Reviewer's report

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

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Reviewer: Grainne McAlonan

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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:

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.

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).

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.

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.

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.

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.

Declaration of competing interests:

I declare that I have no competing interests