Author's response to reviews

Title: Auditory change detection in schizophrenia: sources of activity, symptoms and neuropsychological function in patients with a first episode in adolescence, and patients 14 years after an adolescent illness-onset.

Authors:

Robert D. Oades (oades@uni-essen.de)
Nele Wild-Wall (nele@wild-wall.de)
Stephanie A. Juran (sjuran@web.de)
Jan Sachsse (JanSachsse@web.de)
Lyubov B Oknina (lokrina@nsi.ru)
Bernd Roepcke (bernd.roepcke@uni-essen.de)

Version: 3 Date: 16 December 2005

Author's response to reviews:

From Robert D. Oades,
University of Duisburg-Essen.

Dear Editorial Team and Reviewers,

Thank you very much for your commentaries.

May I first reply (on behalf of my co-authors) to the points made by Dr. Kwon.

1. Approval of Ethics Committee:

Our initial statement was far too brief. The following sentence now added to the start of the Methods section pertains (p. 6).

The study protocol was reviewed and approved by both the board of the University of Essen Psychiatry Clinics and the Ethics Committee of the Faculty of Medicine according to the criteria of the Declaration of Helsinki (00-2-1357-Y).

2. Correlational analysis / Control for type-1 errors.

The statement was perhaps rather buried in the relevant results section. We summarise and rephrase the issue where correlations were first mentioned at the end of the ERP Data Analysis subsection of the Methods (p.9).

Exploratory correlations were sought for 3 sets of MMN measures (frontal, mastoid and dipole-moments) with the CGI sum scores, the main clusters of SANS/SAPS symptoms, and neuropsychological measures of processes putatively related to MMN measures (digit-span, trail-making)[54,55]. Trends are described at P<.05 and type-1 corrected correlations at P<.002.

3. Source localization/individual MRI/averaged template - report from Ha et al. 2003

As the reviewer points out, the variability of the anatomy between individuals and the templates used for source localization are a source of error that we chose to mention in describing the limits to our efforts to describe the putative anatomical loci for the MMN generators (p.19). The report of Ha et al. 2003 examined
various aspects of this issue and is a valuable source of experience on this frustrating issue. We are happy to make reference to it in the last lines of the section.

But, in addition to the problems of inter-individual stability of the model, error is introduced in the placing of sources on the brain atlas. Discrepancies between MRI anatomical representations of the locus of an individual's source and its localization on an averaged template can be marked. One study of this issue reported differences in nearly two thirds of the cases examined (Ha et al., 2003). We have partly corrected for this by representing sources on the anatomy of one of our subjects (figure 4). But without constructing an average brain image from the participants, we have not accounted for the anatomical variability between our subjects.

4. Table 1 - Complexity

We agree that there was too much in table 1 - and have removed the vigilance and discrimination performance data to a new table 2 (adjusting references to now 4 tables).

5. Table 3 Subject numbers queried.

Actually the subject numbers are correct: but we are grateful to the reviewer for drawing our attention to the issue, as we have misleadingly referred to this table where we discuss the statistical evaluation of the individual data in the text. These references have now been corrected and we have attempted to clarify where we write about group or individual data. We have not included the 8 columns of data and 7 of standard deviations that would be necessary to cover the individual data (that result from the smaller group size proposed by the reviewer). We feel that the extra value of adding this degree of detail is limited. This would seem particularly so considering that figures 3 and 4 illustrate these data.

6. Loreta reference. This was an unfortunate oversight implying that reference 36 used Loreta. The sentence was intended to (and now rephrased to) refer to MEG, ERP and imaging studies.

7. p.21 One "ERP" abbreviation has been removed

8. The abbreviation LORETA and what it stands for now appear together for the first time in the middle of p.17

9. We are happy to add the note at the start of the discussion-section that the amplitude values refer to measures at Fz.

10. The Dd abbreviation is unnecessary and has been removed

I now address Dr Lutzenberger's remarks.

1. On the question of overlap with the Oknina et al. report

We agree that the initial 'eye-catching' aims, as expressed in the few lines available in the abstract, sound similar to the previously reported analysis.

"...characteristics of the scalp-recorded MMN, assessed whether the equivalent dipole sources are affected already at illness-onset in adolescence and how these features differ after a 14-year course following an adolescent onset. The strength, latency, orientation and location of frontal and temporal lobe sources of MMN activity early and late in the course of adolescent-onset schizophrenia are analysed and illustrated"
On re-reading this one may appreciate that the expressed aims are a) numerous, and b) of major import. Yet space in the abstract is limited for the elaboration of all our intentions.

Let me first write about the MMN measures. Dwelling on the MMN after a duration deviant is significant as it is this type of deviant that has proved most useful in numerous language-oriented studies based on tone detection and discrimination in healthy subjects, and has provided the most significant results in studies of tone-change detection in psychotic patients.

The importance lies in both the extension of the results (here) compared to the first report, the emphasis and the detail. The extension is important against the background mentioned in the previous paragraph. While the emphasis of the earlier report was on technical aspects of source calculation and localization, the emphasis here is on function, - not only where are the sources, but what is represented by the activity of the different generators (psychological process: short term stores and attention-related mechanisms) and what light do the differences between younger and older patient groups throw on the psychopathological development?

That the reviewer has overlooked these latter aspects, we attribute to the restricted content of our abstract, rather than the main body of the text (that perhaps features in point No. 2). This is our mistake. We have accordingly added brief information to each of the sub-sections of the abstract and extended the title to include reference to symptoms and neuropsychology, There are also two new key words. However, in the body of the text we believe the functional (psychological) aspects of MMN and its impairment are poignantly and extensively introduced on p. 4 and 5 in the introductory background section. (i.e., on short-term memories and switches of information processing). These topics have their own subsection in the discussion.

The extension of the results on the calculated location of the duration deviant MMN (with respect to the previous report on frequency duration) describes several similarities (broad support for the general model and a general lack of support for anatomical signs of illness progression). We also describe the following differences: a) Temporal lobe sources may be found to remain more ventral on the left (an example of stasis over 14 years), - not just lateral to the loci in the comparison group (as in the frequency deviant MMN), b) the right temporal source was more antero-lateral - an apparent progression on the trend in younger patients, c) the cingular source is more posterior (not anterior as in the frequency-deviant MMN) to those in the comparison groups, d) the frontal source was more rostral than in the younger group - which represents a relative "normalization" in comparison with the younger subjects and our previous report.

Even if the reader has reason to take issue with some details there is striking evidence for different processes in different regions of the brain of psychotic patients, where the issue of the bases for or against a material progression of the illness over time remains highly controversial. The evidence we provide refers to a different version of MMN and a substantiation that nearly the same result is obtained in passive and active experimental conditions.

The (neuropsychological) process: despite the elegant work a few years ago by Escera, Schroger and colleagues providing evidence that temporal and frontal lobe processes in MMN can be conceptualised in terms of the stored template and the organization of a switch, respectively, - there have been few attempts by MMN researchers to relate their results to either a detailed inventory of symptoms, or to performance on neuropsychological tests of related functions. (One thinks of Umbricht & Krijles for an initial attempt at the latter, and of Braff and Kasai for the implications in terms of social function.) We believe the positive results for trail-making, the unexpected but logical result (post-hoc) for digit-span and the negative result for visual reproduction and logical memories tests make a considerable and useful stride in the direction of assisting with the interpretation of what may be happening during this automatic process represented by MMN. As important as the fundamental template/sensory-/working-memory formation is for adaptive response, its the poor frontal flexibility that largely contributes to the poor MMN expression.

The (psychopathological) process: I have just written above on the crucial question of correlates of the progression of the illness. In our opinion the association of negative symptoms from onset with poor MMN
expression (anergia, flat-affect and CGI scores) is worth a brief report in itself

In this reply I have here selected some issues: they are all in the text. We would agree that to expand further would justify the criticism of unwarranted speculation. I hope that the sign-posts we have added to the text (see the start of our reply above) help draw the reader's attention to the issues.

2. Dipole calculation/reliability of interpretation

The reviewer emphasises that our putative sources are described on the basis of a calculation, a model. We believe we have nowhere implied otherwise. We have checked our phrasing on this point. We would agree that a definitive "proof" of source location would depend on deep intra-cranial recording. However, we are surprised that he warns us against describing the implications of these results in view of their having been calculated with very strict criteria, and replicated in several ways by several techniques.

In some ways the point raised seems to parallel the acquisition of data on climate change. This involves the formation of several models to explain the meteorological data collected, then predicting the outcome from the model with the 'best fit' - within a certain margin of error deduced from other models (that we also discuss in connection with the MMN example): a legitimate and useful exercise.

First, in the present paper, we show that the Jemel model is a good starting point, it worked for Oknina et al., it works here for Besa, and to a degree for Loreta. It was again replicated in the active discrimination condition.

Second, the model is broadly supported by other techniques and in other labs (independent components analysis, Loreta, and fMRI: -- Marco-Pallares et al., 2005; Molholm et al., 2005; Mitchell et al., 2005; Schall et al., 2003 and others) - even in two subjects (inferior frontal region) in Rosburg et al.'s intracranial/subdural recordings (2005). We add some of these references to our statement in paragraph 2 of our conclusions in support of the now relatively established estimate of MMN dipole locations. Hence we believe it timely for interpretation.

3. Main conclusions

We object to the reviewer's over-simple interpretation of our results in terms of the 'considerable variability' in schizophrenia. His view may partly be due to our poor choice of the word "variation" in the first sentence of the abstract's conclusions. A better expression is "differences" (between groups), that we now use. We initially avoided saying so, only to try not to repeat the same word (used twice in the original sentence that followed).

4. P.7 reference clarification - one of the doubled-up references has been removed.

5. p. 11 Jemel citation style - corrected.

I summary we are very grateful to the reviewers' for their time, effort and their comments that have enabled us to make a number of improvements.

Sincerely

Robert D. Oades