Author's response to reviews

Title: Auditory target processing in methadone substituted opiate addicts. The effect of nicotine in controls.

Authors:

Bernhard W. Muller (bernhard.mueller@uni-due.de)
Michael Specka (michael.specka@uni-due.de)
Nicolai Steinchen (nicolai.steinchen@freenet.de)
Dieter Zerbin (dieter.zerbin@uni-due.de)
Ernst Lodemann (melanie.kownatka@uni-due.de)
Thomas Finkbeiner (psychiatrie@evk-luedo.de)
Norbert Scherbaum (norbert.scherbaum@uni-due.de)

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Author's response to reviews: see over
Dear Dr. Jones

please find attached our revision of our manuscript submission „Auditory target processing in methadone substituted opiate addicts. The effect of nicotine in controls.“ by M. Specka, D. Zerbin, N. Steinchen, E. Lodemann, T. Finkbeiner, N. Scherbaum and myself for consideration to publication in BMC Psychiatry.

We carefully followed the suggestions made by our three reviewers and revised our manuscript accordingly. We added some more background text to the introduction of the P300 component and tried to improve the rationale of our study in the introduction. In the results section we added F-, t-values and Chi²-Values to our results. In the discussion we tried to cut redundancies and added some discussion on the probable interaction of opiates and nicotine which we, however, can not resolve within our study design.

I hope our revision meets your and our reviewers expectations for a publication in BMC Psychiatry.

Sincerely,
Bernhard Müller
Reply to reviewers

We thank our reviewers for their efforts in reading our manuscript and in providing helpful comments. The issues raised in the three reviews are listed below:

Reviewer’s report: Brian O’donnell, 19 June 2007

1. “An interpretative problem in the study is the heterogeneity of the methadone group. ... recommended that these variables be tested for correlation with P300 measures. “

We added a section “P300 data and clinical characteristics” at page 13 para 2. We found no relevant correlations between P300 data and the duration of opiate dependency, methadone use or methadone dosage.

2. “… suggests some pharmacological interaction between methadone use and nicotine use. This should be addressed in the discussion. It would be worthwhile to investigate this issue more systematically in the statistical analyses.”

We addressed this issue in the discussion section at page 16 para 2.

“However it remains unclear, whether chronic nicotine reduces P300 amplitudes or whether subjects with lower P300 amplitudes are more prone to nicotine and use it as some form of self medication. Together with the hypothesis, that opiate and methadone use may increase P300 amplitudes, our data support the notion that effects of nicotine, opiates and effects of additional predisposing factors interact in some complex form [17]. While the interaction of these factors can not be modeled within our data, further studies, assessing nicotine and opiate withdrawal as an experimental variable in smoking opiate dependent patients, will be needed to investigate the differential contributions of nicotine and opiate use in these patients.”

While all patients were smokers, we were unable to use nicotine use as a factor in our patient group. We therefore abstained from further analyses. Future studies will have to more explicitly address this question and may assess both, nicotine and opiate abstinence in these patients, at least as an experimental variable for a limited time.

3. “… description of the statistical analyses is sometimes vague ..... F values and degrees of freedom should be provided as well as p values.

The first issue relates to the analyses between subgroups of patients (with and without additional non-opiate drug use) and controls (with and without nicotine use) when there was no interaction effect between patient status (patients vs controls) and P300 data.

In our aims we formulated two questions: The first was to compare patients and controls in an overall analysis, which revealed no group effect. The second aim was to assess nicotine as a confound in controls and additional non-opioid use in patients. Here we found a group effect. We thought these two analyses as to be independent. We therefore further investigated sub-
groups in follow-up analyses. We tried to clarify this in our aims at page 6 para 3. We modified our results section at page 12 para 1 accordingly.

The second issue related to the description of our statistical analyses. We had to correct some of our p values in the analysis of our latency data which were transferred incorrectly from our result files. However, these did not affect statistical significances. Chi²-Values, t-values, F-values and degrees of freedom in variance analyses were added to the results section for the main analyses.

4. “The Kouri et al. (1996) paper does not seem to be accurately represented in the discussion “

The citation of the Kouri study was meant to give an argument that 1. detoxified patients may show reduced P300 amplitudes and 2. that substitution treatment may normalize this amplitude reduction at least to some extent. However, we found that the whole paragraph replicated a paragraph in our introduction and was redundant. We therefore shortened the whole paragraph. The reference to the Kouri results in our discussion section is now at page 14 para 2.

5. “The discussion could be shortened”

We shortened our discussion with focus on redundancy, with regard to probably extensive discussions of P300 imaging results and with regard to high P300 amplitudes in our study.

1. "check for minor language errors and try to cut on redundancies"

We carefully checked for language errors and shortened our discussion with focus on redundancy, with regard to probably extensive discussions of P300 imaging results and with regard to high P300 amplitudes in our study.

2. "give information on the smoking status of the methadone patients. How does smoking in these patients affect P300 within the patient sample and in comparison to the controls."

Smoking status was assessed in our subjects as a control variable. Within our patients we found no non-smoking subjects. It therefore is difficult to more explicitly analyze the effect of nicotine within the patient group. Further studies may vary smoking status more explicitly as an experimental variable (i.e. with some hours of abstinence) in patients in order to further explore the specific contribution of nicotine on the P300 component in opiate addicted patients.

3. "Discuss that reduced P300 amplitude may antedate nicotine-consumption and that nicotine consume may reflect "self medication"."  

We added this to our discussion at page 16 para 2. While our empirical data do not allow to draw a conclusion on this hypothesis, further studies will have to further assess the effects of nicotine in relation to opiate dependency and opiate substitution.
Reviewer’s report: Georg Juckel, 28 May 2007

1. “demonstrate the rationale of the study in the introduction part in more detail.”

In the introduction we already noted that neuropsychological studies on cognitive function in substituted opiate addicts tried to clarify probable detrimental effects of substitution treatment in these patients (page 5 para 1). We now added an additional clarification of the rationale of this kind of studies in opiate patients at page 5 para 2.

“The clinical relevance of these neurophysiological studies is to gain insight into whether opiate addicted patients show deficits with or without substitution treatment which may impact their ability to return to or to attain more stable socio-cultural and occupational settings.”

2. “not clear to me why and concerning to which literature the authors assume effects of methadone (or other opiates) on the P300 waves.”

We cited two relevant P300 studies on opiate addicted patients. The Attou (2001) study found decreased P300 amplitudes in detoxified and in methadone substituted opiate addicted patients when compared to controls. The Kouri (1996) study found decreased P300 amplitudes in detoxified patients which increased with substitution treatment (page 5, para 2).

While both studies had small sample sizes we took the evidence of these two studies as a hypothesis to be clarified in the assessment of a larger sample of methadone substituted opiate addicted patients in comparison to a group of control subjects (page 6, para 3).

3. “The authors recorded ERPs from 19 electrodes. Why they did not present also results from e.G. the lateral electrodes ?

Our intend was to assess the major effect of patient status and nicotine in controls on the P300 component where it is largest which we consider to be at midline electrodes. Hemisphere related analysis will only give gross indications on left or right hemisphere specific contributions to the P300 and our 19 electrodes preclude more specific analyses like LORETA or BESA analyses. We therefore decided to confine or data analysis to midline electrodes.

4. “They should discuss the finding of the nicotine effect in healthy volunteers broader”

We discuss the effects of nicotine in healthy subjects at page 15 para 2 with regard to acute, and at page 15 para 3 with regard to chronic nicotine use. We extended our discussion of the effect in healthy controls at page 15 para 2 and page 16 para 2:

“While the effect of sustained nicotine use on the P300 is not new, our study demonstrates that nicotine use has to be controlled for in studies on cognitive function in patient samples. A higher proportion of nicotine use in patient groups as compared to controls may act as a confound, indicating differences between patient and control samples which in fact may be due to differences in nicotine use.”
Additionally, we shortened our discussion with focus on redundancy, with regard to probably extensive discussions of P300 imaging results and with regard to high P300 amplitudes in our study.