Author's response to reviews

Title: Abnormal oscillatory brain dynamics in schizophrenia: A sign of deviant communication in neural network?

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Author’s response to reviews: see over
Dear Mr. Hodgkinson,

Thank you for your interest in publishing our paper in *BMC Psychiatry*. We have considered the three reviews very carefully and will detail our responses to their comments. Let us know if you require any additional information.

Sincerely,

Brigitte Rockstroh, PhD
(Professor of Clinical Psychology)
Responses to Reviewers:

Reviewer 1: You asked us to treat this review as discretionary suggestions as the reviewer was not willing to be named.

- The differences between EEG and MEG are well known and do not need to be repeated in detail.
We have reduced this information greatly although we did include information that reports the advantage of MEG for localization of focal activity.

- Data collection was done while patients were lain with open eyes. There could be an effect of eye movement. Why were patients not instructed to keep their eyes closed? How was noise excluded? Was there any ear protection?
Perhaps the reviewer confused fMRI which produces significant noise with MEG which is quiet. Eye movements were monitored and this information was removed from the dipole analysis. We felt that having an individual look at a point would help to reduce eye movements. Having an individual close his or her eyes does not prevent eye movements and may lead to the individual feeling drowsy.

- Was there any retesting to check for within patient reproducibility?
We have in the past found within patient reproducibility although this was not a part of the present design. We have also found that MEG measures do not change with repeated days of measurement.

- The depressive patient group is heterogeneous. The dosage of antidepressants is not clearly shown nor correlated with MEG findings.
We have found no relation to medication. In specific, an analysis of the ASWA pattern between subjects under tricyclic antidepressants, SSRI and a combination of both or with neuroleptics did not result in significant main effects or interactions.

- Within the group of patients with schizophrenia the influence of medication should be considered.
This is described in the results and discussion sections.

- The finding of frontal and central activation must be interpreted in the light of these comments.
We have pointed out in the discussion, why specific hypotheses regarding an influence of medication on the specific ASWA topography must remain highly speculative for the present data set.

- Central activation should be discussed with respect to an artifact of spontaneous magentoencephalographic activity, the central dipole maximum. This might also be an artifact of the eyes being open.
We have clarified our paper so that readers will not confuse the central region of the cortex with the center of the head. We would like to emphasize again that artifacts were
excluded, that the dipole fitting algorithm determined only focal dipoles, thereby serving like a filter. This should prevent artifacts from general spontaneous MEG activity. Moreover, eye movement artifacts would be expressed by (symmetric) frontal dipoles, which were not found, whereas artifacts generated by heartbeats, would show up as a central dipole with low GoF – which were excluded as artifacts. Finally, the central dominance was found only in one subject group, the schizophrenia group, although measurement and artifact correction procedures were identical for all subjects.

Reviewer 2:
Pointwise criticisms:

Page 3, line 2-4: Please give references for this finding in MEG.
Reference has been added

P3 L13: "If..." then? I do not get the sentence straight.
This sentence has been rephrased

P4 L7 from below: Why do you not mention attention?
We agree and have removed the paragraph

P4 L6 fb ft.: That is quite a bold statement. Why do you emphasize the difference with EEG so much? Likewise the intra- versus extra-cellular hypothesis of EEG vs MEG signal is not really settled and not helpful in context of the present paper.
We agree and have rephrased and shortened the paragraph.

P6 L 10: It should be: "...treated for schizophrenia or schizoaffective disorder"
This change has been made

P6 L14: F20.0 is paranoid and F20 Schizophrenia; and not a subtype.
This has been clarified

P6 L2 fb: please be more specific about the drug abuse "mainly cannabis". Were participants asked or did that come from the clinical history?
This has been clarified

P7 middle: "depressive sample" should be something like "the group of patients suffering from depression"
This has been changed

P7 L8 fb: Does these F4 diagnoses meet criteria for Major Depression as well?
We agree that F4-diagnoses should not be mixed with F3 diagnoses in the same sample just because they were treated on the same ward. F4 were the main diagnoses, but we cannot verify, whether these patients also received a F3 diagnosis as second diagnosis. We compared the ASWA topography between the two subsamples (F3 vs F4), which did not result in significant group effects or interactions (p=/>.2). We also calculated the
ANOVA on Z-scores again without the 8 patients with F4-diagnoses, and obtained a similar pattern of results as the one reported (Group x Region: F(6,672)= 10.75, p= .0001, Group: F(2,224)= 19.775, p= .001, Region (F(3,672)= 4.72, p= .003). From this we conclude that patients with affective disorders exhibit similar ASWA patterns and therefore did not change this paragraph in our text.

P8 L1: The control sample was matched with respect to something?
Healthy controls were matched in terms of age and gender to individuals with the various psychiatric disorders. Our overall control group was thus made up of the individual control groups that matched each disorder.

P8: You miss out the sampling rate. It is unclear what results after factor 16 down sampling. And thus how many time points were used for dipole fitting.
This has been clarified in the text

P9 L3: Is 100 nAm equivalent to 1 cm2 of activated cortex? I do not see such a relation.
Tripp gave a simple formula to calculate the dipole moment of a single dendrite, an example calculation based on Tripps formula can be found in Williamson and Kaufman, In Nunez one can find the density of dendrites in a macro column and the area of such a column which leads to an estimate of the activated cortex size.

P9 L9: Does that mean (using nasion etc as reference) that the surface information from the Polemus system was not used?
This has been clarified in the text

P9 L8 fb: In the previous sentence you claim that the logarithm of the density yields a normal distribution; why and how do you do the z-transformation then after?
This has been clarified in the text

P9 L5 fb: What are temporal,.. PARTS of the brain? I know temporal lobe etc.
This has been rewritten

P10 L1: What is the variable Z?
This has been clarified in the text

P10 L7: At least here you should give a better indication how you test normal distribution and how good is actually was.
The entire procedure has now been published (Wienbruch, 2007) and is referred to in the text.
P10 ft: you are using ASWA, SWA, and ASWAM frequently and seemingly quite interchangeably. This is more confusing than helpful. 
*We now use ASWA throughout the paper*

P11 L9ff: In this sentence the subject is missing. Probably "...ASWA was more...". 
*This has been corrected*

P12 L1: How is the ant-post gradient calculated? 
*The entire procedure has now been published (Wienbruch, 2007) and is referred to in the text.*

P12 L10 fb: Sentence is wrong and replace "normal" with "healthy."
*This has been corrected*

P12 L6 fb: replace "twp" with "two."
*This has been corrected*

P13: after "[59]" a bracket is missing.
*This has been corrected*

P13 L8 fb f: This citation is a bit out of the context and hardly to understand. 
*We have rephrased the sentence to clarify the reference.*

P14 L7: My understanding is that you use 2x4 ROIs. The usage of "small" (8cm2) voxel on an intermediate step of the calculation does not have any relevance and could be skipped. 
*The methods have clarified and the reference in the discussion has been rephrased.*

P15 L12: What is that half sentence supposed to say? That haloperidol has a better effect on the symptoms? 
*This sentence was been rewritten*

P15 L 14ff: Here you start putting results again. For comprehensibility this should be in the Results section. 
*As suggested statistics have been removed from the discussion section.*

L4 fb: Replace "mediated" with "medicated."
*This has been corrected*

P17 Why is depression not a "brain disease?" The link of ASWA to protection of the brain seems rather arbitrary and not backed by the data. 
*We have rephrased the paragraph.*

Replace "e.g," with "e.g."
*This has been corrected*
Fig 1: Please write schizophrenia and depression in the figure. I see no additional information in the unthresholded display. The scale on the colorbar should be $Z$ with a normal distributed $Z$, but why is 1.2 already highly significant?

This has been changed and the figure legend has been clarified; indeed the thresholded data provide a voxel by voxel $t$-test approach and do not imply additional information. They can be regarded as distribution of means in the voxels used before the regional dipole density analysis was accomplished. The $Z$-scores were calculated using the mean and SDT of the healthy subjects group and, therefore, are no real $z$-transformation but rather a benchmark for ‘normality’.

Reviewer 3:

- Abstract: 'ASWA maxima were related ...': please define the meaning of 'ASWA maxima'.

This has been changed to better reflect the meaning of the sentence-- the area of the cortex with the most characteristic ASWA

- Introduction, final paragraph: could specific hypotheses be formulated on the basis of previous work?

This has been added to the last paragraph of the introduction

- Design: how reliable are slow-wave data from a 5-min. recording period? Has this been assessed?

Yes, see reviewer 1 section above

- p. 10 (end of data analysis section): were there specific hypotheses for gender differences?

There were no specific hypotheses for gender differences.

- p. 13: ASWA is interpreted in terms of reduced connectivity. Are there other connectivity measures that could be applied to the present data (coherence, phase synchrony?).

Yes, there are a variety of measures that could be applied to better articulate relationships involving connectivity. However, the present study focused on slow wave activity and thus these analyses were not conducted as they would drive the paper in a different direction.

p. 16: what could be the significance of reduced SWA in depression or in relation to negative affect? Please discuss.

This, of course, is of critical importance for future research. We made some limited suggestions in the discussion section but did not have the data to go beyond this level of speculation.

Minor points/typographical errors:

- abstract: please introduce the abbreviation 'ASWA'
- p. 5: '...our previous results what were obtained...' should be '...our previous results that were obtained...'
- p. 9: please introduce the abbreviation 'ACPC'
- p. 9: 'Analysis of the distribution....': there seems to be a word missing at the beginning of this sentence
- p. 10: superfluous parenthesis after'...to parametric testing.)'
- p. 12: 'twp should be 'two'
- p. 12: '...which add to earlier findings' should be '.. .which adds to earlier findings'
- p. 15: '...influence medication...' should be '...influence of medication...
- p. 17: '...that ASWA as a manifestation...' should probably be '... that ASWA is a manifestation...''

The above minor points have been corrected