Author’s response to reviews

Title: P300 amplitude is insensitive to working memory load in schizophrenia

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Author’s response to reviews: see over
Monday, January 31, 2011

Dear Dr. Marek Kubicki:
Cc: Miss Angelina Iliesvska MSc.
The BioMed Central Editorial Team.

Dear Editor:

Herein we resubmit an additional version of our article, entitled “P300 amplitude is insensitive to working memory load in schizophrenia”, to BMC Psychiatry. We believe having adequately complied with the reviewers requirements. There was a critical issue claimed by both reviewers, pointing to our model of redistribution of resources as an explanation of the P300 amplitude at high working memory load conditions. We now agree with the reviewers suggestions, and have deleted this interpretation while favoring a different explanation as suggested by reviewer MN, which fits better Kok’s (2001) model to explain the generators of the P300.

For the benefit of the reviewers, all changes to the text have been marked in blue.

Sincerely yours,

Dr. Pablo Gaspar
Dr. Francisco Aboitiz
We are grateful for the helpful comments. Below we will address the points made by both reviewers, one by one.

There was a critical issue claimed by both reviewers, pointing to our model of redistribution of resources as an explanation of the P300 amplitude at high working memory load conditions. We now agree with the reviewers suggestions, and have deleted this interpretation while favoring a different explanation as suggested by reviewer MN, which fits better Kok’s (2001) model to explain the generators of the P300.

Reviewer 1

Q: The conclusion (as stated in the abstract and the conclusion paragraph of the discussion) that SZ fail to reallocate resources may be flawed. The authors state that "[P300 amplitude] decreases with increasing WM load.... is considered to result from the reallocation of resources into maintenance or rehearsal circuits." However, a failure of decrease is not main deficit seen in this SZ. SZ show decreased baseline amplitude (on the low-level WM task), showing a similar response to all WM load-levels. Does this suggest SZ need to reallocate resources to other circuits even on the low-load task (this appears to have been suggested to some extent in the discussion), suggesting significantly reduced WM capacity (for even minimal loads) in SZ? Alternatively, does this suggest some a more fundamental deficit in the P300 response amplitude that is not specific to or independent of WM processes?

A: We agree with both reviewers that the hypothesis of resource reallocation does not fit our data. Consequently, we have deleted this sentence and all paragraphs referring to the hypothesis of resource reallocation.

Q: p. 10: These sentences are unclear and need to be re-written:
   a. 'decreased confidence in cognitive processing and overlap or dis-overlap of different ERP components.'
   b. 'Stated perhaps in a different way, the contributors to the P300 potential in SZ may reflect the engagement of predominantly attentional rather than memory resources. Memory information is stored preferentially in rehearsal networks.'

On p. 3- what does 'for a complete revision see ref [5]' mean? do the authors mean a *review* of the literature?

A: We have rewritten the Introduction and Discussion in order to comply with the Reviewers demands, and these sentences are no longer present.

Q: The term HS should not be used to described people at high-risk to develop schizophrenia. Simply state 'non-psychotic persons who are at familial high-risk to develop schizophrenia.'
A: This sentence has been changed and rewritten as the reviewer proposes.
Reviewer 2

Q: The remaining problem with the paper is how the research question was conceptualized and how the results were interpreted. As said above, I do believe that SZ subjects’ P300 is not sensitive to WM manipulations. The question is why?

A: We have reconceptualized our interpretation of the results, which we now feel fits better with Kok’s (1996) model.

Q: Since the authors elected to follow the Kok model as their explanatory mechanism for the P300, I recommend that they stick to it.

This model does not state that .. when memory demands exceed the capacity of fronto-parietal circuits, memory resources are reallocated into rehearsal circuits.. etc (page 3).

Here I cite: “The core element in the model is the assumption that P3 amplitude reflects attentional capacity invested in categorization of task relevant (or significant) events.”

A: We have modified this interpretation in both the Introduction and the Discussion.

Q: Kok does assert that P300 is generated in fronto-parietal cortical areas as well as in the anterior cingulate (here the authors should stress that this conceptualization is specific to this model – not all the field would agree to this conceptualization).

A: We have made this point clearer in the Introduction, when speaking of the neural networks related to the P300.

Q: Kok further states that the primary function of the network whose activity is reflected in the P300 is to compare stimulus attributes with an internal (memory) representation of the target. This function is further modulated by attention, working memory, and task difficulty (closely related to working memory demands but not identical with it). The Kok model does assume that categorization is supported by neural systems that themselves are not part of the ‘categorization system’ but this is different from saying that memory demands are reallocated to rehearsal circuits.

Importantly for this paper, the critical question is which mechanism contributing to the generation of the P300 is abnormal in schizophrenia given the task characteristics used.

I do not believe that the authors have evidence that schizophrenia sufferers’ P300 flat profile is due to their inability to distribute resources to other networks; I do not believe that they have evidence that NC distributed such resources; indeed the Kok model says nothing about such a possibility.

A: We agree on this and have consequently deleted all mention of resource reallocation.
Q: I believe that the available option for the authors is to consider which of the operations described by the Kok model may be deficient in schizophrenia:

(1) ability to effectively compare sensory percept with a memory template, (2) attentional/WM resources deployed in the task, or (3) task difficulty.

Since the authors report a reduced P300 in all three conditions (significantly only in 1-back)(it is not clear how reliable this result is when one looks at mean values cited in Table 4) and a tiny but present reduction of the P300 amplitude across the three conditions in the SZ group, my suggestion is that the patient group has a limited ability to effectively compare the sensory percept with a memory template and more limited WM resources relative to NC.

A: We have included a paragraph in the Discussion proposing an explanation that we believe fits well with the reviewer’s suggestions.