Reviewer's report

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

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Reviewer: Swen Hesse

Reviewer's report:

General

Tolmunen and colleagues present a paper, which shows the potential of neurobiological characterization of psychiatric disorders using modern neuroimaging techniques such as single-photon emission tomography (SPECT). With these techniques it is possible to detect small changes of brain neurochemistry at a molecular level in vivo.

The authors demonstrate one case with a clinical equivocal symptomatology including depressive and manic states, which showed higher serotonin transporter (SERT) availability compared to healthy controls and compared to patients with unipolar depression. It is an interesting case report, and to our knowledge, the first, which simultaneously demonstrate SERT and dopamine transporter (DAT) availability in one person with bipolar disorder. The methodology used here represents one of the current state-of-the-art SERT and DAT imaging approaches provided by SPECT technology.

The normalization of SERT capacities from opposite baseline values in patients indicate that depressive symptoms in bipolar disorder and depressive symptoms in major depression may reflect epiphenomena of different points on a neuropsychiatric disorder spectrum. Thus, neurobiological clustering seems to represent a more specific determination than nosological criterion alone.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

- In another recent SERT imaging study in bipolar disorder (which the authors failed to notice) by Ichimiya T, Suhara T, Sudo Y, et al. (Serotonin transporter binding in patients with mood disorders: a PET study with [11C](+)McN5652. Biol Psychiatry 2002;51:715-22), an increased thalamic SERT availability was found, which might correspond with the higher midbrain SERT density detected in the study by Tolmunen and colleagues. The findings of that paper shall further be discussed in the light of brain circuits involving either thalamic or midbrain structures to underscore the suggested serotonergic - dopaminergic imbalance (which, again, seems to be different in bipolar vs. unipolar depression).
- With regard to the low specificity of the used SPECT radiotracer it has to be also kept in mind that the noradrenergic transporter might play a role in depressive (or manic) states, too.
- The patient’s state of mood during baseline scan would further be of interest: Was she in a manic period? Did the midbrain SERT availability correlate with HDRS in depressive controls? How might the changes of SERT and DAT capacities under therapy correspond with the changes of HDRS score.
- The test reproducibility for either DAT or SERT availability estimation is excellent and should be shown by means of individual data.
- Was the striatal uptake pooled?
- Interestingly, controls with moderate to severe (!) depression did not reveal psychopharmacological treatment. Did the authors observe any severe side-effects because of this?

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the
author can be trusted to correct)

The term “case-control study” is somewhat misleading because such studies cover more than one patient.

There are a couple of orthographical mistakes:

- “midbrain and mid-brain” – page 2,
- “eighth” – page 5, “cahthecholamine” – page 9),

few format inadequateness:
- red dot behind “female” in methods section,
- "background" characteristics in results,
- "I[123]" - page 5, and

inconclusive phrases:
- “The structural diagnostic classifications…presented in the literature” – page 3,
- “These associated…” – page 2,
- “If any cerebral focal abnormalities...were detected by MRI scan, the patient was excluded from the study.” – page 6: Are there any among the included subjects?,
- "We found no previous [imaging - ?] studies showing that serotonin has a role in mania." - page 10

Significance levels should be indicated in the Statistics section.

Discretionary Revisions (which the author can choose to ignore)

The findings of recently emerged molecular genetic tests in psychiatric disorders might probably fortify the results of depletion experiments.

There is an opportunity of an absolute quantitation by applying positron emission tomography (PET) instead of SPECT in further DAT and SERT imaging trials.
It is recommendable to the authors to give a link to both genetic analyses and PET.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

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