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

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ABSTRACT

Several large imaging-genetics consortia aim to identify genetic variants influencing subcortical brain volumes. We investigated the extent to which genetic variation accounts for the variation in subcortical volumes, including thalamus, amygdala, putamen, caudate nucleus, globus pallidus and nucleus accumbens and obtained the stability of these brain volumes over a five-year period. The heritability estimates for all subcortical regions were high, with the highest heritability estimates observed for the thalamus (.80) and caudate nucleus (.88) and lowest for the left nucleus accumbens (.44). 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. These results provide additional evidence that subcortical structures are promising starting points for identifying genetic variants that influence brain structure.

Introduction

Over the past few years the first genetic variants influencing variation in human brain structures have been identified based on genome-wide association (GWA) meta-analyses. Such findings are expected to be of great importance for understanding the biological mechanisms underlying cognition and neuropsychiatric disorders. In order to accomplish genome wide significance, large samples are needed. For this, several imaging genomics groups have been working collaboratively together (e.g., Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA), the Cohorts of Heart and Aging Research in Genomic Epidemiology (CHARGE), and the Early Growth Genetics (EGG) consortium). These studies together provided evidence for a significant association between hippocampal volume and rs7294919 on chromosome 12q24 (located between HRK and FBXW8 which is associated with expression of the TESC gene, involved in cell proliferation and differentiation) (Bis et al., 2012; Stein et al., 2012) and between intracranial volume (ICV) and rs10784502 on chromosome 12q14 (associated with expression of the HMGA2 gene, implicated in human growth) (Stein et al., 2012), rs4273712 on chromosome 6q22 (associated with adult height) (Ikram et al., 2012) and rs9915547 on chromosome 17q21 (associated with early brain development) (Ikram et al., 2012). Interestingly, the variant on 17q21 was also associated with head circumference (Taal et al., 2012). In view of these promising results, in the next series of steps the ENIGMA consortium aims to identify genetic variants influencing other subcortical brain structures, including the thalamus, amygdala, putamen, caudate nucleus, globus pallidus and nucleus accumbens. These subcortical brain regions have been found to be affected in several neuropsychiatric disorders (e.g., schizophrenia, attention deficit hyperactivity disorder, autism, anxiety disorders, depression (Holzschneider and Mulert, 2011; Koolschijn et al., 2009; Shepherd et al., 2012; Taurines et al., 2012)), and it is therefore of importance to disentangle the sources (genetic and environmental) that could explain the variation in these phenotypes. As a first step for identifying not only genetic variants, but also environmental factors, associated with the phenotypic variation, the extent to which the genome and/or the environment account for the variation in these volumes should be investigated. 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, which could serve as an indicator of measurement accuracy. Although the heritabilities of global (intracranial, total brain, gray matter, and white matter volumes) and regional (cortical) brain structures have been extensively studied, as reviewed in Blokland et al. (2012), and Peper et al. (2007), only a small number of studies have reported on the heritability of the volumes of subcortical brain areas (Kremen et al., 2010; Stein et al., 2011; Wallace et al., 2006; Wright et al., 2002; Yoon et al., 2011). A meta-analysis that calculated a weighted average of the proportion of variance accounted for by genes (A), shared environment (C), and unshared environment (E) yielded fairly high heritability estimates for all subcortical structures, ranging from 52% for the right thalamus to 82% for the right putamen (Blokland et al., 2012). These high estimates indicate that the

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investigated subcortical structures could serve as endophenotypes and targets for GWA studies. However, because the number of individuals in which the heritability of subcortical volumes was calculated tends to be small, the confidence intervals in this meta-analysis are still wide, for example ranging between 42–80% and 36–69% for the left and right Thalamus, respectively (Blokland et al., 2012). Therefore, further replication of these findings across independent samples and demographic groups is desirable. Also sex differences in heritability have not been systematically investigated.

Here, we estimated the heritability for thalamus, caudate nucleus, putamen, globus pallidus, hippocampus, amygdala and nucleus accumbens in a sample of 176 monozygotic (MZ) twin pairs (107 female pairs/69 male pairs) and 88 dizygotic (DZ) twin pairs (24 female–female pairs, 23 male–male pairs and 41 male–female pairs) aged 11–56 years [mean (SD) = 29.10 (10.07), of which 13.6% were aged between 11 and 17]. Image processing was done following the streamlined ENIGMA protocol. We also report the retest stability for a subsample of 161 subjects who were scanned twice with a 5-year interval, and test if heritability estimates differ in men and women.

Methods

Twin pairs included in the analyses were scanned at three sites in The Netherlands; 134 subjects (6 DZ/61 MZ pairs) were scanned on a 1.5 T Siemens MR scanner at the VU Medical Center Amsterdam (van 't Ent et al., 2007; Wolfensberger et al., 2008), 212 subjects (56 DZ/50 MZ pairs) on a 1.5 T Philips Achieva MR scanner at the University Medical Center Utrecht (UMCU) (Baare et al., 2001), and 182 subjects (26 DZ/65 MZ pairs) on a 3.0 T Philips Intera MR scanner at the Academic Medical Center Amsterdam (den Braber et al., 2010) (additional socio-demographic data for this sample are summarized in Table 1, showing a disbalance over centers with respect to age and sex. Restricting analyses to a subgroup of twin pairs such that the M:F ratio was 1:1 in all centers and average age differences were restricted to 4 years, the results reported in this paper did not change). A group of 161 adults was scanned twice at the UMCU (Brans et al., 2010), for which we report the 5-year stability. In the genetic analyses, data from the first assessment were analyzed. Subcortical volumes were segmented automatically using the publicly available Freesurfer software package (Fischl et al., 2002, 2004).

The proportion of phenotypic variance explained by additive genetic effects (A), common environment (C) and unique environment (E) could be estimated because the study includes monozygotic (MZ) and dizygotic (DZ) twin pairs. If both types of twin pairs resemble each other to the same extent a contribution of common environment (C) is suggested which leads to similarity in both types of twins. If however, the resemblance in MZ twins who share on average 100% of their genes, is larger than in DZ twins who share on average 50% of their segregating genes, a contribution of genes to phenotypic similarity is indicated. An additive mode of gene action is suggested when the resemblance of MZ twins is not larger than twice that in DZ twins. The extent to which MZ twins do not resemble each other, indexes the contribution of unique environmental factors (Boomsma et al., 2002). Formally, the correlation in MZ twins equals $a^2 + c^2$, where parameters $a^2 + c^2$ give the proportions of variance explained by additive genetic effects and common environment shared by twins. The correlation in DZ twin pairs equals $0.5a^2 + c^2$, and the total variance is $a^2 + c^2 + e^2$.

Table 1
Socio-demographic data of the analyzed sample.

Center (n)	Sex (males/females)	Age (mean ± SD)	Handedness (right/left)
VU Amsterdam (134)	50/84	21.3 (8.3)	119/15
University Medical Center Utrecht (212)	115/97	29.8 (7.6)	175/37
Academic Medical Center Amsterdam (182)	60/122	34.0 (10.4)	160/22

These equations can be fitted to the data by maximum-likelihood in structural equation modeling programs as Mx (Neale et al., 2003). Quantitative sex differences in parameters estimated were evaluated by constraining the correlations between men and women within zygosity to be equal. In addition we tested for qualitative sex differences by constraining the DZ same-sex correlation to equal the DZ opposite-sex correlation. If the same genes are expressed in men and women, these correlations are expected to be equal. The significance of a^2 and c^2 parameters was tested by constraining their estimates at zero and testing if this led to a worse fitting model. Comparison of submodels, e.g. AE versus ACE, was done by means of likelihood-ratio tests, whose distribution follows a χ^2 with degrees of freedom (df) equal to the difference in the number of parameters of the two models. If a more restricted model fits the data significantly worse, the more general model is preferred. The constrained model was deemed not significantly worse than the previous model, if the likelihood-ratio tests yielded a p value higher than 0.01. In all analyses, subcortical volumes were covaried for field strength (1.5 T vs. 3.0 T), site (Amsterdam vs. Utrecht) (these together correct for scanner type used), age and handedness. In addition, analyses were performed with and without adjustment for ICV, which yielded highly similar results. We here report the result of the analyses without adjustment for ICV.

Results

MZ and DZ correlations, 5-year test–retest intraclass correlations, and the proportions of variance accounted for by A, C and E for all brain volumes are summarized in Table 2. For all regions, twin correlations for MZ males and MZ females were equal and the twin correlations for DZ males, DZ females and DZ opposite-sex twins also did not differ. This indicates that there is no evidence for sex difference in the heritability of these brain phenotypes and that to a large extent, the same genes influence these brain phenotypes in males and females. Twin correlations were substantially higher in MZ compared to DZ twin pairs, and were often close to being twice as large, indicating that familial correlations are predominantly accounted for by genetic effects rather than shared environment. Test–retest intraclass correlations for most subcortical regions, were of the same order of magnitude as the MZ correlations (with the exception of the left nucleus accumbens, all between 0.62 and 0.94).

For all regions investigated, structural equation modeling, estimating the amount of variance of a trait (here brain volume) explained by A, C and E, showed significant heritability, ranging from .44 for the left nucleus accumbens to .88 for the left caudate nucleus (see Table 2 and Fig. 1). Only a small amount of the variance was attributable to shared environmental effects and removing these effects from the full model did not give a significant worsening of the goodness of fit of the model. In contrast, when the influence of genes was constrained at zero, and familial resemblance attributed to common environment, model fit became much worse, indicating that variance in subcortical volumes is predominantly attributable to genetic and unique environmental effects.

Discussion

Heritability estimates for subcortical regions were high, with the largest estimates observed for the thalamus, caudate nucleus, and putamen. Similar to our findings, several other studies report high heritability estimates for the volumes of the caudate nucleus (Kremen et al., 2010; Stein et al., 2011; Wallace et al., 2006), putamen (Kremen et al., 2010; Wright et al., 2002; Yoon et al., 2011), and pallidus (Kremen et al., 2010; Yoon et al., 2011), although lower heritability estimates for the caudate nucleus have also been reported (Yoon et al., 2011). For the thalamus, heritability estimates vary substantially between studies, ranging from 0 to 68% (Kremen et al., 2010; Wright et al., 2002; Yoon et al., 2011). These inconsistencies in reported heritability estimates for subcortical volumes may be attributable to various factors,

Table 2
ACE model estimates for subcortical volumes, and tests of submodels (adjusted for field strength [1.5 vs. 3.0 T], site [Amsterdam vs. Utrecht], age and handedness).

Brain volume	ACE model estimates + 95% CI and nested fit statistic			AE model estimates + 95% CI and nested fit statistic			Twin correlations		Retest stability
	A (lower/upper)	C (lower/upper)	E (lower/upper)	A (lower/upper)	E (lower/upper)	p	rMZ (176 pairs)	rDZ (88 pairs)	rT0–T5 (n = 161 subjects)
Left thalamus	0.80 (0.53/0.84)	0 (0/0.27)	0.20 (0.16/0.26)	0.80 (0.74/0.84)	0.20 (0.16/0.26)	1	0.80	0.36	0.81
Right thalamus	0.68 (0.41/0.85)	0.14 (0/0.39)	0.19 (0.15/0.24)	0.81 (0.76/0.85)	0.19 (0.15/0.24)	0.69	0.81	0.46	0.88
Left caudate	0.88 (0.66/0.91)	0 (0/0.23)	0.12 (0.09/0.15)	0.88 (0.85/0.91)	0.12 (0.09/0.15)	1	0.88	0.49	0.87
Right caudate	0.86 (0.72/0.89)	0 (0/0.14)	0.14 (0.11/0.18)	0.86 (0.82/0.89)	0.14 (0.11/0.18)	1	0.86	0.36	0.86
Left putamen	0.69 (0.43/0.89)	0.18 (0/0.43)	0.14 (0.11/0.18)	0.86 (0.82/0.89)	0.14 (0.11/0.18)	0.57	0.87	0.49	0.86
Right putamen	0.57 (0.34/0.86)	0.27 (0/0.50)	0.16 (0.12/0.20)	0.84 (0.80/0.88)	0.16 (0.12/0.20)	0.23	0.84	0.55	0.83
Left pallidus	0.75 (0.44/0.80)	0 (0/0.30)	0.25 (0.20/0.32)	0.75 (0.68/0.80)	0.25 (0.20/0.32)	1	0.76	0.27	0.73
Right pallidus	0.65 (0.29/0.72)	0 (0/0.33)	0.35 (0.28/0.44)	0.65 (0.56/0.72)	0.35 (0.28/0.44)	1	0.66	0.31	0.62
Left hippocampus	0.70 (0.37/0.79)	0 .03 (0/0.35)	0.27 (0.21/0.34)	0.73 (0.66/0.79)	0.27 (0.21/0.34)	0.98	0.75	0.33	0.81
Right hippocampus	0.55 (0.28/0.81)	0.23 (0/0.49)	0.22 (0.17/0.28)	0.78 (0.72/0.83)	0.22 (0.17/0.28)	0.39	0.80	0.43	0.79
Left amygdala	0.48 (0.15/0.72)	0.17 (0/0.47)	0.35 (0.28/0.44)	0.65 (0.57/0.72)	0.35 (0.28/0.43)	0.69	0.66	0.39	0.78
Right amygdala	0.63 (0.30/0.76)	0.07 (0/0.37)	0.31 (0.24/0.39)	0.69 (0.61/0.76)	0.31 (0.24/0.39)	0.94	0.69	0.35	0.74
Left accumbens	0.44 (0.12/0.71)	0.21 (0/0.49)	0.36 (0.28/0.45)	0.65 (0.56/0.72)	0.35 (0.28/0.44)	0.52	0.66	0.43	0.45
Right accumbens	0.61 (0.28/0.75)	0.08 (0/0.38)	0.31 (0.25/0.40)	0.69 (0.61/0.75)	0.31 (0.25/0.39)	0.91	0.69	0.43	0.72

A = additive genetic effects; C = common environment; E = unique environment; CI = confidence interval; p = likelihood-ratio test statistics comparing the AE submodel fit (hypothesis of no common environmental effects) with the initial ACE model fit.

such as differences in sample composition (e.g., age, gender), image acquisition, image processing, or the analysis methods used. Since so little is known about sex differences in heritability, we tested whether heritability estimates were different for men and women. Our data support the hypothesis that there are no or few sex differences in heritability (Vink et al., 2012), indicating that the same genes influence these brain phenotypes in males and females. These results thereby suggest that there is no need to separately analyze data from men and women in the search for genes explaining the variance in subcortical volumes. We also estimated the stability of subcortical volume measurements, when using the automated segmentation procedures, in a subsample of 161 subjects who were scanned twice with a 5-year time interval. On average the intraclass correlation coefficient (ICC) for the subcortical regions was .77, with the highest correlation found for the larger subcortical regions (e.g., thalamus, caudate, putamen) and the lowest for smaller regions (e.g. accumbens, globus pallidus). These results agree with previous studies investigating the scan–rescan reliability of subcortical volumes derived from automated segmentation (Morey et al., 2010; Stein et al., 2011). Interestingly, subcortical regions that showed the lowest 5-year test–retest correlations, were also the least heritable of all subcortical structures measured (e.g., left nucleus accumbens). These results suggest that the lower heritability estimates for the smaller subcortical regions might be the result of a greater measurement error (i.e., bias in regional partitioning), as has been suggested (Blokland et al., 2012; Morey et al., 2010). These results also indicate that for most brain volumes (with the exception of the nucleus accumbens), the automated segmentation method provided by Freesurfer is stable for subjects who were scanned twice on the same scanner. The large consortia that aim to identify the genetic variants influencing variation in human brain structure, will include imaging data from different sites and scanners. Within our sample there were 12 subjects who were scanned both on a 1.5 T scanner and on a 3.0 T scanner [mean time interval (SD) in years = 11.2 (1.4)]. When calculating the ICC for these measures within these 12 subjects, results were fairly similar to those obtained in the 161 subjects who were scanned twice on the same scanner [mean ICC: .72 ± .1]. We have previously shown that brain volume measures were comparable between twin and non-twin groups, and

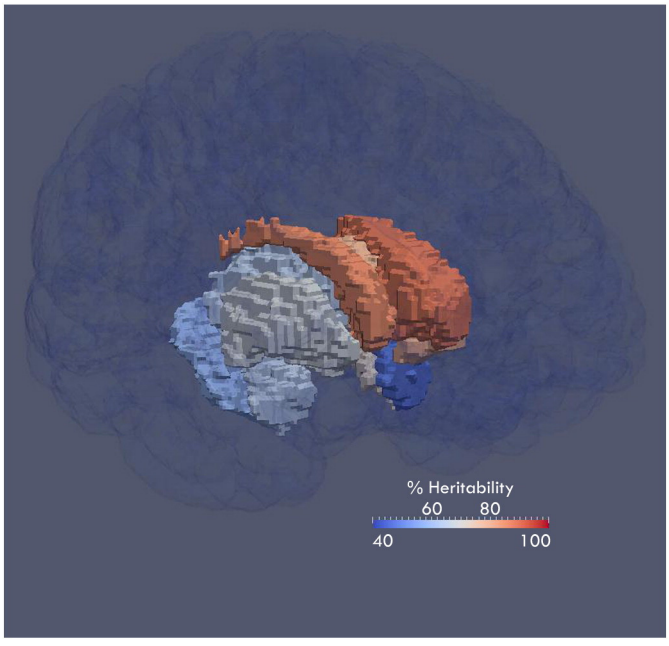

Fig. 1. Heritability estimates of subcortical volumes (adjusted for field strength [1.5 vs. 3.0 T], site [Amsterdam vs. Utrecht], age and handedness) plotted on a glassed brain.

that twin studies provide reliable estimates of heritabilities in brain volume measures which can be generalized to other populations (Hulshoff Pol et al., 2002, 2006).

Overall, these findings provide evidence that subcortical structures such as the caudate nucleus, putamen, thalamus, amygdala and hippocampus reveal high heritability estimates. Results are robust across different scanners and acquisition protocols, are very comparable for males and females and show good temporal stability. This is a rather promising result for imaging genetics studies that are compelled through meta-analysis to combine data from multiple sites in order to gain sufficient power to detect genetic variants associated with the subcortical structures investigated here.

The finding of high heritability for subcortical volumes and subcortical brain changes noted for several psychiatric disorders (Jung et al., 2012; Schneider and Prvulovic, 2013) suggests that subcortical structural measures can be useful intermediate phenotypes in the search for risk genes underlying these disorders. However, studies on the association of subcortical morphometric changes with genetic liability for psychiatric disease are not yet conclusive. For example, many studies have reported (progressive) structural brain changes in unaffected relatives of patients with schizophrenia compared to healthy controls, including unaffected co-twins, parents, offspring and siblings (Boos et al., 2007; Moran et al., in press). In contrast, in two large family samples with over a 100 schizophrenia patients, non-psychotic siblings and healthy controls, in the adult age range, no evidence for structural alterations in any cortical or subcortical brain region was observed in the siblings, suggesting instead a role of environmental factors, such as antipsychotic drug use, and/or a role of disease-related factors, such as duration of psychosis (Boos et al., 2012; Goldman et al., 2008). A recent cross-sectional study provided evidence for abnormal volume–age relationships during adolescence for the hippocampus and basal ganglia structures in familial high risk subjects, indicating that assessment during brain development is important (Dougherty et al., 2012). In addition, brain abnormalities in individuals at risk may be subtle and be revealed more clearly by complex measures, such as local shape parameters as has been shown for the basal ganglia and thalamus (Harms et al., 2007; Mamah et al., 2008) and hippocampus (Johnson et al., 2013).

Despite high heritabilities, our data also indicate that part of the variability in subcortical volumes is explained by environmental influences that are not shared by (adult) twins. Thus, identifying environmental risk factors that could explain variance in subcortical volumes is obviously important and supported by studies that found associations between negative life events (e.g., childhood sexual abuse, childhood stress and childhood maltreatment) and gray matter volume changes (Edmiston et al., 2011; Frodl et al., 2010; Tomoda et al., 2009) related to several psychiatric disorders.

The GWA studies of brain volumes that have been performed so far have proven to be large enough in terms of sample size to detect genetic variants associated with hippocampus volume and ICV, and show comparable effect sizes to those observed in other GWA studies of complex human traits (Flint and Munafo, 2013). Identifying both the genetic and environmental factors, explaining the variance in subcortical volumes, and studying their interaction, will be powerful for increasing our knowledge on normal brain development and hopefully disease pathogenesis.

Conflict of interest

None of the authors has anything to disclose and none has any conflicts of interest.

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