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Short Report

Genetic correlations between subcortical brain volumes and psychiatric disorders

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Summary

Psychiatric disorders as well as subcortical brain volumes are highly heritable. Large-scale genome-wide association studies (GWASs) for these traits have been performed. We investigated the genetic correlations between five psychiatric disorders and the seven subcortical brain volumes and the intracranial volume from large-scale GWASs by linkage disequilibrium score regression. We revealed weak overlaps between the genetic variants associated with psychiatric disorders and subcortical brain and intracranial volumes, such as in schizophrenia and the hippocampus and bipolar disorder and the accumbens. We confirmed shared aetiology and polygenic architecture across the psychiatric disorders and the specific subcortical brain and intracranial volume.

Declaration of interest

None.

Keywords

Genetic correlation; psychiatric disorder; subcortical volume; genome-wide association study; linkage disequilibrium score regression.

Schizophrenia, bipolar disorder (BIP), major depressive disorder (MDD), autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are common and highly heritable ($h^2 = 0.50–0.90$) psychiatric disorders with a complex overlapping polygenic architecture. Large-scale ($n = 63\,766–480\,359$) genome-wide association studies (GWASs) for psychiatric disorders, including schizophrenia, BIP, MDD, ASD and ADHD, as well as cross-disorder analyses of non-overlapping subsamples across these five psychiatric disorders, have been performed by the Psychiatric Genomics Consortium (PGC; https://www.med.unc.edu/pgc/) and the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH; http://ipsych.au.dk/about-ipsych/). Each GWAS has identified 108, 2, 44, 5, 12 and 4 genetic loci associated with risk for schizophrenia, BIP, MDD, ASD, ADHD and cross-disorder liability, respectively (see Supplementary Table 1, available at https://doi.org/10.1192/bjp.2019.277). Subcortical brain volumes are also highly heritable traits ($h^2 = 0.44–0.88$) that are intensively studied in psychiatric neuroimaging research. Recently, the worldwide Enhancing Neuroimaging Genetics through Meta-analysis (ENIGMA; http://enigma.ini.usc.edu/) Working Groups on schizophrenia, BIP, MDD, ASD and ADHD ($n = 3222–8927$) examined alterations in the seven subcortical brain volumes (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen and thalamus) and the intracranial volume (ICV) between patients with these psychiatric disorders and matched healthy individuals.[1–5] As summarised in Fig. 1a, characteristic alterations in the seven subcortical volumes and the ICV were found in patients with these psychiatric disorders compared with healthy controls. In addition to GWASs for these psychiatric disorders, GWASs for the volumes of the seven subcortical regions and the ICV have been conducted by the ENIGMA Consortium, in an analysis known as ENIGMA2. GWASs for the hippocampus, putamen and ICV have identified two, four and one genetic loci that were consistently associated with these brain volumes, respectively, in samples worldwide (see Supplementary Table 1), whereas GWASs for other subcortical volumes have not revealed any genome-wide significant loci ($P > 5.0 \times 10^{-8}$). As the subcortical volumes alterations may be useful intermediate phenotypes to understand genetic mechanisms implicated in the pathophysiology of these psychiatric disorders, there could be genetic correlations of psychiatric disorders with the subcortical volumes and the ICV. Recently, Smeland *et al.* reported genetic overlaps between schizophrenia and volumes of the hippocampus, putamen and ICV at the individual single-nucleotide polymorphism (SNP) level,[6] but the genetic overlaps at polygenic level are poorly understood.[7,8] Here, we report the genetic correlations between five psychiatric disorders (schizophrenia, BIP, MDD, ASD and ADHD) and the seven subcortical brain volumes (accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus) and the ICV, using linkage disequilibrium score regression (LDSC) analysis.

Method

We calculated genetic correlations attributable to genome-wide SNPs (polygenicity; many small genetic effects) between the psychiatric disorders and the subcortical volumes and the ICV. GWAS summary statistics (schizophrenia (Psychiatric Genomics Consortium 2 (PGC2)), BIP, MDD (MDD2), ASD (iPSYCH-PGC GWAS-2017), ADHD (ADHD2017), the cross-disorder GWAS, seven subcortical brain volumes and ICV) from the PGC and the iPSYCH and the ENIGMA2 study were available in public databases (PGC and iPSYCH, https://www.med.unc.edu/pgc/results-and-downloads; ENIGMA2, http://enigma.ini.usc.edu/research/download-enigma-gwas-results/). The sample information and the details regarding the sample collection, genotyping, processing, quality control and imputation procedures applied in each GWAS have been described previously, and are briefly summarised in Supplementary Table 1, Methods and References.

LDSC analysis can estimate the genetic SNP correlations (r_g) from GWASs, and is powerful tool for investigating the genetic architecture of common traits and diseases.[9] Regression weights (linkage disequilibrium scores, 'eur_w_ld_chr/' files https://github.com/bulik/ldsc) were pre-computed using the European ancestry samples of the 1000 Genomes Project. To restrict the analysis to well-imputed SNPs, we filtered the imputed and directly genotyped SNPs in each GWAS to SNPs that overlapped with a HapMap3 SNP panel. Only results for markers with an imputation INFO score

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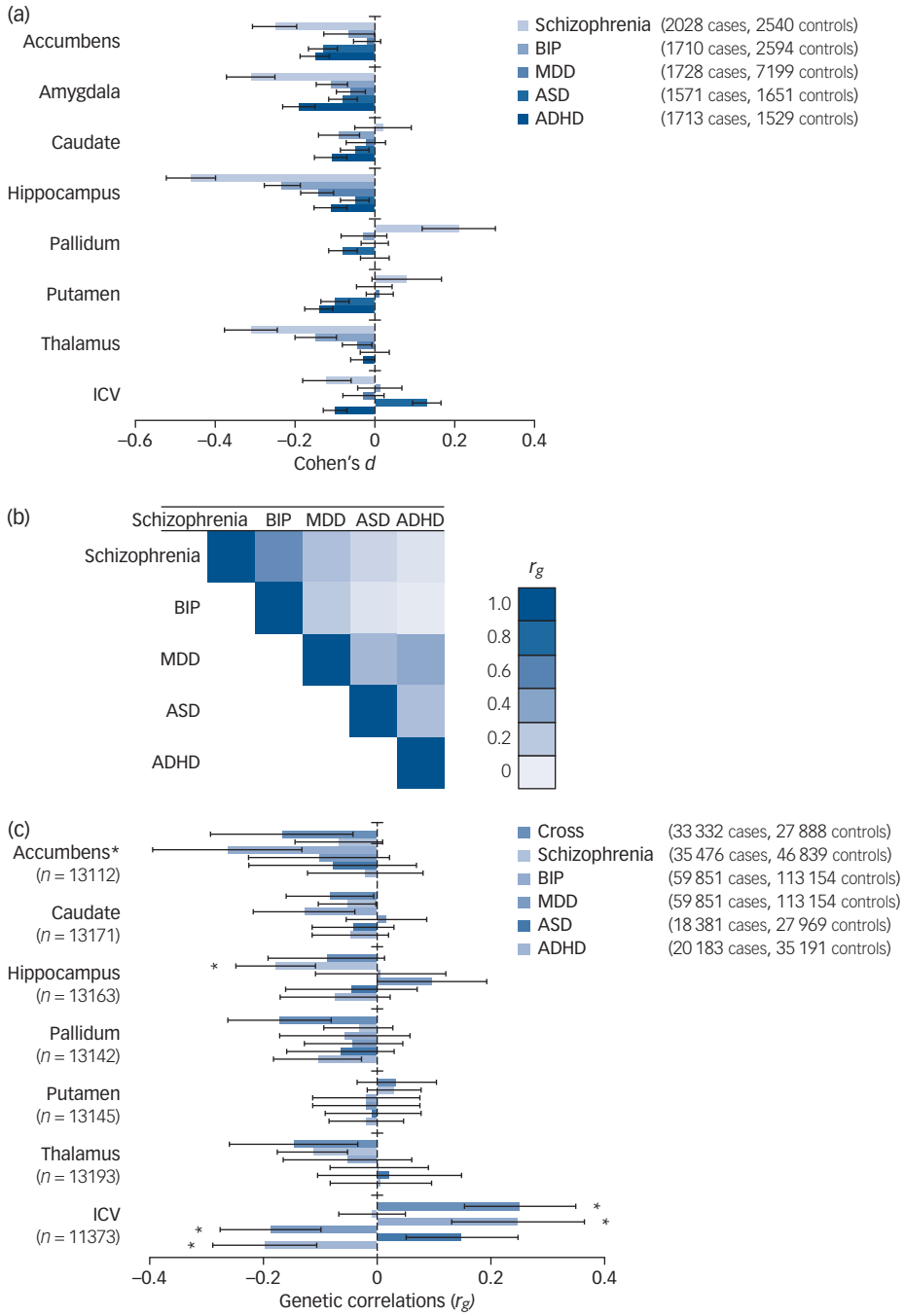

Fig. 1 (a) Alterations (Cohen's *d*) in the subcortical brain volumes and the ICV between groups of individuals with specific psychiatric disorders (schizophrenia, BIP, MDD, ASD and ADHD) and matched healthy controls. (b) Genetic correlations (r_g) across psychiatric disorders. The colour bar shows the r_g values corresponding to the colour in the figure. (c) Genetic correlations (r_g) of psychiatric disorders with subcortical volumes and ICV.

*$P < 0.05$.
Error bars indicate s.e. of the Cohen's *d* or r_g.
ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; BIP, bipolar disorder; ICV, intracranial volume; MDD, major depressive disorder.

>0.90 and minor allele frequency > 0.01 were included in the analysis. Insertion-deletion polymorphisms, structural variants, strand-ambiguous SNPs and SNPs with extremely large effect sizes were removed. As variances in the value of *beta* among SNPs in GWASs for the putamen and ICV were high, these *beta* values were converted to *z*-scores (https://github.com/bulik/ldsc/issues/43). For each GWAS, a linkage disequilibrium regression was carried out by regressing the GWAS test statistics (χ^2) onto each SNP's linkage disequilibrium score. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

As shown in Fig. 1b, there were highly positive genetic correlations ($r_g = 0.13$–0.78) across psychiatric disorders, except for the

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correlation between BIP and ADHD ($r_g \pm$ s.e. = 0.09 ± 0.06, P = 0.11). There was the most highly significant genetic correlation between schizophrenia and BIP ($r_g \pm$ s.e. = 0.78 ± 0.04, $P = 4.75 \times 10^{-85}$), whereas there was the least (only nominally) significant genetic correlation between BIP and ASD ($r_g \pm$ s.e. = 0.13 ± 0.07, P = 0.045). Next, we investigated genetic correlations between five psychiatric disorders (schizophrenia, BIP, MDD, ASD and ADHD) and the cross-disorder GWAS with the seven subcortical volumes and the ICV (Fig. 1c). In this analyses, we could not estimate the genetic correlations with amygdala volume because h^2 of the phenotype was low. Of the remaining seven volumetric phenotypes, we detected marginal negative genetic correlations between risk for schizophrenia and the volume of the hippocampus ($r_g \pm$ s.e. = −0.18 ± 0.07, P = 0.011), BIP and the volume of the nucleus accumbens ($r_g \pm$ s.e. = −0.26 ± 0.13, P = 0.045), MDD and the ICV ($r_g \pm$ s.e. = −0.19 ± 0.09, P = 0.034) and ADHD and the ICV ($r_g \pm$ s.e. = −0.20 ± 0.09, P = 0.030). In contrast, we found marginal positive genetic correlations between risk for BIP and the ICV ($r_g \pm$ s.e. = 0.25 ± 0.12, P = 0.033) and between cross-disorder risk and the ICV ($r_g \pm$ s.e. = 0.25 ± 0.10, P = 0.011). There were no other significant genetic correlations between psychiatric disorders and brain volumes ($P > 0.05$).

Discussion

To our knowledge, this is the first study to investigate genetic correlations between the subcortical brain volumes, including the ICV, and these common psychiatric disorders using the LDSC analysis. We revealed weak overlaps between the genetic variants associated with psychiatric disorders and subcortical brain volumes and ICV in schizophrenia and the hippocampus, BIP and the accumbens, and between BIP, MDD, ADHD and the cross-disorder GWAS and ICV. Compared with highly genetic correlations (r_g) ranging from 0.13 to 0.78 among the five psychiatric disorders, we found relatively low genetic correlations (approximately 0.20) between the psychiatric disorders and the subcortical brain volumes. After applying Bonferroni correction for multiple comparisons, these weak genetic correlations would not be statistically significant. However, the r_g values of around 0.20 were similar to the r_g that has been reported between general cognitive function and schizophrenia.[10] The genetic correlations between general cognitive function and schizophrenia were statistically highly significant because sample sizes for the GWASs for cognitive function were over 20 times larger than the ENIGMA2 GWASs.[11] As the power of the LDSC analysis depends on the sample sizes of the input GWASs, further studies using larger sample sizes are warranted, e.g. with data from PGC3 and/or ENIGMA3.

As the results of the cross-disease analysis might be affected by the sample sizes of the specific disorder groups, we additionally investigated genetic correlations of each psychiatric disorder with subcortical volumes and the ICV in cross-disorder samples (Supplementary Fig. 1). Although the sample sizes in schizophrenia and MDD ($n > 16\,000$) were larger than those in BIP, ASD and ADHD ($n < 12\,000$) in the cross-disorder samples, any specific disorder group would not influence the results in the cross-disorder analysis.

There is limitation to the interpretation of our findings. Some sample overlap was present in our data. Sample overlap creates spurious correlation between z_{1j} and z_{2j}, which inflates $z_{1j}z_{2j}$. The expected magnitude of this inflation is uniform across all markers, and in particular does not depend on linkage disequilibrium score. As a result, sample overlap only affects the intercept from this regression and not the slope, so the estimates of genetic correlation will not be biased by sample overlap.[12]

In conclusion, we confirmed shared aetiology and polygenic architecture across the psychiatric disorders and the specific intracranial and subcortical brain volumes, although these correlations were statistically marginal.

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Supplementary material

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Author contributions

K.O. supervised the entire project and was critically involved in the design, analysis and interpretation of the data. K.O., T. Shimada, Y. Kataoka, T.Y. and P.M.T. collected the data, wrote the manuscript, and was responsible for performing the literature review. K.O., Y. Kawasaki, T. Shioiri and P.M.T. were heavily involved in the collection of the majority of the data and contributed intellectually to the interpretation of the data. All authors contributed to and have approved the final manuscript.

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