Title: Brain structural changes associated with antipsychotic treatment in schizophrenia as revealed by voxel-based morphometric MRI: an activation likelihood estimation meta-analysis

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Reviewer: Ian Ellison-Wright

Reviewer’s report:

Major Compulsory Revisions

1. The authors investigated whether brain structural changes in schizophrenia are associated with antipsychotic use. They applied the meta-analytic technique of Activation Likelihood Estimation (ALE) to voxel-based morphometry (VBM) studies. They identified 11 studies meeting their inclusion criteria (including 360 patients on antipsychotic drugs and 344 controls).

2. The main findings were brain structural changes associated with antipsychotic use: areas of relative volumetric increase in the left anterior cingulate cortex and right putamen; areas of relative volumetric decrease in the left temporal cortex, left inferior frontal gyrus, and superior frontal gyrus.

3. Although potentially an interesting result, there are some methodological issues which need to be clarified.

4. It is not entirely clear in the paper how the primary studies investigated the effect of antipsychotics. For example, the Schaufelberger study appears to compare patients treated with antipsychotics versus patients untreated with antipsychotics. It reported ‘Exploratory analysis across the entire brain revealed no areas of grey matter reduction in those currently treated with antipsychotics (n=84) relative to those 38 who were untreated (P>0.05, corrected).’ Only ‘Small volume-corrected analyses demonstrated significant grey matter reductions in participants treated with antipsychotics relative to the untreated subgroup in the right insular cortex and in the right superior temporal gyrus’. A small volume-corrected result may introduce bias into the meta-analysis so should probably be excluded.

5. It appears that some primary studies were longitudinal (i.e. comparing brain structure in patients before and after antipsychotic use) whereas others were cross-sectional (i.e. comparing brain structure in patients taking antipsychotics versus medication-free). There are also references to healthy controls although it is not clear how these featured in the primary analyses.

6. It would be helpful if Torres et al mapped out the primary analyses used in each of the papers to clarify in each how the effect of antipsychotics was being evaluated.
7. Without this information it is difficult to know whether it is reasonable to combine longitudinal with cross-sectional studies in a single meta-analysis, or whether this is like combining apples with oranges, simply to achieve a large enough sample size. Otherwise it may be necessary to meta-analyse the two sorts of studies separately and then compare the results to see if they are similar.

8. Another difficulty with this analysis is differentiating between the effects of antipsychotics and the effects of potential confounding factors. Although this does not make the analysis invalid, it does need to be more clearly considered in the Discussion.

9. The authors combine gray and white matter coordinate changes in a single analysis: is this a standard ALE technique, if so the authors should justify it, otherwise should the gray and white matter changes be evaluated separately?

Minor Essential Revisions

10. In general, some of the sentences are rather long and could be shorter and simpler to aid the reader.

11. Tables 2 and 3 appear very long – could the information be displayed more concisely?

12. Page 3: ‘However, as these structural brain changes are often subtle and their course is difficult to appreciate in an evolutive manner, only after robust and longitudinal MRI studies the possibility of progressive brain structural changes over time (favoring the addition of a “neurodegenerative” hypothesis to the dominant “neurodevelopmental” model) has been strengthen’ – The last word should read ‘strengthened’.

13. Page 4: ‘Although a neurodevelopmental insult does not preclude an associated neurodegenerative process [34], the idea of progressive structural changes in the brain over time, which could denote neurodegeneration, have been a controversial issue [35-37]’ – ‘have’ should read ‘has’.

14. Page 4: ‘as the findings of different studies seems sometimes inconsistent’ – ‘seems’ should read ‘seem’.

15. Page 4: ‘For many years, albeit a significant part of individuals involved in neuroimaging studies had used antipsychotic drugs, the role of drug treatment as a cause of these changes has been scarcely investigated [49].’ Would read better as: ‘For many years, although a significant number of individuals involved in neuroimaging studies had used antipsychotic drugs, the role of drug treatment as a cause of these changes has been scarcely investigated [49].’

16. Page 5: ‘All these aforementioned inhomogeneities make data interpretation difficult, reinforcing the need for literature reviews and meta-analyses of studies comprehending homogeneous morphometric methodologies and samples of patients on this subject.’ Would read better as: ‘All these aforementioned factors make data interpretation difficult, reinforcing the need for meta-analyses of
studies of this area using homogeneous morphometric methodologies and including multiple samples of patients.'

17. Page 9/10: ‘Among the several variables that possibly could determine or contribute in some extent to the brain structural changes observed in patients with schizophrenia in the numerous neuroimaging studies performed in these recent years, including those specifically related to the illness (age of onset, duration, severity) and the individual (age, gender, scholarity), it is precisely the role of antipsychotics, however, that remains a current and critical question, maybe still far beyond of a definitive answer.’ Would read better as: ‘Among the several variables that could possibly determine or contribute to the brain structural changes observed in patients with schizophrenia in the numerous neuroimaging studies performed in recent years, including those specifically related to the illness (age of onset, duration, severity) and the individual (age, gender, scholarity), it is the role of antipsychotics that remains a critical question, although possibly still beyond a definitive answer.’

18. Page 10: ‘A relatively low number of studies have been addressing this issue, which is difficult, furthermore, by the complex task of harmonizing or balancing the effects of all the other possible variables’ would read better as: ‘A relatively low number of studies have addressed this issue, which is made more difficult by the complex task of harmonizing or balancing the effects of all the other possible variables.’

19. Page 10: ‘Indeed, these concerns previously pointed out, besides the additional difficult of gathering hard-to-recruit subjects with psychiatric diseases of low prevalence rates [101], it all have been led to studies with a relatively small number of patients.’ Would read better as: ‘Indeed, the additional difficulty of recruiting subjects with a psychiatric disease of low prevalence rate [101], has led to studies with relatively small numbers of patients.’

20. Page 10: ‘Evidence from larger studies encompassing more expressive samples of subjects’ – it is unclear what expressive means – do the authors mean ‘chronic’?

21. Page 11: ‘Studies with relatively considerable samples,’ – it is unclear what considerable means – do the authors mean ‘large’ – the samples mentioned do not seem particularly large?

22. Page 11: ‘as about half of the longitudinal studies did not found or reported progressive brain changes’ should read: ‘as about half of the longitudinal studies did not find or report progressive brain changes’

23. Page 11: ‘and that the distinct patterns of effects determined by typicals or atypicals are inconsistent as well’ would read better as: ‘and the distinct patterns of effects determined by typicals or atypicals were inconsistent as well’

24. I would recommend omitting the references to primate studies (112-115) as the effect of antipsychotics in primates may not reflect the effect in humans and experimentation on non-human primates should be avoided.
Discretionary Revisions

25. Page 5: ‘by different VBM studies on a given disorder’ would read better as: ‘by different VBM studies of a given disorder’

26. Page 10: ‘it is not surprising, hence, that sometimes’ would read better as ‘it is not surprising that sometimes’.

**Level of interest:** An article of importance in its field

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

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'