Author's response to reviews

Title: The influence of Methylphenidate on the power spectrum of ADHD children - a MEG study

Authors:

Christian Wienbruch (Christian.Wienbruch@uni-konstanz.de)
Isabella Paul (Isabella.Paul@uni-konstanz.de)
Susanne Bauer (sudebauer@surfeu.de)
Hermann Kivelitz (320062204450-0001@t-online.de)

Version: 3 Date: 9 June 2005

Author's response to reviews: see over
Dear Professor Newmark,

We thank you and the reviewers for the most helpful and valuable comments on the manuscript. Please find enclosed our responses to the specific points. Thank you for considering our manuscript for publication in BMC Psychiatry.

With kindest regards,

Christian Wienbruch
1) Effects of MPH treatment

We fully agree with the reviewer that a placebo-placebo design would have been methodologically cleaner. However, other groups (e.g. [1, 2]) have investigated medication effects using a very similar design to ours even without giving a placebo before the first measurement. With this in mind, our approach seemed appropriate to us.

We did measure an age-matched non-clinical control group very recently, and are currently preparing the manuscript on the between-group results. This is also necessary to estimate predictors which could be of importance for diagnose or drug responsiveness. We did not dare to entitle our submitted paper as ‘part one’ but we intend to submit the comparison with a healthy control group also to BMC Psychiatry.

Although we fully accept this criticism the best placebo-medication design would be to treat investigate both groups – children with ADHD and normal controls of the same age – in a double blind design.

1. It is not possible to treat healthy control children with MPH.

2. Although children suffering from ADHD treated with MPH in a double blind design should not be aware when the drug is administered, they know from their own body sensations and reactions pretty soon if MPH was administered or a placebo. All subjects were treated with MPH for quite a while before the MEG investigation. Additional, as children and their parents gave their written informed consent they knew that one time they would be treated with a placebo and one time with MPH – they just did not know when MPH was administered. Several kids were investigated on the same day. We observed more than once (without influence or interaction from our side!) that they were fully aware if the placebo or the drug was administered.
2) D2 test

The D2 test of attention is considered a sensitive test for measuring short-term attention and is thus highly used in clinical practice in Germany. There is no b-form for this test. The authors state that there will be some gain in performance by repeating the test. However, the amount of gain is dependent on a variety of variables and is thus difficult to quantify. Nevertheless, the authors suggest that an average gain of approximately 25% in test performance might be achieved by repetition. This rating can be considered as very restrictive. In response to the concern, that the D2 test increase might not be solely the consequence of Methylphenidate, we used each child’s first test value and calculated the predicted retest-improvement of 25% and compared this to the test value we actually measured after Methylphenidate (see figure 1). As can be seen, approx. half the children improved clearly more than predicted by a repetition gain, while approx. the other half improved less. Not surprisingly, the children that improved more than predicted by a mere retest-gain were the ones we classified as good medication responders. We thus assume that part of the gain in D2 test performance might be explained by retesting, while a substantial part of the group improvement was the consequence of the psychostimulant medication.

![Discrepancy between predicted values and measured values](image)

*Figure 1: Discrepancy values were calculated between the predicted retest-performance and the actual improvement after MPH application. Negative values mean that children improved more than a mere retest improvement would predict.*
3) Statistical issues

We are puzzled about the concern that it might not be appropriate to base further analyses on the significant interaction TIME\*REGION. Interaction effects are higher in order than main effects. Therefore we cannot follow the reviewer’s apprehension that the significant interaction might not be reliable if neither main effect TIME nor REGION are significant. Despite our lack of understanding of this particular criticism, we would like to note that the main effect REGION was significant (F(2,68)=122.71, p<0.0001). We did not mention the effect in the manuscript, since we did not consider it as being of particular interest for our question.

4) ANOVA results D2-test

ANOVARAs were calculated on percentile values. It is true that percentile values are strictly speaking ordinally scaled. However, given that the percentile scale of this particular test consists of 100 steps, it might be considered as a borderline case. We tested D2-values before and after MPH for normal distribution (Kruskal-Wallis test) and normal distribution hypothesis was maintained (d=0.114, p>0.2 before MPH and d=0.2, p=0.2 after MPH). We additionally calculated a Wilcoxon test for paired samples. D2-test performance before and after MPH differed significantly (Z=5.09, p<0.0001). Thus, ANOVA and non-parametric statistics delivered comparable results.

It is true that the mean D2-test value of 41.2 percentiles before MPH is not dramatically below average. However, it was not our intention to quantify the childrens’ attention-skills. For this purpose it is necessary to apply a large test-battery. We used the D2-test in order to have an external measure for medication effects that might correlate with MEG power changes.

Minor Essential Revisions

Paragraph has been modified. Also an additional paragraph has been included in the MEG Recording section to clarify the different coordinate systems used. As explained in the text EEG electrode positions are usually
defined in relation to anatomical landmarks on the head while the MEG sensors are not. The position of the pickup coils depends on how the subjects head is positioned. Averaging of MEG measures of the same sensor might add additional variance if this particular sensor is not always located directly above the same cortical structure. We tried to reduce this variance by selecting individual, subject specific channel groups closest to anatomical landmarks. (see Data Analysis section)
Reviewer Peter D Teale

Minor revisions

1) Has been changed in the manuscript according to reviewer’s suggestion.

2) Has been changed in the manuscript according to reviewer’s suggestion. See MEG Recording and Data Analysis sections.

3) This was wrong in the manuscript and has been changed according to reviewer’s suggestion.

4) Figure legend has been changed as well as the text in the results section – the hemispheric difference is independent of administration of MPH.

Discretionary revisions

1) Has been changed in the manuscript according to reviewer’s suggestion.

2) Has been changed in the manuscript according to reviewer’s suggestion.