Author's response to reviews

Title: Elevated Serotonin Transporter Density of Midbrain in Mixed Mania: A Case Study

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Version: 2 Date: 10 August 2004

Dear Editor,

We are resubmitting the enclosed manuscript "Elevated Serotonin Transporter Density of Midbrain in Mixed Mania: A Case-Control Study". We hope that after modification the manuscript can now be accepted for publication in BMC Psychiatry.

We also wish to express our gratitude to the reviewers for their excellent comments, which helped us to improve our article and to clarify our wording on many points.

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Yours sincerely,

Tommi Tolmunen

Responses to the editor and reviewers

Our comments concerning the opinions of the reviewers are the following:

REVIEWER #1 Swen Hesse:

Major compulsory revisions:

1. In another recent SERT imaging study on bipolar disorder...
We wish to thank the reviewer for pointing out that we overlooked the study of Ichimiya (2002). Therefore, we have added the discussion below to our manuscript:

"Ichimiya et al. (2002) found increased SERT binding of the radioligand in the thalamus in a sample of patients with either major depression (n = 7) or bipolar disorder (n = 6). In their study the bipolar patients were either depressed or euthymic prior to brain imaging. There were no significant differences in binding potentials in the mid-brain compared to the mood-disorder patients and the healthy controls. Bipolar patients had slightly higher binding potentials in the mid-brain than the healthy controls, while patients with major depression had slightly lower binding potentials than the healthy controls. However, these differences were not significant."

2. With regard to the low specificity of the used SPECT radiotracer...

We have added the discussion below to our manuscript:

"We cannot completely rule out the bias of nor--cit binding to the noradrenergic transporters (NORT). The noradrenergic cell-body rich nucleus ceruleus is close to our target region. This is assumed to contain the nucleus raphe, which is mostly comprised of serotonergic cell-bodies. The dopamine cell-body rich substantia nigra is also located close to our region of interest. However, nor--cit is considered to be more serotonin-specific than previous radioligands (Hiltunen et al. 1998)."

3. Patients' state of mood during baseline scan would be of further interest...

We have added the following sentence to the methods section:

"She was overactive, restless and irritated and coped with a reduced amount of sleep. She had difficulty in concentrating on one thing at a time, and she appeared very lively and talkative. She was therefore diagnosed with bipolar mood disorder type II. In other words, our index patient had a mixed mania without fulfilling the criteria of full-blown mania during the baseline scan."

We added the following sentence to the results section:

"The midbrain SERT availability did not correlate with HDRS scores in depressive controls either at baseline or on follow-up. Neither did the change in the HDRS score correlate with changes in SERT or DAT capacities under therapy."

4. The test reproducibility for either DAT or SERT availability estimation...

We added the data to the methods section.

5. Was the striatal uptake pooled?

The striatal uptake was pooled. We mentioned this in the methods.

6. Interestingly controls with moderate to severe depression...

Because of the brain imaging method we used, we could not include patients who had received or who were about to receive any psychopharmacological treatment. We had to exclude a few severely suicidal patients from our study because of this. We observed no real side-effects because of the study-setting in the patients who were included in our study. None of the patients had to be hospitalized during the twelve-month follow-up period. We did not discuss this topic in the manuscript because we wanted to focus on the biological data.

Minor essential revisions

We corrected all the mistakes that the reviewer pointed out as suggested, including orthographical mistakes, format inadequatenesses and inconclusive phrases. We also changed the headline of this article from "Case-control study" to "Case-study".

Discretionary revisions

We added the following sentence to the statistics section:
"A P-value of less than 0.05 was considered as the criterion for statistical significance."

The reviewer recommended providing a link to genetic analysis and PET. We have added the following section to the discussion:

"Three studies have been published on the association between SERT availability and the serotonin transporter genotype. Two of these were performed on healthy subjects (Jacobsen et al. 2000; Van Dyck et al. 2004), while the third concerned abstinent alcoholics and healthy controls (Heinz et al. 2000). In the study of Van Dyck and co-workers the short homozygotes had a significantly greater SERT availability than the long-short heterozygotes, which indicates a complex relationship between the genotype and SERT availability. Studies combining brain imaging and genotype data are also recommended in the evaluation of bipolar disorder. PET would be a more valid method if adequate radioligands were available (Ichimiya et al 2002), as PET provides absolute rather than relative values for transporter availability."

REVIEWER #2 Georg Berding

Discretionary revisions

1. The reviewer suggested that we add to the data analysis section the mean and standard deviations of the regions of interest (ROI) dimensions obtained with the 60% threshold in the two groups and in the index case, which we performed as recommended. Individual ROI dimensions were not calculated because the software we used only registered the average counts of each ROI.

2. In the first paragraph of the results I was confused...

We replaced the word "lower" (...than the mean SERT-density of the healthy controls...) by the word "higher".

3. Was the decrease in HDRS in depressed patients significant? Was the increase in DAT-binding in the depressed controls significant?

We added the following sentences to the Results section:

"The mean decrease in HDRS scores in depressed patients during the follow-up period was 5 (SD 3.3; t = 3.7, p = 0.02). The increase in DAT-binding was not significant (data not shown)."

4. A quantified color scale was used; each color represents a 10% reduction from the maximum uptake (white). This has been mentioned in the figure text.