Reviewer's report

Title: Card-Placing Test in Amnestic Mild Cognitive Impairment and its Neural Correlates

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Reviewer: Jan Laczó

Reviewer's report:

The authors present an interesting paper aiming to investigate structures that are associated with performance on the newly developed Card Placing Test (CPT) that may reflect heading disorientation in patients with amnestic MCI. They recruited 15 amnestic MCI patients, who were examined with CST part A and B and underwent FDG-PET. Amnestic patients were compared to 29 healthy matched controls. The authors found an inferior performance in both parts of CPT and correlation of CPT part B with hypometabolism of the bilateral posterior cingulated gyrus and precuneus. The authors concluded that the part B of the newly developed CPT reflects the functional status of the posterior cingulate gyrus in patients with amnestic MCI.

This paper contributes to the current knowledge about topographic disorientation and its functional correlates in patients with MCI, however the study has some limitations including the small sample size of amnestic MCI subjects and using uncorrected p-values in the correlation analyses.

- Major Compulsory Revisions

1. In the Methods section the authors should describe in more detail the Petersen’s criteria they used for classification of MCI patients. Did they use the original Petersen's criteria requiring memory impairment and relatively preserved other cognitive functions (criteria for amnestic MCI single domain) or the revised criteria requiring memory impairment with either impairment or preservation of other cognitive domains (where the amnestic MCI patients could have single or multiple domain cognitive impairment). If the authors used the new revised criteria they should clearly state the number of amnestic MCI single domain and amnestic MCI multiple domain patients. Did the authors use to establish memory impairment in the amnestic MCI patients 1,5 or 1 standard deviations below the mean of norms on any memory test?

2. In the Methods section it should be mentioned how the control group was defined. Were the controls free of any cognitive problems and was it confirmed by neuropsychological testing (e.g. not scoring less than 1.5 standard deviations below the mean of age- and education-adjusted norms on any cognitive test)? Otherwise the authors cannot exclude recruitment of subjects with cognitive impairment they may not be aware of.

3. It would be of interest to provide readers with details of the neuropsychological tests the authors used to define the amnestic MCI and control groups (means,
standard deviations and statistical significance). Implementing these data to the Table 1 would be helpful.

4. In the Results section also corrected p-values of the correlation analyses should be reported in addition to uncorrected p-values

5. In the Discussion section the explanations for the correlation between the scores of CPT part B and hypometabolism of the posterior cingulate region should be better discussed.

a) First, the authors found associations between scores of CPT part B (reflecting possibly heading disorientation) and bilateral posterior cingulate gyrus and precuneus, but the original report from Hashimoto et al. (2010) found impairment of the CPT part B in patients with only right cingulate gyrus/precuneus lesions indicating that the right retrosplenial region is the critical site for heading disorientation. In addition several studies reported that damage to the left retrosplenial region is not associated with heading disorientation but with episodic memory deficits (Gainotti et. al, Neurocase, 1998). How the authors explain that they found a correlation with bilateral cingulate gyrus/precuneus hypometabolism in the test reflecting heading disorientation and not episodic memory?

b) Second the authors provide a possible explanation for the correlation between CPT part B and hypometabolism on FDG-PET stating that “….it seems that the CPT B is reflective of levels of general cognitive deficit in patients (with MCI) and hypometabolism in the posterior cingulate gyrus is correlated with levels of their cognition. They argued based on the previous MRI morphometric study that the precuneus is responsible for the multiple cognitive impairments in multiple domain amnestic MCI that may form a transitional state between single domain amnestic MCI and AD. To support this statement the authors should have compared patients with amnestic MCI single domain with their amnestic MCI multiple domain counterparts. Or they should have evaluated only patients with multiple domain amnestic MCI, because including also patients with single domain amnestic MCI may lead to non-significant results due to type 2 error. This may be reflected as a limitation of the study at the end of Conclusions. Further, to distinguish whether the correlation between CPT part B and hypometabolism on FDG-PET is because of the CPT part B is the specific test of heading disorientation dependent the posterior cingulate gyrus or only reflects levels of general cognitive deficits in patients with amnestic MCI the authors should perform further correlation analyses with neuropsychological tests covering each cognitive domain and metabolism on FDG-PET. If the authors found only correlation between the posterior cingulate gyrus and CPT part B, this would be supportive for the first hypothesis and if they found correlation with more neuropsychological tests and hypometabolism of posterior cingulate gyrus, this would be supportive for the second hypothesis.

6. In the Discussion section a low number of the amnestic MCI patients as a major limitation should be more thoroughly discussed.

- Minor Essential Revisions
1. The typo “Peterson” in the Participants subsection of the Methods section should be changed to the correct name “Petersen”.

2. Because of the above mentioned limitations, the statement in the Conclusions: “This study suggests that the CPT B is reflective of the functional status of the posterior cingulate gyrus in patients with aMCI.” should be changed to “This study suggests that the CPT B may reflect the functional status of the posterior cingulate gyrus in patients with aMCI.”

3. There is an inconsistence in the 4th reference about the format of pages. To be more consistent the authors may change “261–82” to “261–282”.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare that I have no competing interests