Twin Research and Human Genetics
Volume 15 ▌ Number 3 ▌ pp. 351–371 ▌ © The Authors 2012 ▌ doi:10.1017/thg.2012.11

Genetic and Environmental Influences on Neuroimaging Phenotypes: A Meta-Analytical Perspective on Twin Imaging Studies

Gabriëlla A. M. Blokland,[1,2,3] Greig I. de Zubicaray,[3] Katie L. McMahon,[2] and Margaret J. Wright[1,3]
[1]Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland, Australia
[2]Centre for Advanced Imaging, University of Queensland, Brisbane, Queensland, Australia
[3]School of Psychology, University of Queensland, Brisbane, Queensland, Australia

Because brain structure and function are affected in neurological and psychiatric disorders, it is important to disentangle the sources of variation in these phenotypes. Over the past 15 years, twin studies have found evidence for both genetic and environmental influences on neuroimaging phenotypes, but considerable variation across studies makes it difficult to draw clear conclusions about the relative magnitude of these influences. Here we performed the first meta-analysis of structural MRI data from 48 studies on >1,250 twin pairs, and diffusion tensor imaging data from 10 studies on 444 twin pairs. The proportion of total variance accounted for by genes (A), shared environment (C), and unshared environment (E), was calculated by averaging A, C, and E estimates across studies from independent twin cohorts and weighting by sample size. The results indicated that additive genetic estimates were significantly different from zero for all meta-analyzed phenotypes, with the exception of fractional anisotropy (FA) of the callosal splenium, and cortical thickness (CT) of the uncus, left parahippocampal gyrus, and insula. For many phenotypes there was also a significant influence of C. We now have good estimates of heritability for many regional and lobar CT measures, in addition to the global volumes. Confidence intervals are wide and number of individuals small for many of the other phenotypes. In conclusion, while our meta-analysis shows that imaging measures are strongly influenced by genes, and that novel phenotypes such as CT measures, FA measures, and brain activation measures look especially promising, replication across independent samples and demographic groups is necessary.

■ **Keywords:** twin study, heritability, magnetic resonance imaging, meta-analysis, review, neuroimaging genetics

Brain structure and function are affected in persons with psychiatric and neurodegenerative diseases (Mosconi et al., 2007; Sacher et al., 2011; Shenton et al., 2001), and in healthy family members at increased genetic risk for those diseases (Winterer et al., 2003). The challenge of linking specific genetic or environmental risk factors to behaviors and brain disorders has led to interest in using neuroimaging measures of brain structural and functional features as intermediate phenotypes (Boomsma et al., 2002; Glahn et al., 2007). The closer we place our measurements to the level of the neuronal circuitry, the less heterogeneous the phenotype. The less heterogeneous the phenotype, the fewer genes are likely to influence the phenotype, and the larger the effect of a single gene may be, making contributing genes easier to identify (de Geus et al., 2008; Gottesman & Gould, 2003). Brain structure and function as assessed by magnetic resonance imaging (MRI) can be measured on a continuous quantitative scale independent of disease state, increasing statistical power to detect genetic effects. Further, these measures are presumably stable over time (Bonekamp et al., 2007; Dickerson et al., 2008), and may require smaller sample sizes to detect association (Rasch et al., 2010).

Twin imaging studies of discordant patient–control samples have revealed significant additive genetic influences on the correlations between schizophrenia liability and

RECEIVED 30 November 2011; ACCEPTED 7 February 2012.

ADDRESS FOR CORRESPONDENCE: Gabriëlla A. M. Blokland, Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Locked Bag 2000, Royal Brisbane Hospital, Herston QLD 4029, Australia. E-mail: gabriella.blokland@qimr.edu.au

total brain volume (TBV) (Rijsdijk et al., 2005), progressive whole brain (66%), frontal lobe (76%), and temporal lobe (79%) volume change (Brans et al., 2008). Rijsdijk et al. (2010) furthermore showed that a common genetic factor explains the phenotypic relationship between left posterior cingulate and right dorsal anterior cingulate gray matter (GM) concentrations and psychopathic traits. Decreases in white matter (WM) were related to the genetic risk of developing bipolar disorder (bivariate heritability, 77%), with up to 45% of this relationship explained by common genetic factors; significant environmental correlations were found for cortical GM (van der Schot et al., 2009).

In the past 15 years there have been a few dozen twin studies of neuroimaging measures in healthy population-based samples. However, due to considerable variation in the methodologies employed, it is difficult to draw clear conclusions regarding the relative magnitude of genetic and environmental influences. Estimates of the proportion of variance in neuroimaging measures accounted for by genetic influences (i.e., heritability) range from 0% to almost 100% (e.g. Chiang et al., 2009; Kremen et al., 2010b). Similarly, estimates of the proportion of variance accounted for by shared environmental factors range from 0% to ~70% (e.g. Chiang et al., 2009; Wright et al., 2002). This may be due to differences in methodology and demographics (age, sex, socio-economic status). It may also reflect the manner in which heritability is assessed, that is, Falconer's heritability versus structural equation modeling. Smaller structures may not reach significant heritability, because these structures are difficult to measure accurately. With voxel-based analyses, strict multiple comparisons applied to minimize false-positive results across the whole brain may also prevent smaller areas from reaching significant heritability, possibly giving an underrepresentation of actual genetic influences on brain areas. Most of all, the generalizability of some of the earlier findings may be limited because of small (twin) sample sizes: many studies have had low power to statistically distinguish between genetic and shared environmental influences, with wide confidence intervals (CIs) around variance estimates. The non-generalizability of the twin method due to differences in the intra-uterine and family environment of twins, compared with singletons (Doyle, 1996; Fowler et al., 1991), has been tested for brain volume in two independent twin–sibling cohorts (Hulshoff Pol et al., 2002; Ordaz et al., 2010). Both studies concluded that twin designs can provide reliable estimates of heritabilities of global brain volume measures, and that these can be generalized to the singleton population.

Here we carried out a meta-analysis of existing twin studies in order to provide more robust estimates of the magnitude of genetic and environmental influences on neuroimaging measures. Furthermore, the goal was to summarize the available data on the sources of variance in MRI phenotypes, to see if more recent findings challenge those of older studies. As sample sizes in imaging genetics studies, until recently, were small, individual studies may not have had sufficient statistical power to accurately estimate the relative importance of genetic and environmental sources of variance. By combining results from individual studies, and weighting them by their respective sample sizes, we can improve the estimates and, potentially, detect patterns obscured due to small sample sizes. Phenotypes which cannot be meta-analyzed are reviewed.

Methods

The studies we examined in this meta-analysis utilized the twin design and genetic modeling to determine the additive genetic (A), shared environmental (C), and unshared environmental (E) sources of variance in neuroimaging measures. All A, C, and E estimates reported in this paper refer to standardized variance components obtained by employing maximum-likelihood modeling procedures that determine the combination of genetic and environmental parameters that best fit the covariance structure of the observed data. Most reports used in our analyses employed maximum-likelihood modeling procedures using the statistical package Mx (Neale et al., 2002).

Selection of relevant twin studies on brain imaging phenotypes for this study started with a search of the electronic database PubMed (http://www.ncbi.nlm.nih.gov/entrez) using the following keywords: *heritability - twin - brain - imaging - MRI - genetic*. The cut-off date for inclusion was 31 December 2011. Abstracts of these search results were examined and relevant articles retrieved for review. One doctoral thesis, one study identified from the abstract list from the Annual Meeting of the American Society of Human Genetics, and three studies identified from the abstract lists from the Annual Meeting of the Organization for Human Brain Mapping, were also added. Studies were excluded from the analysis based on two main criteria. First, only studies that used monozygotic (MZ)/dizygotic (DZ) twin samples and applied genetic modeling to investigate the genetics of brain structure were included. This procedure identified 62 structural twin imaging studies — 52 studies on macrostructure and 10 on WM microstructure — and seven functional twin imaging studies. The majority of the samples were from the US, Australia, and The Netherlands; for the purposes of the meta-analysis, only studies using independent samples were included. Some authors used a subsample of the same cohort. In these cases only one of the reports was included in the meta-analysis, with a preference for: reports with the largest sample; the best balance between number of MZ and number of DZ pairs; availability of 95% CIs; the most suitable measure of brain structure; reporting estimates for the full ACE model (reporting A, C, and E); and (for consistency) estimates based on univariate models as opposed to multivariate models.

The literature search also identified six pedigree studies (five on macrostructure and one on WM

https://doi.org/10.1017/thg.2012.11 Published online by Cambridge University Press

microstructure). Although pedigree studies were not included in the meta-analysis, as they are not able to estimate C influences, they do provide important information. Therefore, they are summarized in the overview tables.

Any given structural phenotype was meta-analyzed when at least two independent studies estimated variance components for that phenotype. We meta-analyzed the standardized variance components for the phenotypes by calculating the weighted average A, C, and E estimates as outlined in Li et al. (2003) and Verweij et al. (2010). Briefly, to estimate the weighted mean, the parameter estimates for each cohort were weighted by the number of participants from complete twin pairs in the sample. Calculations were conducted in Microsoft Office Excel 2010. Estimates were made separately for each phenotype. We also calculated the 95% CIs around each estimate, calculated from the variance in the sample of source studies.

As gyral GM volumes, surface area measures, and amygdala volume were investigated in only one independent sample, these measures were not meta-analyzed. Furthermore, we were not able to meta-analyze voxel-based studies.

Results

Genetic and Environmental Effects on Brain Structure

To date 62 neuroimaging studies, including adults and children, have investigated and compared brain structure in healthy MZ and DZ twins through structural equation modeling. These studies have consistently found that global measures of brain structure are under strong genetic control, including intracranial volume (ICV), TBV, total cerebral volume (TCV), hemispheric volumes, cerebral lobe volumes, and total and regional GM and WM volumes. However, estimates are highly variable across studies for volumes of the cerebellum, subcortical structures, and ventricles; and for area measures of the corpus callosum, regional cortical surface area, and regional cortical thickness (CT), particularly for frontal and temporal GM areas.

Voxel-based approaches find high levels of genetic influence on GM density in frontal and both Broca's and Wernicke's areas, Heschl's gyrus, left occipital and left posterior cingulate, the amygdala, and middle temporal cortices (up to 83%) (Cannon et al., 2006; Hulshoff Pol et al., 2006; Peper et al., 2009; Thompson et al., 2001). High heritability is found for WM density of the corpus callosum, corticospinal tract, superior occipital-frontal and longitudinal fasciculi, and optic radiation (up to 93%) (Hulshoff Pol et al., 2006; Peper et al., 2009). CT has been shown to be most highly heritable in frontal and parietal areas, and to a lesser extent the posterior cingulate, medial, and superior temporal cortices (Joshi et al., 2011; Lenroot et al., 2009; Rimol et al., 2010; Yoon et al., 2010). Heritability of changes in CT is highest in superior and middle frontal areas, superior temporal areas, cingulate, sensorimotor cortices, primary visual and lateral occipital cortices in preadolescence (van Soelen et al., 2012), and in the left orbitofrontal, left and right superior temporal, left superior frontal, left and right lateral parietal, and right lateral and right medial occipital cortices in adulthood (Brans et al., 2010). Studies using deformation-based/tensor-based morphometry found strong genetic influences in the corpus callosum (Brun et al., 2009; Yoon et al., 2011), in early-maturing brain regions such as the occipital lobes (Brun et al., 2009), and bilaterally in the lateral fronto-orbital gyrus, cerebellum, several subcortical structures, brain stem, in the left frontal WM, inferior temporal gyrus and uncus, the right temporal WM, and superior frontal gyrus (Yoon et al., 2011). These voxel-based studies show that areas of strong heritability cross anatomical boundaries.

More recently, studies have started investigating measures of WM microstructure and have found high regional heritability of measures of WM fiber integrity derived from diffusion tensor imaging (DTI), such as fractional anisotropy (FA) or geodesic anisotropy (GA), and mean, longitudinal, or radial diffusivity (Brouwer et al., 2010; Chiang et al., 2008; Chiang et al., 2009; Jahanshad et al., 2010; Pfefferbaum et al., 2001). Brouwer and colleagues, furthermore, found significant heritability for magnetization transfer ratio, a proposed marker for myelination level, in the corpus callosum and superior longitudinal fasciculus. Imaging phenotypes with low heritability, such as gyral patterning of the cortex (Bartley et al., 1997; Eckert et al., 2002; Hasan et al., 2011) may be markers of both shared and non-shared environmental events that influence brain development.

For each of the studies, information about the cohort, age range, sample size, and phenotypes are presented in Table 1 (structural MRI) and Table 2 (DTI). Supplementary tables report exact variance component estimates.

The large majority of the studies employed structural MRI, measuring a total of 489 phenotypes (including eight voxel-wise phenotypes) across studies. Here we meta-analyzed 102 (∼21%) of those phenotypes. A smaller number of studies employed DTI, measuring a total of 137 phenotypes (including seven voxel-wise phenotypes) across studies. Here we meta-analyzed four (∼3%) of those phenotypes.

The largest published twin study on structural MRI included 121 MZ pairs and 162 DZ pairs (Quiggle et al., 2011). Generally, structural MRI phenotypes have been studied in very different age groups, with 1 study in newborns (∼2%); 13 studies in children and adolescents (∼28%); 9 studies in young adults (∼20%); 15 studies in adults (∼33%); and 8 studies in elderly twins (∼17%). For example, lobar CT was assessed in only two independent samples, an adult and a child sample. Likewise, regional CT was assessed in up to three independent samples, a children/adolescents sample, a young adult sample, and an adult sample. The large

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TABLE 1

Structural MRI Twin and Family Studies

Reference	Cohort	*n* pairs MZ/DZ	Age range	Phenotypes[a]
Baaré et al., 2001	NTR/UMCTS	54/58	19-69	TBV#, cGM #, cWM #, LV bilat#, ICV#
Bartley et al., 1997	NIMH	10/9	18-54	TBV, LH #, RH #, gyral symmetry, gyral patterns
Betjemann et al., 2010	CLDRC	41/30	11-23	TCV#, cGM#, cWM#, PFC
Brans et al., 2010	NTR/UMCTS	38/41	30 (8)[c]	V-W CT Δ over 5 yrs
Brun et al., 2008	QTIMS	23/23	22-25	FR lobe L/R/ bilat, TEMP lobe L/R/ bilat, PAR lobe L/R/bilat, OCC lobe L/R/ bilat
Brun et al., 2009 (also see Brun et al., 2011)	QTIMS	23/23	22-25	TBV#, FR lobe#, PAR lobe#, TEMP lobe#, OCC lobe#, Limbic lobe, LV bilat, BG#, THAL L-R#, V-W TBM
Brun et al., 2010	QTIMS	80/83	20-30	34 ROIs SA L/R, 34 ROIs GM L/R, 34 ROIs CT L/R
Cannon et al., 2006 (also see Thompson et al., 2001)	FNTR	10/10	48 (3)[c]	V-W GMd
Carmelli et al., 1998	NHLBI	74/71	68-79	ICV#, TBV#, CSF, WM hyperintensities
Carmelli et al., 2002b	NHLBI	72/67	69-80	FR lobe L/ R, TEMP lobe L/R, PAR lobe L/R, OCC lobe L/R, LV ant+post horn L/R, LV TEMP horn L/R
Carmelli et al., 2002a	NHLBI	72/70	69-80	WM hyperintensities
Chen et al., 2011	VETSA	110/93	51-59	V-W SA clustering
Chou et al., 2009	QTIMS	38/28	20-27	LV bilat#, LV L/R, V-W LV shape
Eyler et al., 2011a	VETSA	110/92	51-59	LV L/R, inf LV L/R, 3rdV, THAL L/R, CAUD L/R, PUT L/R, GP L/R, HIP L/R, AMYG L/R, NAcc L/R
Eyler et al., 2011b	VETSA	110/92	51-59	FR L/R SA, PAR L/R SA, OCC L/R SA, lat TEMP L/R SA, med TEMP L/R SA, CING cortex L/R SA
Geschwind et al., 2002	NHLBI	72/67	69-80	FR lobe L/R, TEMP lobe L/R, PAR lobe L/R, OCC lobe L/R, RH #, LH #, TBV
Gilmore et al., 2010	UNC	41/50	0-1 week	ICV#, LV bilat#, GM#, WM#, early myelinated WM, CSF, cortical GM, cortical uWM, SubCort GM, CB#, PFC GM, FR GM#, PAR GM#, OCC GM#, PreFR uWM, FR uWM#, PAR uWM#, OCC uWM#, PreFR, FR lobe#, PAR lobe#, OCC lobe#, GM L/R, uWM L/R, RH#, LH#, CC msa#; *Regional GM/uWM/vol*: sup PF L/R, inf PF L/R, sup FR L/R, inf FR L/R, sup PAR L/R, inf PAR L/R, sup OCC L/R, inf OCC L/R
Hulshoff Pol et al., 2006	NTR/UMCTS	54/58	19-69	V-W GMd, V-W WMd
Joshi et al., 2011	QTIMS	89/97	21-27	V-W CT, V-W cortical vol
Kremen et al., 2010b (also see Kremen et al., 2010a)	VETSA	110/92	51-59	ICV#, cGM L/ R, cWM L/ R, WM hypointensities, THAL L/R#, CAUD L/R#, PUT L/R#, GP L/R#, NAcc L/R, HIP L/R#, AMYG L/R, CB GM L/R, CB WM L/R, LV L/R#, inf LV L/R, 3rdV#, 4thV; *Regional CT*: SFG L/R#, MFG ros L/R#, MFG cau L/R#, OpIFG L/R#, TriIFG L/R#, OrbIFG L/R#, OFC lat L/R#, OFC med L/R#, OFC FR pole L/R#, PreCG L/R#, OFC PCL L/R, PostCG L/R#, SMG L/R#, sup PAR L/R, inf PAR L/R, PCUN L/R#, LG L/R#, PCAL L/R, CUN L/R#, lat OCC L/R, STG L/R#, MTG L/R#, ITG L/R#, HG L/R, Banks STS L/R, ERC L/R, PHG L/R#, TEMP pole L/R, FG L/R, ACC ros L/R#, ACC cau L/R#, PCC ros L/R#, CING RSC L/R#
Lenroot et al., 2009	PTS/NIMH	107/47	5-18	V-W CT age 5-18, V-W CT age 5, 12, 18
Panizzon et al., 2009	VETSA	110/92	51-59	*Regional SA/CT*: total GM, FR L/R, TEMP L/R, PAR L/R, OCC L/R, lat OFC L/R, SFG L/R, sup PAR L/R, ERC L/R, PHG L/R, PostCG L/R, PC L/R, PCUN L/R, MTG L/R, lat OCC L/R
Panizzon et al., 2012	VETSA	89/68	51-60	HIP L/R
Pennington et al., 2000[b]	CLDRC	9/9	19 (4)[c]	Cortical Factor, Subcortical Factor, TCV, cGM L/R
Peper et al., 2009	NTR	45/62	9	ICV#, TBV#, LV bilat#, GM#, WM#, CB#, V-W GMd, V-W WMd
Pfefferbaum et al., 2000	NHLBI	45/40	68-78	CC msa total#, CC msa genu, CC msa isthmus, CC msa splenium, CC msa height, CC msa length, LV L/R/bilat#, ICV
Pfefferbaum et al., 2001	NHLBI	15/18	70-82	CC msa
Pfefferbaum et al., 2004	NHLBI	34/37	68-79	*T1/T2/* Δ: CC msa total, msa genu, msa body, msa splenium, msa height, msa length, LV L/R/bilat
Posthuma et al., 2000	NTR/UMCTS	53/58	19-69	CB#, ICV
Posthuma et al., 2003; Posthuma et al., 2002	NTR/UMCTS	54/58	19-69	GM, WM, CB
Quiggle et al., 2011	QTIMS	121/162	20-30	*Regional CT*: SFG L/R#, MFG L/R#, IFG L/R#, PreCG L/R#, OFG lat L/R#, OFG med L/R#, CING L/R#, MedFG L/R#, SPG L/R#, SMG L/R#, AG L/R#, PCUN L/R#, PostCG L/R#, STG L/R#, MTG L/R#, ITG L/R#, uncus L/ R#, OTG med L/R#, OTG lat L/ R#, PHG L/R#, OCC pole L/R#, SOG L/R#, MOG L/R#, IOG L/R#, CUN L/R#, LG L/R#, insula L/R#, HIP L/R
Rimol et al., 2010	VETSA	110/92	51-59	V-W CT
Scamvougeras et al., 2003	NIMH	14/12	16-41	CC msa#
Schmitt et al., 2007	PTS/NIMH	127/30	5-18	TCV, LV bilat, CC msa, THAL L-R#, BG#, CB

https://doi.org/10.1017/thg.2012.11 Published online by Cambridge University Press

TABLE 1
Continued.

Reference	Cohort	*n* pairs MZ/DZ	Age range	Phenotypes[a]
Schmitt et al., 2008	PTS/NIMH	107/47	5-18	*Regional CT*: SFG L/R#, MFG L/R#, IFG L/R#, PreCG L/R#, OFG lat L/R#, OFG med L/R#, CING L/R#, MedFG L/R#, SPG L/R#, SMG L/R#, AG L/R#, PCUN L/R#, PostCG L/R#, STG L/R#, MTG L/R#, ITG L/R#, uncus L/ R#, OTG med L/R#, OTG lat L/ R#, PHG L/R#, OCC pole L/R#, SOG L/R#, MOG L/R#, IOG L/R#, CUN L/R#, LG L/R#, insula L/R#
Schmitt et al., 2009	PTS/NIMH	107/47	5-18	V-W CT
Schmitt et al., 2010	PTS/NIMH	127/30	5-18	FR GM, OCC GM#, PAR GM, TEMP GM, FR WM, OCC WM#, PAR WM, TEMP WM
Stein et al., 2009	QTIMS	81/44	20-30	HIP L/R#, V-W HIP shape
Stein et al., 2011	QTIMS	85/99	20-30	CAUD L/R#, CAUD average
Sullivan et al., 2001	NHLBI	44/40	68-78	HIP bilat#, LV TEMP horn bilat, CC msa, ICV, HIP L/R, LV TEMP horn L/R
van Erp et al., 2004[b]	FNTR	28/26	49 (4)[c]	HIP bilat#, ICV#, cortical GM, HIP corrected for cortical GM
van Leeuwen et al., 2009	NTR	45/62	9	TBV, cGM#, cWM#
van Soelen et al., 2011a	NTR	T1: 38/46 T2: 23/28	T1: 9 T2:12	*T1/T2/ Δ:* TBV, TCV#, cGM, cWM, CB, CB GM, CB WM, LV bilat, 3rdV#
van Soelen et al., 2011b	NTR	T1: 38/46 T2: 23/28	T1: 9 T2:12	GM, mean CT, SA, GM T2, mean CT T2, SA T2
van Soelen et al., 2012	NTR	T1: 38/46 T2: 23/28	T1: 9 T2:12	V-W CT Δ 9-12 yrs
Wallace et al., 2006	PTS/NIMH	90/37	5-18	TCV#, GM, WM, FR lobe#, PAR lobe#, TEMP lobe#, FR GM, PAR GM, TEMP GM, FR WM, PAR WM, TEMP WM, CAUD, CC msa#, LV bilat, CB#
Wallace et al., 2010	PTS/NIMH	107/53	4-19	TBV#, GM#, WM#, FR GM#, PAR GM#, TEMP GM#, FR WM#, PAR WM#, TEMP WM#, LV bilat#, CAUD
Wright et al., 2002	NIMH	10/10	18-54	TBV#, LV bilat#; *Regional GMd*: PreCG L/R, SPL L/R, PMC L/R, PostCG R/L, PCUN L/R, DLPFC L/R, FR pole L/R, OFC L/R, (V1) L/R, (V2,V3) L/R, PS cortex L/R, ITG L/R, MTG L/R, STG L/R, PC gyrus L/R, ant mid-CING gyrus L/R, AC gyrus L/R, PHG L/R, CING RSC L/R, PC gyrus L/R, med FR lobe L/R, uncus L/R, OTG L/R, inf post TEMP lobe L/R, ant TEMP pole L/R, AG L/R, SMG L/R, HG L/R, STG L/R, inf PostCG L/R, IFG L/R, DLPFC L/R, VLPFC L/R, insula L/R, HIP L/R#, THAL L/R#, corpus striatum L/R, PUT L/R#, CB L/R, brain stem L/R
Yoon et al., 2010	QNTS	57/35	8	TBV#, LH#, RH#, LV L/R/bilat#, GM#, GM L/R, cortical GM L/R, subcortical GM L/R, WM#, WM L/R, CC msa#, LH CT, RH CT, FR L/R CT#, TEMP L/R CT#, PAR L/R CT#, OCC L/R CT#, V-W CT
Yoon et al., 2011	QNTS	57/35	8	TCV#, cerebrum L, cerebrum R, GM, GM L/R, WM, WM L/R, CC msa, FR GM L/R#, FR WM L/R#, TEMP GM L/R#, TEMP WM L/R#, PAR GM L/R#, PAR WM L/R#, OCC GM L/R#, OCC WM L/R#, PUT L/R#, THAL L/R#, CAUD L/R#, GP L/R#, LV L/R, CB L/R, V-W DBM

majority of DTI studies (~60%) have been carried out in a young adult sample, and the four meta-analyzed DTI phenotypes were based on samples that differed greatly in age: children, young adults, and elderly cohorts. The largest published twin study on DTI included 129 MZ pairs and 170 DZ pairs (Chiang et al., 2011).

Table 3 shows the results of the meta-analysis for genetic contributions to brain structural phenotypes. Overall, only 62 phenotypes were examined in three or more studies, and only 35 phenotypes were studied in more than 1,000 individuals. The largest number of independent studies has been carried out for lateral ventricular volume, with eight studies and 1,466 individuals from twin pairs, but the CIs are still wide. Only four phenotypes — ICV, TBV, lateral ventricle, and midsagittal area of the corpus callosum — included five or more cohorts, and only three of those phenotypes include over 1,000 twins. Other volumetric measures include two to four cohorts with an average $N = 641$ (range: 274–956). CT was limited to two or three cohorts with an average $N = 1{,}045$ (range: 588–1,278). For DTI, only four phenotypes were available for meta-analysis, including two cohorts each.

Additive genetic estimates were significantly different from zero for all meta-analyzed phenotypes, except FA of the callosal splenium and CT of the uncus, left parahippocampal gyrus, and left insula. The highest heritability was found for total WM volume (based on four cohorts and a total of 900 twins), and frontal WM volume (based on three cohorts and a total of 686 twins). The lowest heritability was found for uncus CT, which was based on only two cohorts, with a total of 874 twins.

Figure 1 depicts the relative influences of A, C, and E. What is apparent from these meta-analyses is that, although individual studies often found the common environmental

https://doi.org/10.1017/thg.2012.11 Published online by Cambridge University Press

TABLE 1
Continued.

Reference	Cohort	*n* pairs MZ/DZ	Age range	Phenotypes[a]
Family/pedigree studies				
Atwood et al., 2004	FHS	1330 indiv	34-88	WM hyperintensities
DeStefano et al., 2009	FHS	1538 indiv	34-97	TBV, FR lobe, TEMP lobe, PAR lobe, OCC lobe, HIP, LV, TEMP horn, WM hyperintensities
Glahn et al., 2010	SAFHS	333 indiv	26-85	PCC/PCUN GMd, med PFC GMd, TEMP–PAR L GMd, TEMP–PAR R GMd, CB L GMd, CB R GMd, CB tonsil GMd, PHG L GMd
Kochunov et al., 2009	SAFHS	357 indiv	19-85	WM hyperintensities, Subcortical WM hyperintensities, Ependymal WM hyperintensities
Winkler et al., 2010	SAFHS	486 indiv	26-85	*Regional CT/SA/GM s-b/GM v-b*: SFG, MFG ros, MFG cau, OpIFG, TriIFG, OrbIFG, OFC lat, OFC med, FR pole, PreCG, PCL, ERC, PHG, TEMP pole, FG, STG, MTG, ITG, HG, Banks STS, PostCG, SMG, SPC, IPC, PCUN, LG, PCAL, CUN, OCC lat, CING ros ant, CING cau ant, CING post, CING isthmus, insula

Note: Abbreviations: 3rdV, third ventricle; 4thV, fourth ventricle; A, additive genetic; AC, anterior cingulate; ACC, anterior cingulate cortex; AG, angular gyrus; AMYG, amygdala; ant, anterior; BG, basal ganglia; C, common environment; CAUD, caudate nucleus; cau, caudal; CB, cerebellum; CC, corpus callosum; cGM, cerebral gray matter; CING, cingulate cortex; CS, central sulcus; CSF, cerebrospinal fluid; CST, corticospinal tract; CT, cortical thickness; CUN, cuneus; cWM, cerebral white matter; DBM, deformation-based morphometry; DLPFC, dorsolateral prefrontal cortex; DZ, dizygotic; E, unique environment; ERC, entorhinal cortex; F, female; FG, fusiform gyrus; FR, frontal; GM, grey matter; GMd, grey matter density; GP, globus pallidus; HG, Heschl's gyrus; HIP, hippocampus; ICV, intracranial volume; IFG, inferior frontal gyrus; indiv, individuals; inf, inferior; IOG, inferior occipital gyrus; IPC, inferior parietal cortex; ITG, inferior temporal gyrus; lat, lateral; LG, lingual gyrus; LH, left hemisphere; LV, lateral ventricle(s); M, male; med, medial; MedFG, medial frontal gyrus; MFG, middle frontal gyrus; MFL, medial frontal lobe; MOG, middle occipital gyrus; msa, midsagittal area; MTG, middle temporal gyrus; MZ, monozygotic; NA, not available; NAcc, nucleus accumbens; OCC, occipital, occipito; OFC, orbitofrontal cortex; OFG, orbitofrontal gyrus; OpIFG, pars opercularis; ORB, orbital, orbito; OrbIFG, pars orbitalis; OTG, occipito-temporal gyrus; PAR, parietal; PC, posterior cingulate; PCC, posterior cingulate cortex; PCAL, pericalcarine cortex; PCL, paracentral lobule; PCUN, precuneus; PF, prefrontal; PHG, parahippocampal gyrus; PMC, premotor cortex; post, posterior; PostCG, postcentral gyrus; PreCG, precentral gyrus; PS, peristriate; PUT, putamen; RH, right hemisphere; rostral, ros; RSC, retrosplenial cortex; SA, surface area; s-b, surface-based; SFG, superior frontal gyrus; SFL, superior frontal lobe; SMG, supramarginal gyrus; SOF, superior orbitofrontal; SOG, superior occipital gyrus; SPC, superior parietal cortex; SPG, superior parietal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; STL, superior temporal lobe; STS, superior temporal sulcus; sup, superior; T1, T2, time 1, time 2; TBM, tensor-based morphometry; TBV, total brain volume; TCV, total cerebral volume; TEMP, temporal; THAL, thalamus; TriIFG, pars triangularis; uWM: unmyelinated white matter; V1, V2, V3, primary, secondary, tertiary visual cortex; v-b, volume-based; VLPFC, ventrolateral prefrontal cortex; V-W, voxel-wise; WM, white matter; WMd, white matter density; Δ, change.
Cohort/Study Abbreviations: CLDRC, Colorado Learning Disabilities Research Center; FHS, Framingham Heart Study; FNTR, Finnish National Twin Registry; NHLBI, National Heart, Lung, and Blood Institute Twin Study; NIMH, National Institute of Mental Health; NTR, Netherlands Twin Registry; QNTS, Quebec Newborn Twin Study; QTIMS, Queensland Twin Imaging Study; PTS, Pediatric Twin Study; SAFHS, San Antonio Family Heart Study; TEDS, Twins Early Development Study; UMCTS, Utrecht Medical Centre Twin Sample; UNC, University of North Carolina; VETSA, Vietnam Era Twin Study of Aging.
[a] Phenotypes are volumes unless otherwise specified; [b] These studies reported on a patient sample and a healthy control sample. Only the estimates for the healthy controls sample are included here; [c] No age range reported, only mean (standard deviation); [#] Estimate included in meta-analysis for that phenotype.

component to be insignificant or zero, when combining the samples, most phenotypes appear to have a common environmental variance component, although this component is often much smaller than the additive genetic and unique environmental components.

Figure 2 shows CIs around the meta-heritability estimates. CIs are tight for ICV, TBV, TCV, total GM and WM volumes, hemispheric volumes, three of the four regional FA measures, most of the average lobar CT measures, and about half of the regional CT measures; but CIs are wide for most lobar volumes, cerebellum, subcortical structures, lateral ventricle volumes, midsagittal area of the corpus callosum, splenium FA, and about half of the regional CT measures.

Our meta-analyses clearly confirm brain structure is under strong genetic control, including ICV, TBV, TCV, hemispheric volumes, cerebral lobe volumes, total and regional GM and WM volumes (heritabilities for WM volumes tend to be higher than for GM volumes), cerebellar volumes, and subcortical structures, as well as area measures of the corpus callosum.

Plotting the average size of meta-analyzed structures against the meta-estimate of heritability (Figure 3) shows that smaller structures tend to have lower heritability values than global-based and lobar-based measures. Also, while the global- and lobar-based measures consistently show high heritability, smaller structures show great variability across regions.

Genetic and Environmental Effects on Brain Function

Compared to brain structure, there is still relatively little known about the heritability of task-related blood-oxygenation-level-dependent (BOLD) signal phenotypes as measured with functional MRI (fMRI), but evidence is now emerging that task-related brain activity as measured with fMRI might be significantly heritable, although results are mixed, ranging from no genetic effect to strong genetic influences (Blokland et al., 2008; Blokland et al., 2011; Côté et al., 2007; Koten et al., 2009; Matthews et al., 2007; Park et al., 2012; Polk et al., 2007). Sample descriptions and variance component estimates for fMRI studies are summarized in Table 4. For fMRI studies it was impossible to

https://doi.org/10.1017/thg.2012.11 Published online by Cambridge University Press

TABLE 2
Diffusion Tensor Imaging Twin and Family Studies

Reference	Cohort	*n* pairs MZ/DZ	Age range	Phenotypes
Brouwer et al., 2010	NTR & UMCTS	39/43	9	CC genu MTR, CC splenium MTR, UF L/R MTR, SLF L/R MTR, CC genu FA#, CC splenium FA#, UF L/R FA#, SLF L/R FA#, CC genu RD, CC splenium RD, UF L/R RD, SLF L/R RD, CC genu LD, CC splenium LD, UF L/R LD, SLF L/R LD
Chen et al., 2009	UNC	15/15	T1: 1 T2: 2	V-W FA, MD, V-W FA Δ, MD Δ
Chiang et al., 2008	QTIMS	22/23	20-30	V-W GFA, V-W JSD
Chiang et al., 2009	QTIMS	23/23	20-30	FR L FA, FR R FA, PAR L FA, PAR R FA, TEMP L FA, TEMP R FA, OCC L FA, OCC R FA, V-W FA
Chiang et al., 2011	QTIMS	129/170	12-30	V-W FA
Hageman et al., 2009	QTIMS	23/23	20-30	CC FA, CC MD, CC Lattice Index
Jahanshad et al., 2010	QTIMS	60/45	20-30	aTR FA, CST FA, CING gyrus FA, Cingulum FA, Forceps major FA, Forceps minor FA, inf OFF FA, ILF FA, SLF FA#, UF FA#, TEMP SLF FA, aTR tGA, CST tGA, CING gyrus tGA, Cingulum tGA, Forceps major tGA, Forceps minor tGA, inf OFF tGA, ILF tGA, SLF tGA, UF tGA, TEMP SLF tGA, aTR MD, CST MD, CING gyrus MD, Cingulum MD, Forceps major MD, Forceps minor MD, inf OFF MD, ILF MD, SLF MD, UF MD, TEMP SLF MD, V-W FA & tGA
Lee et al., 2008	QTIMS	22/23	20-30	V-W FA, GA
Lee et al., 2009 (also see Lee et al., 2010a; Lee et al., 2010b)	QTIMS	25/25	20-30	V-W FA, GA, tGA, Log(DT), FR L/R WM FA, FR L/R WM tGA, OCC L/R WM FA, OCC L/R WM tGA, PAR L/R WM FA, PAR L/R WM tGA, TEMP L/R WM FA, TEMP L/R WM tGA, Total WM FA, Total WM tGA, FR L/R GM FA, FR L/R GM tGA, OCC L/R GM FA, OCC L/R GM tGA, PAR L/R GM FA, PAR L/R GM tGA, TEMP L/R GM FA, TEMP L/R GM tGA, Total GM FA, Total GM tGA
Pfefferbaum et al., 2001	NHLBI	15/18	70-82	CC genu FA#, CC splenium FA#
Family/pedigree studies				
Kochunov et al., 2010	SAFHS	467 indiv	19-85	FA, LD, RD, CC genu FA, CC body FA, CC splenium FA, Cingulum FA, CR FA, EC FA, IC FA, OFF FA, SLF FA, SS FA, CC genu LD, CC body LD, CC splenium LD, Cingulum LD, CR LD, EC LD, IC LD, OFF LD, SLF LD, SS LD, CC genu RD, CC body RD, CC splenium RD, Cingulum RD, CR RD, EC RD, IC RD, OFF RD, SLF RD, SS RD

Note: Abbreviations: aTR, anterior thalamic radiation; CC, corpus callosum; CING, cingulate; CR, corona radiata; CST, corticospinal tract; DZ, dizygotic; EC, external capsule; FA, fractional anisotropy; FR, frontal; GA, geodesic anisotropy; GM, grey matter; IC, internal capsule; ILF, inferior longitudinal fasciculus; indiv, individuals; inf, inferior; JSD, Jensen-Shannon divergence; L, left; LD, longitudinal diffusivity; MD, mean diffusivity; med, medial; MTR, magnetization transfer ratio; MZ, monozygotic; NA, not available; OCC, occipital, occipito; OFF, occipito-frontal fasciculus; OR, optic radiation; PAR, parietal; R, right; RD, radial diffusivity; SLF, superior longitudinal fasciculus; SS, sagittal stratum; sup, superior; T1, T2, time 1, time 2; TEMP, temporal; tGA, tangent of geodesic anisotropy; UF, uncinate fasciculus; V-W, voxel-wise; WM, white matter; Δ, change.
Cohort/Study Abbreviations: NHLBI, National Heart, Lung, and Blood Institute Twin Study; NTR, Netherlands Twin Registry; QTIMS, Queensland Twin Imaging Study; SAFHS, San Antonio Family Heart Study; UMCTS, Utrecht Medical Centre Twin Sample; UNC, University of North Carolina.
Estimate included in meta-analysis for that phenotype.

calculate meta-estimates, since only seven twin studies and one family study have been carried out thus far, with great variability in the designs used and phenotypes investigated. Studies are reviewed below.

In a preliminary study we attempted to quantify the heritability of brain activation during performance of an *n*-back working memory task as measured with BOLD fMRI in several frontal and parietal cortical regions of interest (ROIs) (Blokland et al., 2008). Our results suggested that individual variation in working-memory-related brain activation is, to some extent, influenced by genes, although non-genetic factors also play a large role. More recently, we extended this study to include a larger sample of twins, estimating heritability at the voxel level rather than on an ROI basis (Blokland et al., 2011). In this voxel-wise study, we found considerable influence of genetic factors on working-memory task-related brain activation, with genes accounting for up to 65% of the variance, particularly in inferior, middle, and superior frontal gyri, left supplementary motor area, pre-central and post-central gyri, middle cingulate cortex, superior medial gyrus, angular gyrus, superior parietal lobule (including precuneus), and superior occipital gyri. Functional MRI provides us with the potential to investigate whether heritable individual differences in cognition (Deary et al., 2006) are related to brain activation patterns that differ qualitatively among individuals. Interestingly, we found that task-related brain activation is not strongly associated with task performance or full-scale intelligence quotient (FIQ) (phenotypic correlations did not exceed .35), suggesting that there may be genetic and environmental influences on task-related brain activity that are independent of how well the task is actually being performed. Koten et al. (2009) also investigated genetic influences on *n*-back working memory brain activation voxel-wise, in a small sample of 10 male MZ twin pairs with one extra non-twin brother each. They found significant genetic influences on brain activation in visual cortex, temporo-parietal and frontal areas, and anterior cingulate cortex. However, this heritable activation was not task-related per se, as it occurred during the distraction phase of the task

https://doi.org/10.1017/thg.2012.11 Published online by Cambridge University Press

TABLE 3

Variance Component Estimates for Imaging Phenotypes According to the Meta-Analysis

	Variance Component Estimates (95% CI)[b]			*n*		
Phenotype[a]	A%	C%	E%	samples	indiv	References[c]
Global Volumes						
intracranial volume	79.2 (72.9, 85.4)	7.3 (0, 24.2)	13.7 (2.1, 25.3)	6	1422	Baaré et al., 2001; Carmelli et al., 1998; Gilmore et al., 2010; Kremen et al., 2010b; Peper et al., 2009; van Erp et al., 2004
total brain volume	82.8 (71.6, 94.0)	7.1 (0, 17.3)	9.9 (6.8, 13.0)	7	1364	Baaré et al., 2001; Brun et al., 2008; Carmelli et al., 1998; Peper et al., 2009; Wallace et al., 2010; Wright et al., 2002; Yoon et al., 2010
total cerebral volume	83.5 (74.9, 92.2)	2.8 (0, 8.6)	13.6 (4.2, 23.1)	4	748	Betjemann et al., 2010; van Soelen et al., 2011a; Wallace et al., 2006; Yoon et al., 2011
total GM	72.4 (62.1, 82.7)	9.9 (0.1, 19.7)	17.5 (8.6, 26.3)	4	900	Gilmore et al., 2010; Peper et al., 2009; Wallace et al., 2010; Yoon et al., 2010
total WM	85.2 (82.3, 88.1)	1.0 (0, 2.8)	13.6 (10.1, 17.2)	4	900	Gilmore et al., 2010; Peper et al., 2009; Wallace et al., 2010; Yoon et al., 2010
cerebral GM	67.4 (43.2, 91.7)	16.5 (0, 42.8)	15.9 (14.0, 17.8)	3	580	Baaré et al., 2001; Betjemann et al., 2010; van Leeuwen et al., 2009
cerebral WM	79.3 (66.8, 91.8)	1.0 (0, 2.9)	19.7 (9.2, 30.3)	3	580	Baaré et al., 2001; Betjemann et al., 2010; van Leeuwen et al., 2009
total LH	73.3 (66.7, 80.0)	12.6 (3.7, 21.4)	14.1 (9.2, 19.0)	4	682	Bartley et al., 1997; Geschwind et al., 2002; Gilmore et al., 2010; Yoon et al., 2010
total RH	62.2 (52.7, 71.6)	21.6 (16.3, 26.9)	16.5 (10.0, 23.0)	4	682	Bartley et al., 1997; Geschwind et al., 2002; Gilmore et al., 2010; Yoon et al., 2010
frontal lobe	68.6 (48.5, 88.7)	13.3 (0, 35.4)	18.1 (12.0, 24.2)	3	528	Brun et al., 2009; Gilmore et al., 2010; Wallace et al., 2006
temporal lobe	74.3 (42.8, 100)	14.6 (0, 48.3)	11.1 (8.9, 13.2)	2	346	Brun et al., 2009; Wallace et al., 2006
parietal lobe	72.7 (51.3, 94.1)	13.0 (0, 36.1)	14.7 (11.6, 17.8)	3	528	Brun et al., 2009; Gilmore et al., 2010; Wallace et al., 2006
occipital lobe	60.3 (33.7, 87.0)	26.3 (0, 56.3)	13.3 (10.1, 16.6)	2	274	Brun et al., 2009; Gilmore et al., 2010
frontal GM[h]	64.8 (41.0, 88.7)	11.9 (0.0, 28.4)	22.1 (10.4, 33.8)	3	686	Gilmore et al., 2010; Wallace et al., 2010; Yoon et al., 2011
temporal GM[h]	76.5 (48.1, 100)	6.9 (0.0, 19.6)	16.8 (0.7, 32.8)	2	504	Wallace et al., 2010; Yoon et al., 2011
parietal GM[h]	59.4 (53.3, 65.4)	11.6 (3.2, 20.0)	29.0 (15.3, 42.7)	3	686	Gilmore et al., 2010; Wallace et al., 2010; Yoon et al., 2011
occipital GM[h]	49.9 (45.1, 54.8)	17.0 (8.4, 25.6)	32.9 (22.3, 43.5)	3	680	Gilmore et al., 2010; Schmitt et al., 2010; Yoon et al., 2011
frontal WM[h]	84.0 (73.7, 94.3)	0.0 (0.0, 0.0)	16.0 (5.7, 26.3)	3	686	Gilmore et al., 2010; Wallace et al., 2010; Yoon et al., 2011
temporal WM[h]	75.7 (51.3, 100)	6.6 (0.0, 18.6)	17.8 (5.4, 30.1)	2	504	Wallace et al., 2010; Yoon et al., 2011
parietal WM[h]	69.0 (61.1, 77.0)	7.0 (1.9, 12.1)	24.0 (11.0, 37.0)	3	686	Gilmore et al., 2010; Wallace et al., 2010; Yoon et al., 2011
occipital WM[h]	62.3 (45.6, 79.1)	7.9 (0.0, 17.4)	29.8 (13.5, 46.1)	3	680	Gilmore et al., 2010; Schmitt et al., 2010; Yoon et al., 2011
Cerebellar Volume						
cerebellum	60.0 (33.6, 86.4)	25.2 (4.3, 46.1)	14.8 (8.2, 21.3)	4	872	Gilmore et al., 2010; Peper et al., 2009; Posthuma et al., 2000; Wallace et al., 2006
Subcortical Volumes						
putamen L	78.4 (57.7, 99.1)	3.6 (0, 16.4)	18.2 (8.9, 27.4)	3	628	Kremen et al., 2010b; Wright et al., 2002; Yoon et al., 2011
putamen R	81.6 (78.0, 85.3)	0 (0, 0)	19.0 (14.0, 24.0)	3	628	Kremen et al., 2010b; Wright et al., 2002; Yoon et al., 2011
caudate L	72.3 (59.4, 85.2)	11.5 (8.9, 14.1)	16.2 (3.5, 28.9)	3	956	Kremen et al., 2010b; Stein et al., 2011; Yoon et al., 2011
caudate R	64.0 (49.9, 78.1)	14.7 (9.4, 19.9)	21.3 (12.4, 30.2)	3	956	Kremen et al., 2010b; Stein et al., 2011; Yoon et al., 2011
thalamus L-R	55.0 (31.8, 78.1)	28.3 (1.9, 54.8)	16.7 (13.4, 20.0)	2	406	Brun et al., 2009; Schmitt et al., 2007
thalamus L	61.0 (42.4, 79.6)	2.5 (0, 7.2)	36.7 (21.7, 51.7)	3	628	Kremen et al., 2010b; Wright et al., 2002; Yoon et al., 2011
thalamus R	52.4 (35.6, 69.2)	17.7 (11.8, 23.5)	29.9 (18.2, 41.6)	3	628	Kremen et al., 2010b; Wright et al., 2002; Yoon et al., 2011
globus pallidus L	70.7 (61.1, 80.3)	3.4 (0.2, 6.6)	25.9 (19.4, 32.3)	2	588	Kremen et al., 2010b; Yoon et al., 2011
globus pallidus R	75.3 (74.7, 76.0)	0 (0, 0)	24.7 (24.0, 25.3)	2	588	Kremen et al., 2010b; Yoon et al., 2011
basal ganglia	62.3 (45.3, 79.4)	20.5 (0, 42.2)	17.2 (12.5, 21.8)	2	406	Brun et al., 2008; Schmitt et al., 2007
hippocampus L-R	45.5 (36.0, 54.9)	6.1 (0, 14.9)	48.4 (30.2, 66.7)	2	276	Sullivan et al., 2001; van Erp et al., 2004
hippocampus L	58.5 (51.2, 65.7)	0.7 (0, 1.8)	41.3 (35.4, 47.1)	3	694	Kremen et al., 2010b; Stein et al., 2009; Wright et al., 2002
hippocampus R	53.2 (36.0, 70.5)	5.4 (0, 13.6)	41.4 (32.3, 50.5)	3	694	Kremen et al., 2010b; Stein et al., 2009; Wright et al., 2002
Cortical Thickness						
frontal L	76.1 (72.3, 80.0)	0.7 (0.0, 1.3)	23.2 (18.7, 27.7)	2	588	Panizzon et al., 2009; Yoon et al., 2010
frontal R	65.0 (54.7, 75.3)	2.7 (0.2, 5.3)	32.3 (19.4, 45.1)	2	588	Panizzon et al., 2009; Yoon et al., 2010
temporal L	60.8 (56.3, 65.3)	2.1 (0.1, 4.0)	38.5 (33.4, 43.6)	2	588	Panizzon et al., 2009; Yoon et al., 2010

https://doi.org/10.1017/thg.2012.11 Published online by Cambridge University Press

TABLE 3
Continued.

Phenotype[a]	Variance Component Estimates (95% CI)[b] A%	C%	E%	*n* samples	indiv	References[c]
Cortical Thickness						
temporal R	62.6 (53.6, 71.6)	6.2 (0.4, 12.0)	31.2 (16.4, 46.0)	2	588	Panizzon et al., 2009; Yoon et al., 2010
parietal L	69.3 (59.7, 78.9)	2.1 (0.1, 4.0)	28.6 (17.1, 40.2)	2	588	Panizzon et al., 2009; Yoon et al., 2010
parietal R	65.2 (47.2, 83.2)	0 (0, 0)	34.8 (16.8, 52.8)	2	588	Panizzon et al., 2009; Yoon et al., 2010
occipital L	69.7 (67.2, 72.3)	1.4 (0.1, 2.7)	28.9 (25.0, 32.7)	2	588	Panizzon et al., 2009; Yoon et al., 2010
occipital R	54.8 (49.0, 60.6)	13.1 (0.8, 25.3)	32.1 (25.7, 38.6)	2	588	Panizzon et al., 2009 Yoon, et al., 2010
superior frontal gyrus L	60.8 (49.7, 72.0)	10.2 (0.0, 23.1)	31.7 (20.6, 42.8)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
superior frontal gyrus R	53.6 (42.4, 64.8)	12.4 (0.0, 28.1)	34.9 (21.7, 48.0)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
middle frontal gyrus L[e]	49.2 (41.9, 56.5)	11.1 (0.0, 25.1)	42.8 (26.9, 58.8)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
middle frontal gyrus R[e]	48.1 (43.9, 52.3)	10.2 (2.5, 17.9)	43.0 (32.6, 53.4)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
inferior frontal gyrus L[f]	40.7 (33.8, 47.7)	13.3 (0.0, 30.1)	44.7 (32.8, 56.5)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
inferior frontal gyrus R[f]	41.5 (34.4, 48.7)	12.8 (0.0, 29.1)	48.7 (40.6, 56.8)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
medial frontal gyrus L	44.2 (38.2, 50.1)	22.0 (0.0, 44.5)	34.5 (18.6, 50.3)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
medial frontal gyrus R	36.7 (35.4, 38.0)	24.6 (0.0, 49.8)	38.0 (13.5, 62.5)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
orbitofrontal cortex lat L	32.4 (19.7, 45.0)	6.2 (0.0, 14.1)	62.8 (55.2, 70.4)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
orbitofrontal cortex lat R	37.1 (24.5, 49.8)	6.2 (0.0, 14.1)	57.1 (50.1, 64.2)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
orbitofrontal cortex med L	24.7 (15.3, 34.0)	12.0 (0.0, 27.1)	63.8 (57.1, 70.6)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
orbitofrontal cortex med R	34.9 (26.7, 43.1)	2.7 (0.0, 6.0)	62.9 (52.9, 72.8)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
precentral gyrus L	53.3 (43.1, 63.6)	6.2 (0.0, 14.1)	37.4 (30.6, 44.1)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
precentral gyrus R	49.7 (41.7, 57.7)	8.7 (1.0, 16.4)	39.0 (27.4, 50.6)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
postcentral gyrus L	59.4 (51.4, 67.5)	3.1 (0.0, 7.0)	36.6 (24.0, 49.1)	3	1278	Kremen, et al., 2010b; Quiggle, et al., 2011; Schmitt, et al., 2008
postcentral gyrus R	50.7 (36.5, 64.9)	11.1 (0.0, 25.1)	36.0 (31.5, 40.6)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
cingulate L[g]	26.3 (16.4, 36.2)	19.7 (0.8, 38.5)	55.8 (47.8, 63.8)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
cingulate R[g]	27.6 (21.7, 33.4)	20.0 (2.9, 37.0)	52.0 (39.8, 64.3)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
superior temporal gyrus L	50.3 (43.7, 56.9)	2.2 (0.0, 5.0)	46.6 (37.2, 56.0)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
superior temporal gyrus R	52.6 (45.0, 60.3)	4.2 (0.0, 10.2)	42.4 (31.2, 53.5)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
middle temporal gyrus L	23.9 (4.8, 43.1)	13.7 (0.0, 31.2)	63.7 (60.3, 67.0)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
middle temporal gyrus R	32.7 (21.5, 43.9)	10.6 (0.0, 24.1)	57.1 (50.8, 63.4)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
inferior temporal gyrus L	35.3 (21.9, 48.7)	8.4 (0.0, 19.1)	56.3 (53.4, 59.1)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
inferior temporal gyrus R	28.9 (15.9, 41.9)	12.4 (4.3, 20.5)	58.8 (48.0, 69.7)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
parahippocampal gyrus L	19.6 (0.0, 40.0)	15.9 (0.0, 32.3)	63.1 (49.5, 76.8)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
parahippocampal gyrus R	28.1 (6.4, 49.9)	10.4 (0.0, 23.1)	57.0 (34.1, 80.0)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
uncus L	2.4 (0.0, 5.1)	9.7 (0.0, 19.6)	88.5 (81.9, 95.1)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
uncus R	0.4 (0.0, 1.0)	12.3 (0.0, 24.9)	89.3 (79.4, 99.2)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
supramarginal gyrus L	46.6 (35.5, 57.6)	6.6 (0.0, 15.1)	45.0 (42.1, 47.9)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
supramarginal gyrus R	44.1 (38.7, 49.6)	4.9 (0.0, 11.1)	48.8 (40.3, 57.3)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
precuneus L	39.3 (16.3, 62.3)	10.2 (0.0, 23.1)	48.8 (23.7, 73.9)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
precuneus R	41.2 (25.3, 57.1)	6.6 (0.0, 15.1)	50.4 (30.8, 70.0)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
cuneus L	51.2 (26.1, 76.2)	5.8 (0.0, 13.1)	48.4 (22.9, 73.9)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
cuneus R	41.5 (29.6, 53.4)	5.3 (0.0, 12.1)	53.6 (44.3, 62.9)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008

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TABLE 3
Continued.

Phenotype[a]	Variance Component Estimates (95% CI)[b] A%	C%	E%	*n* samples	indiv	References[c]
Cortical Thickness						
superior parietal lobule L	37.8 (29.8, 45.7)	14.9 (0.0, 30.1)	43.4 (16.3, 70.6)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
superior parietal lobule R	47.2 (43.9, 50.5)	11.7 (0.0, 23.6)	36.6 (16.7, 56.4)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
angular gyrus L	33.1 (23.8, 42.3)	12.3 (0.0, 24.9)	52.7 (28.9, 76.5)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
angular gyrus R	32.3 (19.7, 44.9)	13.6 (0.0, 27.5)	50.2 (19.8, 80.7)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
occipito-temporal gyrus med L	48.7 (25.5, 71.8)	1.3 (0.0, 2.6)	50.0 (25.5, 74.5)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
occipito-temporal gyrus med R	49.8 (30.6, 69.0)	4.2 (0.9, 7.5)	46.6 (24.8, 68.5)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
occipito-temporal gyrus lat L	29.3 (28.0, 30.6)	11.7 (0.0, 23.6)	52.6 (32.7, 72.4)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
occipito-temporal gyrus lat R	46.6 (32.7, 60.5)	3.2 (0.0, 6.5)	49.5 (31.6, 67.4)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
occipital pole L	40.5 (33.9, 47.1)	16.2 (0.0, 32.7)	42.0 (30.7, 53.2)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
occipital pole R	32.6 (29.9, 35.2)	8.2 (4.9, 11.5)	59.2 (53.2, 65.1)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
lingual gyrus L	42.8 (28.1, 57.5)	3.5 (0.0, 8.0)	53.6 (37.9, 69.4)	3	1278	Kremen, et al., 2010b; Quiggle, et al., 2011; Schmitt, et al., 2008
lingual gyrus R	36.9 (12.0, 61.8)	5.8 (0.3, 11.2)	57.3 (37.8, 76.8)	3	1278	Kremen et al., 2010b; Quiggle et al., 2011; Schmitt et al., 2008
superior occipital gyrus L	39.4 (30.8, 48.0)	11.7 (0.0, 23.6)	48.9 (28.4, 69.4)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
superior occipital gyrus R	40.9 (36.9, 44.9)	10.4 (0.0, 21.0)	48.8 (34.2, 63.3)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
middle occipital gyrus L	29.8 (26.5, 33.1)	16.8 (0.0, 34.1)	53.4 (39.5, 67.3)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
middle occipital gyrus R	30.5 (25.9, 35.2)	17.5 (0.0, 35.4)	53.3 (32.1, 74.5)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
inferior occipital gyrus L	24.3 (11.7, 36.9)	18.4 (15.8, 21.1)	50.8 (34.3, 67.4)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
inferior occipital gyrus R	34.0 (22.8, 45.3)	4.5 (0.0, 9.2)	56.9 (36.4, 77.4)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
insula L	13.0 (0.0, 26.3)	14.9 (0.0, 30.1)	68.8 (63.5, 74.1)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
insula R	21.6 (13.0, 30.2)	9.1 (0.0, 18.3)	68.7 (67.4, 70.0)	2	874	Quiggle et al., 2011; Schmitt et al., 2008
Ventricular Volumes						
lateral ventricle L-R	44.0 (24.2, 63.7)	22.1 (6.6, 37.6)	33.9 (27.7, 40.2)	8	1466	Baaré et al., 2001; Chou et al., 2009; Gilmore et al., 2010; Peper et al., 2009; Pfefferbaum et al., 2000; Wallace et al., 2010; Wright et al., 2002; Yoon et al., 2010
lateral ventricle L	70.0 (59.7, 80.3)	2.9 (0, 8.7)	27.1 (22.5, 31.7)	3	758	Kremen et al., 2010b; Pfefferbaum et al., 2000; Yoon et al., 2010
lateral ventricle R	62.5 (37.7, 87.2)	8.7 (0, 26.2)	28.8 (21.2, 36.5)	3	758	Kremen et al., 2010b; Pfefferbaum et al., 2000; Yoon et al., 2010
third ventricle	73.7 (64.4, 83.0)	0 (0, 0)	26.3 (17.0, 35.6)	2	572	Kremen et al., 2010b; van Soelen et al., 2011a
White Matter Area Measure						
corpus callosum msa	56.8 (29.7, 83.8)	22.2 (3.4, 40.9)	21.1 (2.3, 39.8)	5	842	Gilmore et al., 2010; Pfefferbaum et al., 2000; Scamvougeras et al., 2003; Wallace et al., 2006; Yoon et al., 2010
White Matter Microstructure						
corpus callosum genu FA	36.9 (26.2, 47.5)	9.3 (1.1, 17.4)	53.9 (51.3, 56.4)	2	230	Brouwer et al., 2010; Pfefferbaum et al., 2001
corpus callosum splenium FA	29.9 (0, 62.5)	14.3 (1.7, 26.8)	55.8 (35.8, 75.9)	2	230	Brouwer et al., 2010; Pfefferbaum et al., 2001
uncinate fasciculus FA[d]	21.1 (19.4, 22.8)	9.7 (7.6, 11.7)	69.2 (68.9, 69.6)	2	374	Brouwer et al., 2010; Jahanshad et al., 2010
superior longitudinal fasciculus FA[d]	23.0 (19.5, 26.5)	2.6 (0, 7.3)	74.4 (66.2, 82.6)	2	374	Brouwer et al., 2010; Jahanshad et al., 2010

Note: Abbreviations: A, additive genetic; C, common environment; CI, confidence interval; E, unique environment; FA, fractional anisotropy; GM, grey matter; lat, lateral; L, left; LH, left hemisphere; L-R, bilateral; med, medial; msa, midsagittal area; *n* samples, *n* independent samples included in meta-estimate; *n* indiv, *n* individuals from complete twin pairs; R, right; RH, right hemisphere; WM, white matter.

[a] Phenotypes are volumes unless otherwise specified.

[b] Included variance component estimates are estimates under the full ACE model where available.

[c] References in this table are only those of the studies included in the meta-estimate. For a complete list of references for each phenotype, please refer to Tables 1 and 2.

[d,e,f,g,h] Variance component estimates for one study included in meta-estimate were average of [d] LH and RH estimates (Brouwer, et al., 2010); [e] estimates for rostral and caudal middle frontal gyrus (Kremen, et al., 2010b); [f] estimates for pars orbitalis, pars opercularis, and pars triangularis of inferior frontal gyrus (Kremen, et al., 2010b); [g] estimates for rostral and caudal anterior cingulate, rostral posterior cingulate, and retrosplenial cortex (Kremen, et al., 2010b); [h] LH and RH estimates (Yoon, et al., 2011).

rather than during the encoding and retrieval phases, that is, the task components of interest in a working memory task. Matthews et al. (2007) also used a cognitive task and found that genetic influences accounted for 38% of the variance in activation of the dorsal anterior cingulate cortex during an interference task.

Furthermore, Polk and co-workers (2007) showed that neural activity patterns in ventral visual cortex were significantly more similar in MZ twins than in DZ twins for face and place stimuli (although not for orthographic stimuli), suggesting that genetics plays a significant role in determining the cortical response to faces and places. Park et al. (2012) found heritable activation in the left visual and motor cortices in response to a simple visuo-motor checkerboard task.

Côté et al. (2007) found no indication of a genetic (or shared environmental) influence on the neural correlates of sadness, with both MZ and DZ twin correlations

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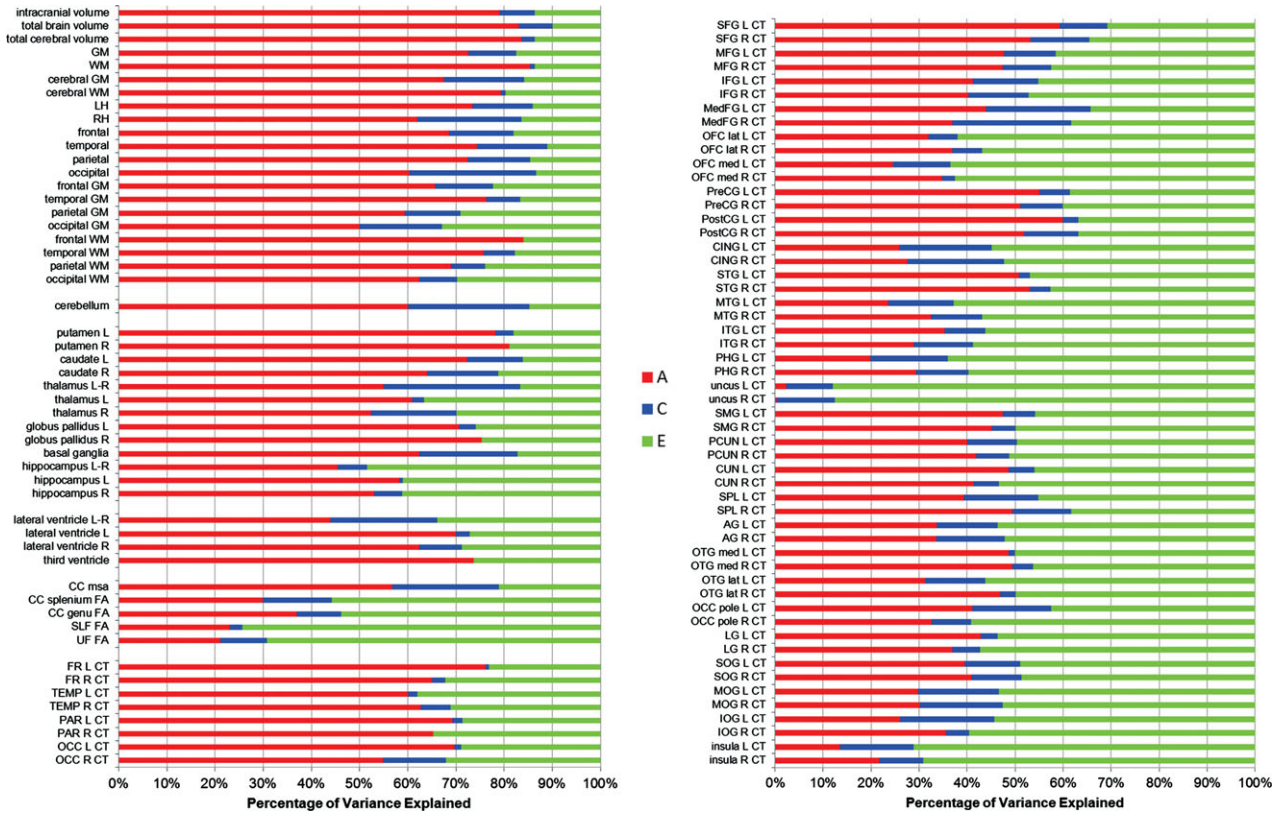

FIGURE 1

Relative influences of variance components A, C, and E on neuroimaging measures according to the meta-analysis.

nonsignificant for two areas of the brain previously correlated with the subjective experience of sadness. It is important to note that in our fMRI study (Blokland et al., 2008) we found that the method employed by Côté and colleagues, that is, using voxel counts and peak Z-scores within ROIs, suffers from restriction of range issues that may partly account for their negative findings.

Recently, in a large pedigree study, Glahn et al. (2010) investigated the genetic control over the default-mode network (DMN), a coherent resting-state brain network thought to characterize basal neural activity. Heritability for DMN functional connectivity was 42%. Genetic correlations between DMN regions indicate the same genetic factors contribute to variation in functional connectivity throughout the DMN. Left parahippocampal gyrus was genetically correlated with all other DMN regions. The posterior cingulate/precuneus, medial prefrontal cortex, and right cerebellum appeared to form a sub-network.

Discussion

Results of twin studies investigating the extent to which individual differences in brain structure and function are due to genetic and environmental influences have tended to be inconsistent. We carried out the first meta-analysis of twin studies of neuroimaging measures.

Overall, by aggregating the results of a number of previous twin studies, our meta-analyses provided more robust estimates of the relative magnitudes of genetic and environmental influences on neuroimaging measures. Because our analyses average estimates over samples of different sizes and demographic make-up, our findings are likely to be more generalizable than the source studies. Whereas older, smaller studies did not have sufficient power to detect the influence of shared environment, more recent, larger studies have reported significant shared environmental influences. When combining studies, we found a significant shared environmental variance component for many phenotypes. Our results indicate that A, C, and E factors each contribute significantly to brain structure, with CIs for these estimates considerably narrower than those in the source studies. This confirms that brain structure does not have a single or simple cause, and suggests that both genetic and environmental factors are potential targets for early detection and treatment of brain disorders.

According to the meta-analysis, global volumes, cerebellar volumes, subcortical volumes, ventricular volumes, corpus callosum area, and lobar CT measurements are all

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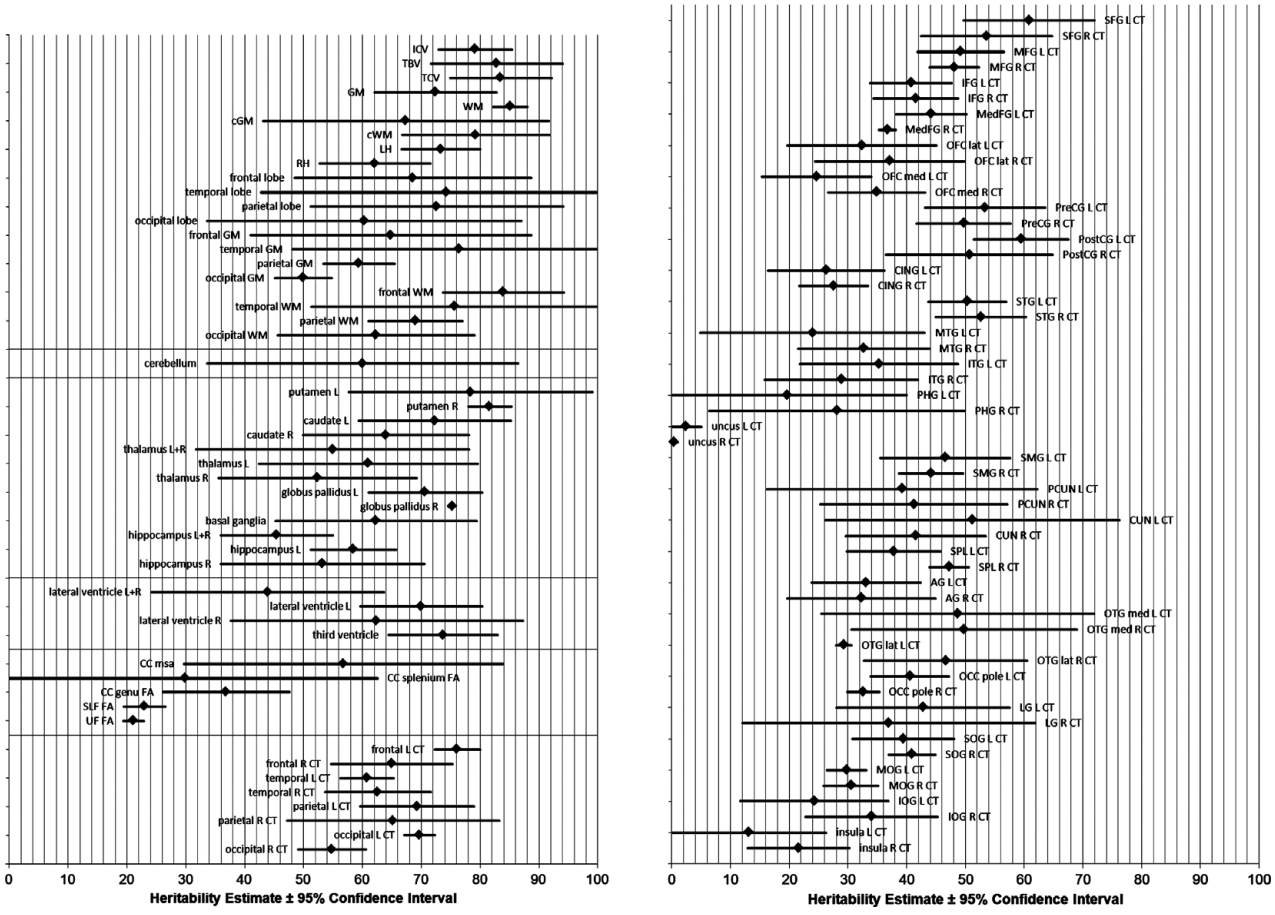

FIGURE 2

Heritability estimates with corresponding 95% confidence intervals according to the meta-analysis.

highly heritable; regional CT measurements are moderately to highly heritable; and regional FA measurements are moderately heritable. When looking at the CIs, we now have good heritability estimates for about half of the lobar and regional CT measures, in addition to the large volumetric measures. Even with only two or three studies carried out in samples that vary widely in age, many of the regional CT measures have tight CIs. The regional CT measures with wide CIs show the importance of replication across independent samples and demographic groups. Although the largest number of studies has investigated total lateral ventricle volume, the genetic influence is moderate, and CIs for this measure are still wide, suggesting that this may not be a good phenotype for genetic analysis. Investigating lateral ventricular volume for the left and right hemispheres separately may prove preferable. Corpus callosum midsagittal area seems to be a problematic phenotype as well. This phenotype was studied in five independent samples, but CIs remain wide. Subcortical volumes appear to have high heritability, but because the number of samples/individuals is small, CIs are still wide. Although CIs for FA measures were tight, these are based on only two studies and a small number of twin pairs, so the meta-analyses for these measures are limited in the conclusions we can draw from them, and more DTI studies are needed to know what the actual heritability is.

Because almost all global and regional brain measures analyzed were heritable to some extent, it might appear that any of such measures could serve as endophenotypes, or as targets for genetic linkage and association studies. However, the validity of the conclusions that can be drawn from neuroimaging genetics studies depends largely on the accuracy of the trait measurement. Given the large estimate for nonshared environmental variance found here, it is important to ascertain how much of the variance can be attributed to measurement error; this error places an upper limit on heritability estimates because the variance that is measurement-specific is removed from the pool of variance that can be explained by genotype. Smaller structures tend to have lower heritability values than global-based and lobar-based measures and show considerable variability across regions and studies, perhaps because of a greater proportion of measurement error, (i.e., bias in regional partitioning). There is actually relatively little known about reliability of structural MRI within healthy individuals, even for frequently used measures such as lateral ventricular volume and corpus

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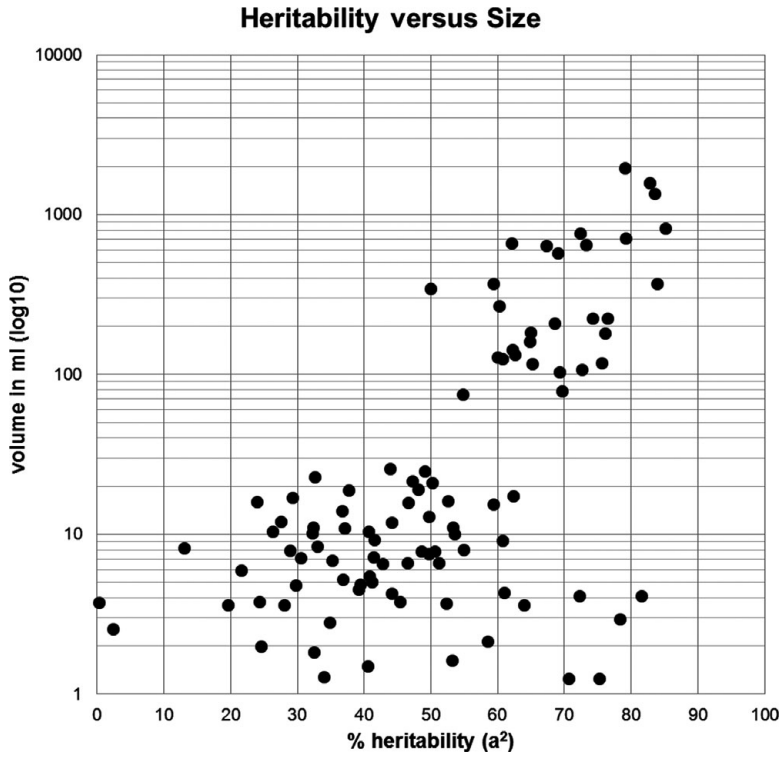

FIGURE 3

Meta-estimates of heritability plotted against the respective average sizes of structures (volumetric measures) obtained from the avg152T1 MNI template. Volumes were automatically segmented using the IBASPM Toolbox (Individual Brain Atlases using Statistical Parametric Mapping), authored by Lester Melie Garcia and Yasser Aleman-Gomez. Volumes are measured in milliliters (cm^3), and displayed on a base 10 logarithmic scale for the purposes of separating data points representing smaller volumes (<15 ml). This graph includes all global volumes, cerebellar volume, subcortical volumes, all gyral cortical thickness regions of interest, and total lateral ventricle volume. This graph demonstrates that smaller structures tend to have lower heritability values than global-based and lobar-based measures. Smaller structures also show considerable variability in their heritability estimates.

callosum area. A few studies have shown that reproducibility for structural and DTI measures appears to be quite good (e.g. Bonekamp et al., 2007; Dickerson et al., 2008; Jovicich et al., 2009); but Quiggle et al. (2011), for example, report a wide range of test-retest reliabilities for CT. Reliability is likely to vary with sample composition (e.g., age, gender, patients versus controls), magnetic field strength, scan interval, and processing and analysis methods, including the algorithm used by software, measure of reproducibility (e.g., intra-class correlation, coefficient of variation, or repeated measures ANOVA), ROI definition, and measure of structure (e.g., CT, surface area [SA], or GM volume). For example, in analyses of heritability of global brain structure, the functional units of the brain (the neurons that generate active electrical signals — GM) have often not been separated from the fibers that connect them (myelinated and unmyelinated axons — WM), possibly obscuring the genetic architecture. Especially important in this context is the finding that, although cortical surface area and CT are both highly heritable, they are essentially unrelated genetically at the global, lobar, and regional levels of analysis (Panizzon et al., 2009; Winkler et al., 2010). These results demonstrate that cortical volume, which is a composite of surface area and CT, combines at least two distinct sources of genetic influences. They also suggest that using volume in a genetically informative study, or as an endophenotype for a disorder, may confound the underlying genetic architecture of brain structure, and that SA and CT (driven by distinct cellular mechanisms) should be considered separately in imaging genetics studies. In order to ensure optimum sensitivity to detect the relative influences of genes and environment, refinement of image acquisition, processing, and analysis methods are some of the major challenges in the field of neuroimaging genetics (de Zubicaray et al., 2008).

Several twin studies have concluded that most of the genetic variance in global brain structure is determined by genes that are shared between the major neural subdivisions (Pfefferbaum et al., 2004; Pfefferbaum et al., 2000; Schmitt et al., 2009; Schmitt et al., 2008; Schmitt et al., 2007). Multivariate genetic modeling has revealed that the majority of variation in the volume of the cerebrum, cerebellum, thalamus, and basal ganglia is due to a single genetic factor (Schmitt et al., 2007); that the strong correlation between ICV and corpus callosum is entirely due to shared genetic effects (Pfefferbaum et al., 2000); that the genetic variance in the absolute change in corpus callosum height is

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TABLE 4
Functional MRI Twin and Family Studies

Reference	Cohort	*n* pairs MZ/DZ	Age range	Paradigm	Brain areas	Variance component estimates (SE or 90% CI) a^2 (%)	c^2 (%)	e^2 (%)
Blokland et al., 2008	QTIMS	29/31	21–27	*n*-back working memory task (BOLD% signal difference of 2 minus 0-back)	MFG L	37	0	63
					MFG R	19	2	79
					AG L	0	19	81
					AG R	19	0	81
					SMG L	24	0	76
					SMG R	11	12	77
Blokland et al., 2011	QTIMS	75/66	20–28	*n*-back working memory task (BOLD contrast 2-back > 0-back)	V-W	0–65	0	0–100
Côté et al., 2007	QNTS	47/57	8	Emotional paradigm (sad minus neutral film excerpts – SR & Z-score)	med PFC L/R	0	0	100
					VLPFC L/R	0	0	100
Koten et al., 2009	NTR	10/0 SIBS: 10 indiv	28.6 (9.8)[a]	*n*-back working memory task	V-W	0– >80	NA	NA
Matthews et al., 2007	UCSD	10/10	20–56	Multi-source interference task (incongruent minus congruent trials)	dorsal ACC	38 (0–74)	0	62 (26–100)
					PCC	0	37 (0–69)	63 (18–100)
					insula R	0	37 (0–69)	63 (31–100)
					insula L	0	32 (0–66)	68 (34–100)
					ventral ACC	0	8 (0–52)	90 (48–100)
Park et al., 2012	UMICH	13/11	18–29	Checkerboard visuomotor task	visual cortex L	72	NA	NA
					visual cortex R	56	NA	NA
					motor cortex L	75	NA	NA
Polk et al., 2007	UMICH	11/11	18–29	Visual processing task (faces, places, pseudowords)	ventral visual cortex	NA	NA	NA
Family/pedigree studies								
Glahn et al., 2010	SAFHS	333 indiv; 29 pedigrees; average family size (range) = 9 indiv (5–32)	26–85	Default mode network FC	PCC/PCUN FC	42 (17)[b]	NA	NA
					med PFC FC	38 (15)	NA	NA
					TEMP–PAR L FC	33 (19)	NA	NA
					TEMP–PAR R FC	42 (16)	NA	NA
					CB L FC	10 (13)	NA	NA
					CB R FC	30 (16)	NA	NA
					CB tonsil FC	22 (19)	NA	NA
					PHG L FC	27 (14)	NA	NA

Note: Abbreviations: A, additive genetic; ACC, anterior cingulate cortex; AG, angular gyrus; C, common environment; CB, cerebellum; CI, confidence interval; DZ, dizygotic; E, unique environment; F, female; FC, functional connectivity; indiv, individuals; L, left; M, male; med, medial; MFG, middle frontal gyrus; MZ, monozygotic; NA, not available; PAR, parietal; PCC, posterior cingulate cortex; PCUN, precuneus; PFC, prefrontal cortex; PHG, parahippocampal gyrus; R, right; SE, standard error; SIBS, siblings; SMG, supramarginal gyrus; SR, spatial range; TEMP, temporal; VLPFC, ventrolateral prefrontal cortex; V-W, voxel-wise; Δ, change.
Cohort/Study Abbreviations: NTR, Netherlands Twin Registry; QNTS, Quebec Newborn Twin Study; QTIMS, Queensland Twin Imaging Study; SAFHS, San Antonio Family Heart Study; UCSD, University of California San Diego; UMICH, University of Michigan.
[a] No age range reported; only mean (standard deviation); [b] h^2 (standard error).

entirely due to genes involved in the expansion of ventricles (Pfefferbaum et al., 2004); that strong genetic ($r_g = .68$) and environmental ($r_e = .58$) correlations explain the relationship between corpus callosum height and lateral ventricle size (Pfefferbaum et al., 2000); and that a single genetic factor accounts for 60% of the genetic variability in regional CT (Schmitt et al., 2008). However, Rimol and colleagues (2010) found strong evidence of regionally specific patterns, rather than a single, global genetic factor, by mapping correlations between three selected seed points and all other points on the cortical surface. The primary visual (V1) seed point had strong genetic correlations with posterior sensory and motor areas, the anterior temporal seed point with anterior frontal regions, and the middle frontal seed point with inferior parietal regions. The patterns do not conform to traditionally defined brain structure boundaries, and are largely consistent with a division between primary and association cortex, as well as broadly defined patterns of brain gene expression, neuroanatomical connectivity, and brain maturation trajectories. No single explanation appears to be sufficient, suggesting the need for further investigation to identify genetic and environmental relationships between brain structures.

It should be mentioned that, because of the small number of independent samples, in this meta-analysis we combined samples regardless of age and gender. However, twin studies during childhood and adolescence have shown that genetic and environmental factors may contribute to the development of the cortex in a regional and age-specific manner; that is, the heritability of different brain areas changes over the course of development in a regionally specific fashion (Lenroot & Giedd, 2008; Lenroot et al., 2009; Wallace et al., 2006). Variance components analysis of cortical thickness revealed that primary and sensory cortex show greater heritability early in development, while in later-maturing areas that underlie complex cognitive processes — the dorsal prefrontal cortex and temporal lobes — heritability increases with maturation (Lenroot et al., 2009). This phenomenon

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may be linked to the timing of gene expression and may be related to cognitive development and to the age of onset of various neuropsychiatric disorders. It could also have important educational and/or therapeutic implications. Studies by Peper, van Soelen and colleagues (Peper et al., 2009; van Soelen et al., 2011b) show that pubertal development may be directly involved in the decreases in GM areas that accompany the transition of our brains from childhood into adulthood. Whether other brain measures, such as global GM and WM volumes, show a reduction or an increase in heritability with increasing age is not quite clear yet, as findings are mixed (Gilmore et al., 2010; Wallace et al., 2006). In studies of elderly twins, heritability estimates for TBV are similar to those described in studies of younger adult twins (Geschwind et al., 2002; Pfefferbaum et al., 2000). Thus, both the specific brain region and the age of the population should be taken into account when using neuroimaging measures as an intermediate phenotype to link genes, environment, and behavior, as neuroimaging measures may be suitable at one developmental stage and not another (Lenroot & Giedd, 2008; Lenroot et al., 2009).

Until recently, twin imaging samples were not large enough to estimate the relative influences of genes and environment on neuroimaging measures in males and females separately, so little is known about sex differences in heritability. Gender differences are known to exist for both brain structure and function (Lenroot & Giedd, 2010), and it is not inconceivable that these differences are not merely limited to mean effects. The relative importance of genes and environment may be different for males compared to females, and different sets of genes may be responsible for phenotypic differences. Chiang et al. (2011) were the first to investigate sex limitation for brain measures. Using DTI in 705 adolescent and young-adult twins and their siblings, and by fitting voxel-wise gene–environment interaction models, Chiang and colleagues determined that genetic influences on WM fiber integrity (indexed by FA) were greater in males than in females, greater in adolescence versus adulthood, greater in those with higher socioeconomic status, and in those with above-average FIQ compared to those with below-average FIQ.

A genetic correlation between brain structure and cognition has been reported repeatedly. Multivariate analyses have revealed moderate to high genetic correlations between WM fiber integrity, total brain, GM, WM, lobar, and lateral ventricular volumes and FIQ, performance IQ, verbal IQ, working memory, verbal memory, executive function, reading ability, and processing speed (Betjemann et al., 2010; Carmelli et al., 2002a; Carmelli et al., 2002b; Chiang et al., 2009; Hulshoff Pol et al., 2006; Posthuma et al., 2002; van Leeuwen et al., 2009; Wallace et al., 2010). Differential findings for verbal versus nonverbal skills suggest that distinct mechanisms contribute to the phenotypic relationships between brain volumes and these skills (Wallace et al., 2010). In a longitudinal twin study, van Soelen et al. (2011b) demonstrated that cortical thinning on the brink of puberty (9–12 years) is accompanied by an increasing association with FIQ, which is driven by genetic factors. Although these findings point to a neural network that shares a common genetic origin with intelligence, suggesting that volumetric measures can serve as intermediate phenotypes for general cognitive ability, it is important to note that not all structures throughout the brain share that common genetic origin with cognition. Further studies are warranted to resolve the direction of causation between these two domains of measures.

The observation of a high degree of heritability of normal brain structure is reinforced by findings regarding the effects of genetic polymorphisms on brain structure. Several a priori selected candidate genes show reproducible effects on brain structure and task-related as well as resting-state brain activation (Thompson et al., 2010). These include genes that are involved in neurotransmission (e.g., genes coding for common variants in neurotransmitter receptors and transporters), brain morphogenesis, and neurodevelopment (de Geus et al., 2008). With the improvement of high-density genotyping techniques, the candidate gene approach is now being partially replaced by genome-wide association (GWA) analyses that have the potential to identify novel polymorphisms that might be associated with variability in normal brain structure and function. Furthermore, as genetic sequencing becomes less expensive, the relative contribution of rare versus common variants to imaging phenotypes and GWA scanning signals is likely to be better understood (Choi et al., 2009; Dickson et al., 2010). Thompson et al. (2010) recently reviewed the status of imaging genomics. In an attempt to address one of the major issues in imaging genomics (McCarthy et al., 2008), namely the large samples needed to discover genetic polymorphisms and replicate hits associated with individual variance in brain structure and function, several imaging genomics groups are now working collaboratively as part of the ENIGMA Consortium (Enhancing Neuroimaging Genetics through Meta-Analysis; http://enigma.loni.ucla.edu). Encouragingly, meta-analysis of the GWA data from 16 studies (>6,400 subjects), with association conducted at ~1.3 million autosomal SNPs, yielded significant hits for both hippocampal volume and TBV (ENIGMA Consortium, 2011). This collaboration has great potential for many new discoveries, providing valuable information about the physiological mechanisms underlying brain and behavior, and about factors that affect the expression of neurological and psychiatric illnesses.

Although imaging genetics is slowly transforming into imaging genomics, given the expense and resource-intensive nature of the latter, twin modeling should still be the first step to determine whether it is worthwhile to perform gene-finding analyses on a given imaging phenotype, and is also the best option to assess whether there

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are genetic correlations between phenotypes. To the best of our knowledge, no twin studies have been carried out that directly combine data on brain structure and brain function to see if these are genetically correlated phenotypes. In a large Mexican-American pedigree study, Glahn et al. (2010) found that the genetic factors that influence DMN functional connectivity and GM density seem to be distinct, suggesting that unique genes influence the structure and function of the DMN. This is consistent with our repeated finding that task-related brain activation does not correlate strongly with GM volume (Blokland et al., 2008; Blokland et al., 2011). It is not unlikely that different physiological mechanisms with distinct genetic etiologies are involved in brain structure and function.

It is apparent that there is still relatively little certainty about the heritability of brain function as measured with task-based and resting-state fMRI. Therefore, this will be a focus for future twin research. Findings of heritability for individual differences in fMRI measures converge with similar results from twin studies of the electroencephalogram, particularly of event-related potentials that are reported to be up to 60% heritable (van Beijsterveldt & van Baal, 2002). Heritability findings for fMRI measures suggest that it is likely that genetic influences may vary with task paradigm, brain region, and how brain activation/deactivation is quantified; they demonstrate the importance of determining an appropriate measure of brain activation. One must also consider the possibility that heritability of brain activation may reflect genetic commonalities in vascular or blood-flow responses generated by nonspecific demand or effort not related directly to the cognitive process being manipulated (Duncan & Owen, 2000). Replicability across samples and paradigms will likewise need to be addressed.

From voxel-based studies, both structural and functional, it is apparent that genetic and environmental effects cross anatomical boundaries (Blokland et al., 2011; Joshi et al., 2011; Lenroot et al., 2009; van Soelen et al., 2012; Yoon et al., 2010), such that voxel-based approaches may have preference over ROI approaches in imaging genetic studies. Although a common genetic factor appears to influence much of the brain (Schmitt et al., 2009), there are considerable regional differences across the brain (Chen et al., 2011; Rimol et al., 2010). Voxel-wise approaches seem most adept at finding those differences as well.

In conclusion, this meta-analysis demonstrates that results for many imaging measures require further replication across independent samples and demographic groups, especially for such measures as (voxel-based) CT and surface area, FA, and BOLD signal. As twin imaging cohorts are growing in size, they will be gaining the statistical power to do so, with great potential for important discoveries about the underlying mechanisms involved in brain functioning, behavior, and brain disorders.

Acknowledgments

G.A.M.B. is supported by an ANZ Trustees PhD Scholarship in Medical Research, Queensland, Australia. G.I.Z. is supported by an ARC Future Fellowship.

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