Reviewer 1: Rosenberg, Paul

Paul Rosenberg

Johns Hopkins School of Medicine (USA)

The Study	Yes	No
Is the research question clearly defined?	✓	
Is the overall study design appropriate and adequate to answer the research question?	✓	
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?	✓	
Are the patients representative of actual patients the evidence might affect?	✓	
Are the methods adequately described?		✓
Is the main outcome measure clear?	✓	
Are the abstract/summary/key messages/limitations accurate?	✓	
Are the statistical methods described?	✓	
Are they appropriate?		✓
Is the standard of written English acceptable for publication?	✓	
Are the references up to date and relevant? (If not, please provide details of significant omissions below.)	✓	
Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?	✓	

If you answered No to any of the above, please supply details below.

I suggest using either a logistic regression or survival analysis (see my comments to authors below).

The methods are poorly written (see comments below).

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?	✓	
Are they credible?	✓	
Are they well presented?	✓	
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?	✓	
Are they discussed in the light of previous evidence?	✓	
Is the message clear?		✓

If you answered No to any of the above, please supply details below.

The authors need to address the question of localization: why are MRS changes in occipital cortex predictive of MCI progression (see my comments to authors below)

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?	✓	
Are research ethics (e.g. consent, ethical approval) addressed appropriately?	✓	
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?	✓	

In compliance with the BMJ Open system of open peer review – please sign your review in the box below. Include your name, position, institution and country. Please also include a statement of competing interests. If you have filled out an ICMJE Conflicts of Interests form – please attach this using the box beneath instead.

Paul B. Rosenberg MD
Assistant Professor of Psychiatry and Behavioral Sciences
Johns Hopkins School of Medicine (USA)

Statement:

I have no competing interests.

I accept research funding from the National Institute of Aging, American Foundation for Aging Research, Pfizer, Merck, Lilly, and Janssen.

No honoraria or consulting.

posteriomedial bilateral parietal cortex and left medial occipital lobe predicted progression.

The results are very interesting and may have significant impact on the field, I'm not sure without seeing more analyses (see below). But there are many issues with the analyses and writing, specifically:

1. In my opinion the proper data analytic strategy is to perform a survival analysis using Cox proportional-hazards regression to assess the effect of baseline covariates on MCI progression to AD. I.e., progression to AD = "failure". This is the most powerful way to analyze the data, I think, and they have followup approximately every six months so they have the proper data structure for a survival analysis. The standard method is univariate analyses first, then add typical confounders including age, education, baseline cognitive tests, and ApoE4. The ROC should be the last analysis presented, demonstrating the utility of the measure. Maybe they did this to calculate ROC but the methods are poorly described.
2. The authors fail to address the localization of the findings in the Discussion. They leap into a discussion of the hippocampus -- problems with MRS data in the hippocampus -- but they do not discuss, why occipital lobe? Why left-sided? Overall the AD field has not "bought" the prior results of occipital MRS as a risk factor -- too counterintuitive since occipital cortex is relatively spared -- and this paper replicates that result to some extent. This needs to be explained!
3. The Background is poorly organized --
 - a. "MCI is characterized by ...memory loss" only amnesic MCI is.
 - b. The authors leap to "Therefore we need a biomarker to predictor conversion to dementia to start treatment as soon as possible" without mentioning the real reason -- that pathology starts long before symptoms in Ad.
 - c. "Apart from genetic mutations in familial cases there is no marker accurate enough for AD". This sentence does not convey the meaning that the authors likely intend -- "there are no markers which are sufficiently sensitive and specific risk factors for prodromal AD" might be more accurate.
 - d. The discussion mentions FDG-PET and PIB-PET but not the Background, but these are important imaging markers which might be good risk factors as defined above.
 - e. The Background is very poorly organized, bouncing between different biomarkers without a clear focus.
4. The paper needs to define the objectives of this study which are both diagnostic and predictive; the latter is of course much more important.
5. The Background and Discussion need to clearly delineate which prior studies are cross-sectional and which are longitudinal. I would not spend significant time on cross-sectional, longitudinal is what is important.
6. The Background needs to review prior MRS findings in a straightforward manner. I would only mention the existence of the four standard MCI biomarkers (volumetrics, CSF A β /tau ratio, FDG-PET, PIB-PET) in the Background, and save the findings for the Discussion.
7. The impact of this paper will lie in whether MRS is as good a predictor or even better than the others, and how practical will it be to bring into the clinic. The authors need to clearly address these issues in the discussion.
8. The authors need to either perform a correction for partial volumes or demonstrate why it is not needed.
9. End of Background: "We hypothesize that occipital and parietal values are similarly predictive" in which direction are they predicting an association.
10. The use of abbreviations is very haphazard, many are used without being defined.
11. The Memory Impairment Screen is not well known, what is it?
12. Don't capitalize Magnetic Resonance in mid-sentence (in the methods).
13. I am not personally qualified to critique MRS techniques, this needs a specialist in MRS.
14. It is customary in MRS literature to present sample spectra comparing two groups. In this case, converters vs. nonconverters. Also, I only have one spectrum (not properly labeled) in my figures.
15. "The intra-class correlation coefficients were also remarkable" just give the numbers not the editorializing here, the numbers speak for themselves.
16. Table 1 should include duration of followup and number of followup visits (mean and SD)
17. The authors need to assess whether there were demographic differences between included and excluded cases.

Reviewer 2: Jessen, Frank

Frank Jessen

University of Bonn, Dept of Psychiatry

The Study	Yes	No
Is the research question clearly defined?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Is the overall study design appropriate and adequate to answer the research question?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Are the patients representative of actual patients the evidence might affect?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Are the methods adequately described?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Is the main outcome measure clear?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
If you answered No to any of the above, please supply details below.		
control subjects are not described, MCI converters and non-converters are not differentially described		
covariate analyses are missing		
the literature on MRI n MCI is not sufficiently covered		
<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?	✓	
Are they credible?	✓	
Are they well presented?		✓
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?	✓	
Are they discussed in the light of previous evidence?		✓
Is the message clear?	✓	

If you answered No to any of the above, please supply details below.

the presentation of data, particularly regarding the control group is insufficient
the evidence on MRS in MCI is not reported sufficiently

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?	✓	
Are research ethics (e.g. consent, ethical approval) addressed appropriately?	✓	
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Comments

If you have any further comments for the authors please enter them below.

The description of the control (procedure of recruitment, demographic variable etc.) are missing. Baseline demographic and cognitive description of MCI converters vs. non-converters is missing. Also, these data were not included as covariates in the statistical analysis.

The discussion is general poor

The effect that NAA is reduced in controls in the PCC, but NAA/Cr is not, while NAA/Cr is reduced in converters, while NAA is not, needs to be discussed

There is no discussion on the effect that the prediction is similar in occipital lobe as the PCC, even though the PCC is an anatomical region with a strong hypothesis in AD, while the occipital lobe is not.

The literature on MRS in MCI needs to be discussed in greater detail rather than reporting several other biomarkers.

Authors Response to Decision Letter for (BMJ Open-2010-00007)

Magnetic Resonance Spectroscopy in the prediction of early conversion from amnestic Mild Cognitive Impairment to dementia.

BMJ Open
Editorial Office
Richard Sands, editor.

Ref. Ms 10-00007. Magnetic Resonance Spectroscopy in the prediction of early conversion from amnestic Mild Cognitive Impairment to dementia.

Dear editor:

After reading with interest the referees' report we have made changes in the text accordingly. All changes are highlighted in red to better identification. The changes are as follows:

REVIEWER 1.

1. Survival analysis has been performed (see methods and results sections), with Kaplan-Meier method and Cox regression model with the suggested covariates. In the figures the dot plots have been replaced by the figures 3 and 4 depicting the survival curves.
2. Why the changes in the occipital lobe are commented in discussion section
3. The adjective amnestic is added, and also the argument that pathology begins long before symptoms in AD. References 4,5 and 6 are new to better justify the search for accurate biomarkers in the introduction. PET studies are mentioned in the introduction section.
4. Objectives are better defined in the last paragraph of background.
5. In the background and discussion we comment more about longitudinal studies than on cross sectional studies.
6. The standard biomarkers are only mentioned without entering into details.
7. The practical usefulness of MRS is commented in the discussion with pros and cons.
8. We don't have the software to make corrections for atrophy or CSF, but the ratios to creatine and water suppression minimise this caveat.
9. The direction of prediction is to predict early conversion to dementia.
10. Abbreviations are put in the text with consistence.
11. We explain briefly the memory impairment screen in the methods section.
14. We present two spectra: one for non-converters, and another one for converters (figure 2 a,b).
16. In table 1 includes duration of follow-up and the number of visits.
17. Differences in age and sex are reported in the first paragraph of results.

REVIEWER 2

1. The control group is described in page 7, second paragraph.
2. Covariate analysis with Cox regression model and discriminant analysis is reported in methods and results. Baseline demographics comparison is also reported.
3. We have added more comments on longitudinal studies in the background
4. The NAA levels are reduced in controls in the occipital lobe (which is not logical) and it is discussed (it may be due to the limitations of the technique in quantifying these levels; the ratios are more reliable; see reference 61). In the PCC the NAA levels in controls are not reduced see table 2).
5. We discuss the finding of the lower values in the occipital lobe in converters with 2 more references (53 and 54).
6. The data from other biomarkers in the discussion are condensed but a comparison is needed with MRS.

I hope you find now the manuscript suitable for publication.

Very truly yours,

Dr Pedro J Modrego.

Magnetic Resonance Spectroscopy in the prediction of early conversion from amnestic Mild Cognitive Impairment to dementia.

BMJ Open-2010-000007.R1

Reviewer 1: Rosenberg, Paul

The Study	Yes	No
Is the research question clearly defined?	✓	
Is the overall study design appropriate and adequate to answer the research question?	✓	
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?	✓	
Are the patients representative of actual patients the evidence might affect?	✓	
Are the methods adequately described?	✓	
Is the main outcome measure clear?	✓	
Are the abstract/summary/key messages/limitations accurate?	✓	
Are the statistical methods described?	✓	
Are they appropriate?	✓	
Is the standard of written English acceptable for publication?	✓	
Are the references up to date and relevant? (If not, please provide details of significant omissions below.)	✓	
Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?	✓	

If you answered No to any of the above, please supply details below.

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?	✓	
Are they credible?	✓	
Are they well presented?		✓
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?	✓	
Are they discussed in the light of previous evidence?	✓	
Is the message clear?	✓	

If you answered No to any of the above, please supply details below.

NOTES ON "MRS in the prediction of early conversion from amnesic MCI to dementia"

The authors have addressed most of the issues raised in my earlier review.

Comments:

- The authors appropriately divided NAA/Cr at the "average" but they meant "mean" and clarify this in the figures, they should change the wording in the text as well.
- Figure 5 has a poorly labeled legend, needs to be translated into comprehensible terms

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?	✓	
Are research ethics (e.g. consent, ethical approval) addressed appropriately?	✓	
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?	✓	

Comments

If you have any further comments for the authors please enter them below.

My comments are very minor and does not, in my opinion, require a formal re-review

Authors Response to Decision Letter for (BMJ Open-2010-000007.R1)

Magnetic Resonance Spectroscopy in the prediction of early conversion from amnesic Mild Cognitive Impairment to dementia.

BMJ Open
Editorial Office
Richard Sands, editor. 29 November 2010

Ref. Ms 10-00007-R1. Magnetic Resonance Spectroscopy in the prediction of early conversion from amnesic Mild Cognitive Impairment to dementia.

Dear editor:

After reading the referee's report we have made changes the two minor changes in the text accordingly. The changes are highlighted in red to better identification. The changes are as follows:

In the results section, converters versus non converters, survival analysis, we have changed below/above average for below/above the mean.

The legend of figure 5 has been reworded.

I hope you find now the manuscript suitable for publication in BMJ Open. Thank you very much for your attention in the process.

Very truly yours

Dr PJ Modrego

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