Reviewer's report

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

Version: 4 Date: 9 January 2011

Reviewer: Margaret Niznikiewicz

Reviewer's report:

The paper “P300 amplitude is insensitive to working memory load in schizophrenia” is a much improved paper. The basic premise of the paper is that P300 amplitude recorded in the n-back task in normal control group diminishes as function of working memory load, while it does not in schizophrenia group. I do believe that this is a real finding and it is of interest; (The authors may want to read Shelley et al. 1996 ERP study that uses CPT-AX task and reports somewhat similar results.)

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?

1. It is true that working memory has been conceptualized by many authors as consisting of several subcomponents such that frontal and parietal networks participate in a dynamic way in many operations that can be described as necessitating working memory, and the authors cite papers in support of such a view.

2. The authors also cite three papers (Kok, 2001; Gevin et al., 1996; and McEvoy et al., 1998) that make a point that a. P300 is not a unitary phenomenon but a family of related potentials that are likely sensitive to different aspects of working memory operations – and that it is critically important what the task is since this task will decide which aspect of these working memory operations will be assessed and reflected in the P300 and b. Kok specifically – and authors cite his paper as a source of their theorizing about P300 – makes detailed statements about what P300 is, what experimental conditions contribute to its generation and neuroscience interpretation of these experimental conditions.

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.” 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). 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.

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: ability to effectively compare sensory percept with a memory template, attentional/WM resources deployed in the task, or 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.

In addition, for future studies, using two different baseline conditions (500 and 200) is not recommended. When one epochs EEG, one settles on a pre-stimulus baseline and uses it in all analyses and operations.

The preferred way to analyze these ERP data would be to use individual subject values from each of the 5 ROIs for the three conditions in the model: two within factors: of condition (3 levels) and of region (5 levels) with 1 between factor (group: 2 levels). Main effect and interactions would inform further analysis steps.

**Level of interest:** An article of importance in its field

**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.