Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis

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Summary

Background
Neuroimaging studies have shown structural alterations in several brain regions in children and adults with attention deficit hyperactivity disorder (ADHD). Through the formation of the international ENIGMA ADHD Working Group, we aimed to address weaknesses of previous imaging studies and meta-analyses, namely inadequate sample size and methodological heterogeneity. We aimed to investigate whether there are structural differences in children and adults with ADHD compared with those without this diagnosis.

Methods
In this cross-sectional mega-analysis, we used the data from the international ENIGMA Working Group collaboration, which in the present analysis was frozen at Feb 8, 2015. Individual sites analysed structural T1-weighted MRI brain scans with harmonised protocols of individuals with ADHD compared with those who do not have this diagnosis. Our primary outcome was to assess case-control differences in subcortical structures and intracranial volume through pooling of all individual data from all cohorts in this collaboration. For this analysis, p values were significant at the false discovery rate corrected threshold of p=0·0156.

Findings
Our sample comprised 1713 participants with ADHD and 1529 controls from 23 sites with a median age of 14 years (range 4–63 years). The volumes of the accumbens (Cohen's d=−0·15), amygdala (d=−0·19), caudate (d=−0·11), hippocampus (d=−0·11), putamen (d=−0·14), and intracranial volume (d=−0·10) were smaller in individuals with ADHD compared with controls in the mega-analysis. There was no difference in volume size in the pallidum (p=0·95) and thalamus (p=0·39) between people with ADHD and controls. Exploratory lifespan modelling suggested a delay of maturation and a delay of degeneration, as effect sizes were highest in most subgroups of children (<15 years) versus adults (>21 years): in the accumbens (Cohen's d=−0·19 vs −0·10), amygdala (d=−0·18 vs −0·14), caudate (d=−0·13 vs −0·07), hippocampus (d=−0·12 vs −0·06), putamen (d=−0·18 vs −0·08), and intracranial volume (d=−0·14 vs 0·01). There was no difference between children and adults for the pallidum (p=0·79) or thalamus (p=0·89). Case-control differences in adults were non-significant (all p>0·03). Psychostimulant medication use (all p>0·15) or symptom scores (all p>0·02) did not influence results, nor did the presence of comorbid psychiatric disorders (all p>0·5).

Interpretation
With the largest dataset to date, we add new knowledge about the bilateral amygdala, accumbens, and hippocampus reductions in ADHD. We extend the brain maturation delay theory for ADHD to include subcortical structures and refute medication effects on brain volume suggested by earlier meta-analyses. Lifespan analyses suggest that, in the absence of well powered longitudinal studies, the ENIGMA cross-sectional sample across six decades of ages provides a means to generate hypotheses about lifespan trajectories in brain phenotypes.