Reviewer's report

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

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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.

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?

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.
- 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.

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.

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

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.