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Heritability of subcortical brain measures: a perspective for future genome-wide association studies

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Introduction

Based on genome-wide association meta-analyses, several large imaging-genetics consortia have recently been successful in identifying the first genetic variants influencing hippocampal and intracranial volume (Bis et al., 2012; Stein et al., 2012; Ikram et al., 2012).

In view of these promising results, these consortia currently aim to identify genetic variants influencing subcortical brain structures, such as the thalamus, amygdala, putamen, caudate nucleus, globus pallidus and nucleus accumbens.

As a first step, it is worthwhile to investigate to what extent a genetic component accounts for the variation in these volumes. And since these large consortia make use of fully automated segmentation protocols, it would be furthermore of interest to assess the stability of these volume measurements.

We here investigated the extent to which genetic variation accounts for the variation in these subcortical volumes and obtained the stability of these brain volumes over a five-year period.

Methods

Participants

Heritability of subcortical volumes was estimated in a sample of 176 monozygotic (MZ) twin pairs and 88 dizygotic (DZ) twin pairs aged 11-56 years.

Retest stability was calculated in a subsample of 161 subjects who were scanned twice with a 5-year interval.

Segmentation of subcortical brain volumes & statistical analysis

Subcortical volumes were segmented automatically using Freesurfer (Fischl et al., 2002).

Standard twin models, estimating the amount of variance explained by additive genetic effects (A), common environment (C) shared by family members and unique environment (E) were evaluated in open MX, a structural equation modeling program which provides maximum-likelihood estimates of free parameters in the ACE model (Neale et al., 2003).

Results

MZ and DZ twin correlations, 5-year test-retest intraclass correlations, and the proportion of variance accounted for by A, C and E for all brain volumes are summarized in ***table 1*** and ***figure 1 and 2***, respectively.

Brain volume	Twin correlations		Retest stability
	rMZ	rDZ	rT0-T5
L.thalamus	0.80	0.36	0.81
R.thalamus	0.81	0.46	0.88
L.caudate	0.88	0.49	0.87
R.caudate	0.86	0.36	0.86
L.putamen	0.87	0.49	0.86
R.putamen	0.84	0.55	0.83
L.pallidus	0.76	0.27	0.73
R.pallidus	0.66	0.31	0.62
L.hippocampus	0.75	0.33	0.81
R.hippocampus	0.80	0.43	0.79
L.amygdala	0.66	0.39	0.78
R.amygdala	0.69	0.35	0.74
L.accumbens	0.66	0.43	0.45
R.accumbens	0.69	0.43	0.72

Table 1. *Twin correlations and 5-year test-retest intraclass correlations for all subcortical brain volumes. L= left; R = right.*

The heritability estimates for all subcortical regions were high, with the highest heritability estimates observed for the left thalamus (.80) and left caudate nucleus (.88) and lowest for the left nucleus accumbens (.44) (*figure 1 & 2*).

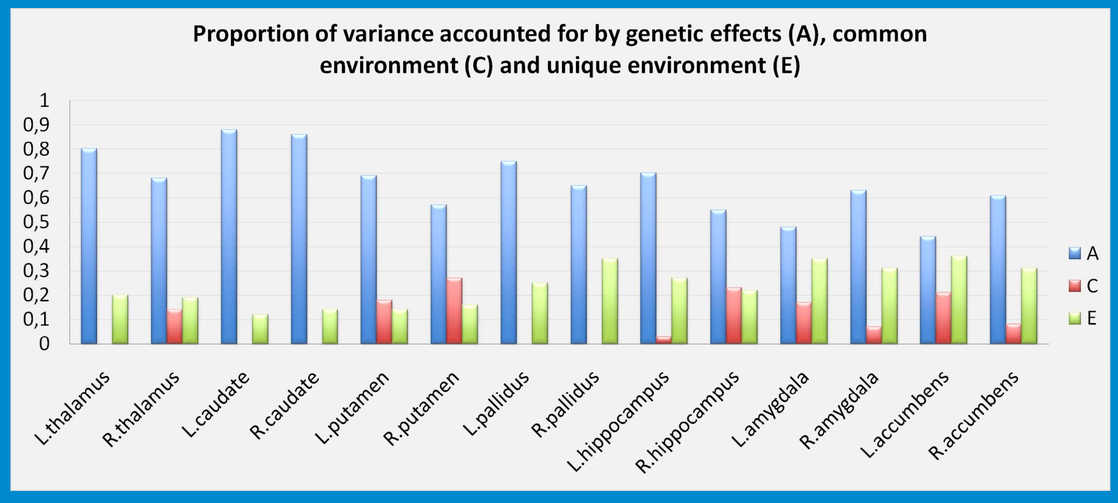

Figure 1. *Heritability estimates of subcortical brain volumes (covaried for field strength [1.5 vs. 3.0T], site [Amsterdam vs. Utrecht], age and handedness).*

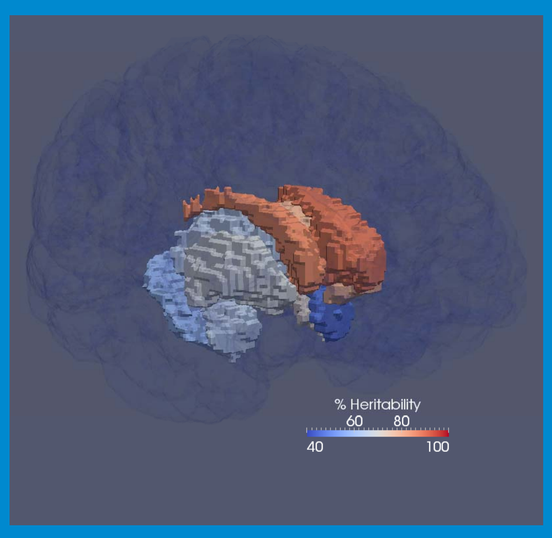

Figure 2. *Heritability estimates of subcortical volumes plotted on a glassed brain.*

Five-year stability was substantial and higher for larger [e.g., thalamus (.88), putamen (.86), caudate nucleus (.87)] compared to smaller [nucleus accumbens (.45)] subcortical structures (*table 1*).

For all regions, twin correlations for males and females were equal, which indicates that there is no evidence for sex differences in the heritability of these brain phenotypes and that to a larger extent, the same genes influence these phenotypes in males and females.

Conclusions

Overall, these findings provide evidence that subcortical structures such as the caudate nucleus, putamen, thalamus, globus pallidus and hippocampus reveal high heritability estimates. Results are very comparable for males and females and show good temporal stability.

These results provide evidence that subcortical structures are promising starting points for identifying genetic variants that influence brain structure.

References:

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