Author's response to reviews

Title: Structural brain change in Attention Deficit Hyperactivity Disorder identified by meta-analysis

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Version: 2 Date: 15 June 2008

Author's response to reviews: see over
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15 June 2008

Dear Dr Norton

Re: Structural brain change in Attention Deficit Hyperactivity Disorder identified by meta-analysis

We are pleased to re-submit this article for publication by BMC Psychiatry.

The comments of the reviewers were helpful and we have revised the manuscript to incorporate all recommendations. These changes have strengthened the paper. We have detailed the changes below.

Many thanks for your consideration,

Yours sincerely

Dr Ian Ellison-Wright
Submitting Author

Dr Zoë Ellison-Wright

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Review 1

Reviewer's report

Title: Structural brain change in Attention Deficit Hyperactivity Disorder identified by meta-analysis

Version: 1 Date: 30 May 2008

Reviewer: Xavier Castellanos

Reviewer's report:
- Major Compulsory Revisions

The authors sought to map gray matter changes in Attention Deficit Hyperactivity Disorder (ADHD) using meta-analytic methods. A systematic search was conducted for voxel-based structural magnetic resonance imaging studies of patients with ADHD (or with related disorders) in relation to comparison groups. The authors carried out meta-analyses of the coordinates of gray matter differences. For the meta-analyses they hybridised the standard method of Activation Likelihood Estimation (ALE) with the rank approach used in Genome Scan Meta-Analysis (GSMA). This system detects three-dimensional conjunctions of co-ordinates from multiple studies and permits the weighting of studies in relation to sample size. For gray matter decreases, there were 7 studies including a total of 114 patients with ADHD and 143 comparison subjects. Meta-analysis of these studies identified a significant regional gray matter reduction in ADHD in the right putamen/globus pallidus region.

This is a well-written tightly reasoned manuscript with an interesting result. The principal weakness is noted by the authors – the moderately limited number of studies, which likely has resulted in type II errors. This does not invalidate their positive result.

Response: We thank the reviewer for his helpful comments which have given us an opportunity to strengthen the manuscript.

1. The principal remaining weakness is one of omission. The authors note that their approach consists of the novel combination of a meta-analytic technique that has become widely used in neuroimaging, ALE, and the GSMA rank approach. They report equivalent findings with and without weighting studies by sample size, but it is not clear whether the aggregation of the GSMA rank approach to the ALE appreciably affected or improved the meta-analysis. Would the authors discuss this?

Response: The GSMA rank approach did improve the power of this meta-analysis to detect changes. In the Results section (pages 10-11) we have added the
sentence: ‘By comparison, analysis of the co-ordinate data using an ALE approach identified 30% fewer voxels with voxelwise p=0.0001 and this ALE result was not significant over the whole image with the False Discovery Rate set at P < 0.05.’

2. One remaining point may represent a minor error. The authors note (pp.14-15) that their finding is the result of the conjunction of coordinates from 5 studies out of 7. They include the van’t Ent et al. study as providing one of the positive data sets. However, I could not find data in that study of significant coordinates in the basal ganglia and on p. 1011, van’t Ent et al. state: ‘We did not find any evidence for volume changes of basal ganglia structures including the caudate and putamen…’ The other four studies do have convergent findings, and such convergence may have been sufficient, but please confirm if this is correct.

Response: The reviewer is correct in quoting this paper and we agree that this needs clarification. There is a slight ambiguity in van’t Ent’s attribution of the co-ordinate 32,-2, 15 (Montreal MNI space, Table 2, cluster C) to the right insula since this transforms to 28, -5, 18 (Talairach) and the Talairach atlas locates this between the insula and putamen. Figure 2 in their paper indicates that the clusters attributed to the right and left insula extend medially. They also describe post hoc tests (Figure 6, their paper) which may implicate the right putamen (cluster F, page 1011, right column, line 2, their paper). However, given van’t Ent’s comments about the basal ganglia, we have modified our Discussion (pp14-15) to state: ‘The gray matter reduction in the right putamen/globus pallidus region was identified as significant because of the conjunction of co-ordinates from four studies [15, 17, 18, 20] out of seven (and one study [19] which identified a region between the right insula and right putamen).’

- Minor Essential Revisions

Even more trivially: in the abstract, third sentence of the Results section, please do not begin a sentence with an Arabic numeral.

Response: We have corrected this to read: ‘Four studies reported gray matter increases in ADHD but no regional increase was identified by meta-analysis.’

On p. 15, the putamen and globus pallidus are described as “both components of the striatum…” The caudate and putamen are “both components of the striatum,” but the globus pallidus is not considered a striatal region. The globus pallidus and the putamen together form the lenticular nucleus.

Response: We followed Gray’s Anatomy terminology but should have stated ‘the putamen and globus pallidus… are both components of the corpus striatum.’ We accept that the striatum more usually refers to the caudate and putamen and that the globus pallidus and the putamen together form the lenticular nucleus. We have
now clarified this and included neuroanatomical references (see Response to Reviewer 2).

Table 1: please remove the hyphens in ‘methyl-phenidate.’

Response: We have corrected this in Table 1.

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

**Quality of written English:** Acceptable

**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.
Reviewer's report

Title: Structural brain change in Attention Deficit Hyperactivity Disorder identified by meta-analysis

Version: 1 Date: 3 June 2008

Reviewer: Grainne McAlonan

Reviewer's report:
In this study the authors have conducted a meta-analysis of studies using voxel-based morphometry of structural brain changes in ADHD. Activation Likelihood Estimation analysis is supplemented by a rank approach used in Genome scan meta-analysis to identify 3D conjunctions of co-ordinates from different studies and can take into consideration sample size. I believe this is a very useful adjunct to the standard ALE method and is to be welcomed. This adapted meta-analysis method may potentially be applied to any number of conditions. I have the following comments/suggestions which I would classify as discretionary:

Response: We thank the reviewer for her helpful comments which have given us an opportunity to revise and improve the manuscript.

Introduction
The authors describe the limitations of previous Region of Interest studies of brain volume in ADHD – namely changes in brain regions which are not pre-selected or difficult to measure, will be overlooked. This leads on to a reasonable explanation of advantages in voxel-based methods and hence their rationale for conducting a meta-analysis of voxel-based studies using voxel-based methods. However, to balance a critique of region of interest methods, the disadvantages of voxel-based approaches should be noted. Voxel-based studies of ADHD are not completely consistent. These discrepancies should be mentioned along with the potential reasons for lack of replication, including data processing/analysis parameters and differences in samples examined.

Response: We have now included these limitations in the Background (p5): ‘However, the results of voxel-based morphometry studies are not always consistent. This may result from different analysis methods (including spatial transformation of the images or statistical thresholds) or variation in the samples of patients and controls (e.g. age or medication status).’

The authors base their hypothesis of the changes they will find in the present meta-analysis, on the results of a previous meta-analysis of region of interest
studies of ADHD. This is a little surprising given their attention to the problems with region of interest approaches and their motivation to look at VBM studies. It rather detracts from the strength of the technique they are promoting. VBM allows a whole brain assessment therefore it might be more satisfying to construct an hypothesis upon a more comprehensive platform, including perhaps neuropsychological theories, or even functional imaging findings (as at least the whole brain is sampled in fMRI).

Response: We agree with the reviewer that there are limitations in basing the hypothesis solely on region of interest studies of ADHD. Our hypothesis was also informed by the Dickstein et al (2006) meta-analysis of functional imaging studies of ADHD (fMRI and PET). We have clarified this and emphasised the reviewer’s comment regarding the construction of hypotheses based on whole-brain evidence: 'On the basis of the previous meta-analyses of region of interest studies [6] and functional imaging studies of ADHD [3], we hypothesised that in ADHD there would be gray matter deficits in the right caudate and right and left frontal lobes. In the future, hypotheses regarding structural changes in ADHD may be informed by whole-brain studies including voxel-based morphometry, functional imaging and neuropsychological theories.'

Methods and results
The methods and results sections are clearly written and accessible. The methods are sound and, as previously mentioned, I believe the addition of Genome scan meta-analysis techniques to supplement ALE approaches is very nice indeed.

In table 1 it would be good to see the name of the first author of the studies listed – saves referring to the numbered list and allows those with a reasonable knowledge of the literature to quickly grasp which studies are included.

Response: We agree that this would be helpful and have made this change in Table 1.

Discussion
The limitations of the present study are well documented, in particular, the paucity of studies adopting VBM techniques in ADHD. However I would also draw attention to the following:

The authors mention spatial resolution as a possible problem when examining putamen and globus pallidus. They consider these structures are both components of the striatum. I don’t think the globus pallidus is part of the striatum. Both structures are part of the basal ganglia and together they comprise the lentiform nucleus. The dorsal striatum is made up of the caudate and putamen. This section would benefit from a clarification and the addition of neuroanatomical references. The authors go on to note that the putamen and globus pallidus have functional differences, but need to reference this statement
and perhaps expand upon what this means for ADHD.

Response: Reviewer 1 also commented on our use of ‘striatum’ and we have corrected this with a clarification and neuroanatomical references. We have now referenced our statement relating to the functional differences between putamen and globus pallidus and the potential implications for ADHD (pp15-16):

‘A third limitation is that the meta-analysis does not have the spatial resolution to differentiate between a gray matter reduction in the putamen and globus pallidus. Although they are both components of the lentiform nucleus [38, 39] there are important differences in their neural connectivity. The striatum (caudate nucleus and putamen) sends efferent projections to the globus pallidus (which is divided into external and internal segments). It has been hypothesised that striatal cells disinhibit the thalamus (facilitating actions) via the globus pallidus interna (direct pathway) or increase inhibition of the thalamus (opposing actions) via a circuit including globus pallidus externa, subthalamic nucleus and globus pallidus interna (indirect pathway) [4]. Therefore a deficit in either putamen or globus pallidus could cause abnormalities in these cortical-striatal-pallidal-thalamic pathways, although at separate points and potentially with different consequences.’

There are other limitations of meta-analyses in general and ALE in particular. The ‘file drawer’ problem could be mentioned (indeed one wonders why so few studies have been published using VBM in ADHD, so this might be a real issue here?). In addition the significance level of the results returned in different component studies cannot incorporated into the analysis.

Response: We have now addressed these two issues in our Discussion (p16):

‘A fourth limitation is that there may be publication bias in the voxel-based morphometry literature on ADHD. Studies giving negative results may be less likely to be published than studies giving positive results (sometimes referred to as the ‘file drawer problem’, since negative studies are not published but remain in researchers’ file drawers). Negative studies should not affect the results of this meta-analysis (since it analyses the spatial distribution of published co-ordinates) but a bias in favour of publishing studies with co-ordinates which the researchers considered to be in interesting locations could bias the meta-analysis to detect changes in these locations. Although the meta-analysis did not incorporate the significance level of the results returned in different component studies, one advantage of the Genome Scan Meta-Analysis approach is that it provides a systematic method for integrating studies with different analysis methods and statistical thresholds [12].’

Thank you for the opportunity of reviewing this work. I think the supplementation to ALE is a valuable contribution, with potentially wider application. I hope the comments are helpful.

**Level of interest:** An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

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

Response: In the process of reviewing our manuscript we have given a more succinct description of our statistical analysis (p 9) by referring to the paper by Levinson et al (2003). We have changed: ‘If all permutations gave a lower value than the actual value, the probability was set at 0.0001, the minimum for the number of permutations. This is a conservative estimate of the probability, which may be between 0 and 0.0001.’ To: ‘The data set being tested was included in the ranking of all known outcomes [12].’