Review of Twin and Family Studies on Neuroanatomic Phenotypes and Typical Neurodevelopment

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This article reviews the extant twin studies employing magnetic resonance imaging data (MRI), with an emphasis on studies of population-based samples. There have been approximately 75 twin reports using MRI, with somewhat under half focusing on typical brain structure. Of these, most are samples of adults. For large brain regions such as lobar volumes, the heritabilities of large brain volumes are consistently high, with genetic factors accounting for at least half of the phenotypic variance. The role of genetics in generating individual differences in the volumes of small brain regions is less clear, mostly due to a dearth of information, but rarely because of disagreement between studies. Multivariate analyses show strong genetic relationships between brain regions. Cortical regions involved in language, executive function, and emotional regulation appear to be more heritable than other areas. Studies of brain shape also show significant, albeit lower, genetic effects on population variance. Finally, there is evidence of significant genetically mediated relationships between intelligence and brain structure. At present, the majority of twin imaging studies are limited by sample sizes small by the standards of behavioral genetics; nevertheless the literature at present represents a pioneering effort in the pursuit of answers to many challenging neurobiological questions.

Over the last half century, studies of twin and familial relationships have generated a wealth of information on the causes of individual differences in behavior and psychopathology. Numerous family studies, particularly those using twin designs, have provided evidence that a multitude of human behavioral traits are strongly influenced by our genetic makeup (Boomsma et al., 2002; Sullivan & Kendler, 1999). More recently, quantitative genetic studies of neurobiological phenotypes (so called 'endophenotypes'), including measures of brain structure and function using magnetic resonance imaging (MRI), have received increased interest, primarily as potential bridges between genes and selected behavioral measures. Even though the extant endophenotype literature already has made substantial contributions to our understanding of neurogenetics, all evidence indicates that we are on the verge of a dramatic revolution in our science. These changes will likely result in a closer relationship with conventional neuroscience, and possibly even the emergence of a novel subdiscipline in behavioral genetics.

Understanding the biological substrates of the mind ranks among the most ambitious scientific tasks ever attempted, and all available neurobiological tools must remain on the table, as each provides a unique perspective on a very complex problem. MRI, however, does have several advantages (as well as disadvantages) relative to other modalities. MRI is quite a versatile technology that enables (a) the examination of soft tissues in vivo with extremely high resolution (approximately 1 mm^3) relative to other imaging techniques (Bushberg et al., 1994), (b) the assessment of function by measuring brain hemodynamics (fMRI), (c) visualization of white matter tracts via diffusion tensor imaging (DTI), and (d) assessment of neurotransmitter and metabolite levels in the living brain via magnetic resonance spectroscopy (MRS; Casey & de Haan, 2002). This versatility, in combination with its lack of ionizing radiation, makes MRI particularly useful for large neuroanatomic studies on typical populations. Disadvantages include expense compared to EEG, lower temporal resolution for functional studies compared to EEG or magnetoencephalography (MEG), substantially decreased anatomical resolution

compared to pathological specimens, and a more limited ability to visualize the distribution of molecules of interest as compared to positron emission tomography (PET).

To date, nearly all reports on twins using MRI have been anatomic. An anatomic image effectively is a downsampled, digital version of the original human brain, in which each voxel (a three dimensional, or volumetric, pixel) in the image represents a true physical volume. Thus, anatomic MRI allows for several options in image processing which enable both volumetric (measurement of volumes) and morphometric (measurement of shape) analyses at multiple levels of resolution. The present manuscript represents a review of the existing twin reports using MRI, with an emphasis on normal brain structure. Relevant papers were identified via PubMed and ISI Web of Science database searches using the intersection of the terms twin, brain, and MRI (or magnetic resonance imaging). Reports were excluded from consideration if they represented case reports, or if they used twins as a convenience sample in order to address nongenetic questions.

Heritability of Volumetric Phenotypes

There have been approximately 35 reports on typical neurodevelopment in twins using MRI. About half of these reports have used structural equation modeling (SEM), with others basing their estimates on Falconer estimation. These reports employed a diversity of volumetric and morphometric techniques (Table 1), but most included a volumetric component. The analysis of data from studies of psychopathology provides some additional information, albeit limited, on the normal heritability of MRI-derived phenotypes (Table 2); many of these papers are focused on a few specific regions of interest (ROIs) that are pertinent to a particular neurobiological question.

Considered together, twin MRI reports have demonstrated a strong, highly statistically significant role of genes in the generation of the variability in human brain volumes, particularly for larger structures (Baaré et al., 2001a; Pennington et al., 2000; Pfefferbaum et al., 2000). For example, in their large sample, methodologically-rigorous analyses, found that genetic factors were responsible for .90, .82, and .88 of the total variance in total brain, gray, and white matter volumes, respectively, in 112 adult twin pairs (Baaré et al., 2001a). Figure 1 provides a between-study comparison of heritability estimates for these large structures.

Heritability estimates based on variance components analysis for neuroanatomic *substructures* are substantially less frequent than for global volumetric measures. It is common that only one or two estimates of heritability have been reported for a given region of interest. For example, there are only three published twin studies that report findings for cerebral lobar tissue (Carmelli et al. 2002b; Geschwind et al., 2002; Wallace et al., 2006); all three suggest that genes play

the predominant role in generating population variance in these structures, with some evidence that the role of genes in the occipital lobe is weaker than in other regions. Similarly, there are only three reports that parse cerebellar variance into genetic and non-genetic components (Posthuma et al., 2000; Wright et al., 2002; Wallace et al., 2006); heritability estimates from these studies are .89, .67, and .49.

Though large volumetric measures consistently show high heritabilities, the role of genetic factors on individual differences of smaller structures is more variable. Of these substructures, the lateral ventricles, corpus callosum, and the hippocampus are by far the most well studied. There is extremely strong evidence that the variance in the area of the corpus callosum is dominated by genetic factors (Oppenheim et al., 1989; Pfefferbaum et al., 2000; Scamvougeras et al., 2003; Sullivan et al., 2001). In contrast, heritability estimates for both the hippocampus (Baaré et al., 2001b; Narr et al., 2002; Rijsdijk et al., 2005; Sullivan et al., 2001; Van Erp et al., 2004; Van Haren et al., 2004; Wright et al., 2002) and lateral ventricles (Baaré et al., 2001a; Baaré et al., 2001b; Pfefferbaum et al., 2000; Reveley et al., 1984; Reveley et al., 1982; Rijsdijk et al., 2005; Wright et al., 2002) are generally lower, but with a great deal of variability from study to study.

Other neuroanatomic structures have rarely been measured in full twin designs, if at all. A few studies on monozygotic (MZ) pairs have shown high inter-twin correlations for subcortical structures. For example, White et al. (2002) report correlations of .84 for caudate, .75 for putamen, and .75 for thalamic volumes in12 MZ pairs, while Ettinger et al. (2007) estimate the intraclass correlation for thalamus at .69 in 27 normal MZ pairs as part of a study on schizophrenia. For most ROIs, however, the information regarding variance components comes solely from a study by Wright et al. on 10 MZ and 10 dizygotic (DZ) twin pairs, which included measures from individual cerebral gyri (roughly based on Brodmann's areas), as well as subcortical gray, thalamus, cerebellum, and brain stem: 92 parcellated regions (all gray matter) in total (Wright et al., 2002). While numerous regions had statistically significant familial influences, only the precentral gyrus had statistically significant effects due to genes specifically. Regions with heritability estimates greater than .50 included the superior parietal lobe, posterior cingulate gyrus, corpus striatum, putamen, and cerebellum. Though this study suffers from low power and multiple testing issues, it is currently the de facto source for estimates of the magnitude of genetic influences in typical populations for nearly all small substructures in the brain.

With the possible exception of the lateral ventricles, there is little evidence that the shared environment plays a role in generating neuroanatomic (either morphological or volumetric) variability, although this may be obscured by nonadditive effects of genes.

Table 1

Comparison of Qualitative Study Design Characteristics for All Existing Twin Reports Using MRI in Typically Developing Populations

Study	Population	Substructures measured?	Morphological measures?	Voxel-level measures?	Brain and behavior?	Multivariate analyses?	SEM-based statistics?	Longitudinal design?
Reveley, 1984	Adult	Y[2]	N	N	N	N	Y	N
Oppenheim, 1989	Adult	Y[2]	Y[2]	N	N	N	N	N
Steinmetz, 1994	Adult	N	Y	N	N	N	N	N
Steinmetz, 1995	Adult	Y	N	N	Y[7]	N	N	N
Bartley, 1997	Adult	Y	Y	N	N	N	Y	N
Biondi, 1998	Adult	Y	Y	N	N	N	N	N
Bonan, 1998	Adult	Y	Y	N	N	N	N	N
Carmelli 1998	Adult	N	N	N	N	N	Y	N
Haidekker, 1998	Adult	N	Y	N	N	N	N	N
Tramo, 1998	Adult	Y	N	N	Y	N	N	N
Carmelli, 1999	Adult	N	N	N	Y	N	N	N
Lohman, 1999	Adult	N	Y	N	N	N[6]	N	N
Le Goualher, 2000	Adult	N	Y	N	N	N	N	N
Pennington, 2000	Pediatric[1]	Y	N	N	Y	Y	N	N
Pfefferbaum, 2000	Adult	Y[2]	N	N	N	Y[3]	Y	N
Posthuma 2000	Adult	N	N	N	N	Y	Y	N
Barré, 2001	Adult	N	N	N	N	Y	Y	N
Pfefferbaum, 2001	Adult	Y[2]	N	N	N	N	Y	N
Sullivan, 2001	Adult	Y	N	N	N	N	Y	N
Thompson, 2001	Adult	N	N	Y	Y	N	N	N
Carmelli 2002a	Adult	Y	N	N	Y	N	Y	N
Carmelli 2002b	Adult	N[5]	N	N	Y	N	Y	N
Eckert, 2002	Pediatric	Y	N	N	N	N	N	N
Geschwind, 2002	Adult	Y	N	N	Y[7]	N	Y	N
Hulshoff Pol, 2002	Adult	Y[2]	N	N	N	N	Y	N
Posthuma 2002	Adult	N	N	N	Y	Y	Y	N
Reed, 2002	Adult	Y[2]	N	N	N	N	N	N
White, 2002	Adult	Y	N	N	N	N	N	N
Wright, 2002	Adult	Y	N	N	N	Y[3*]	Y	N
Scamvougeras, 2003	Adult	Y[2]	N	N	N	N	N	N
Styner, 2003	Adult	Y	Y	N	N	N	N	N
Mohr, 2004	Adult	N	Y	N	N	N	N	N
Pfefferbaum, 2004	Adult	Y[2]	Y[2]	N	N	Y	Y	Y[4]
Wallace et al., 2006	Pediatric	Y	N	N	N	N	Y	N
Hulshoff Pol, 2006	Adult	Y	N	Y	Y	N	Y	N
Schmitt et al., 2007	Pediatric	Y	N	N	N	Y	Y	N

Note: 'Substructures measured' is an indication of whether parcellation data for ROIs are reported for structures other than total brain, intracranial volume, or hemispheric volumes. A 'Y' for brain and behavior is indicative that the study not only measured psychometric and imaging variables, but also attempted to describe brain-behavioral relationships. In contrast, the 'Multivariate Analyses' column identifies studies that model relationships between neuroanatomic variables.

[1] Greater than 70% of the twin sample was reading disabled

[2] Only midsagittal structures (lateral ventricles and/or corpus callosum) were measured

[3] Bivariate, or bivariate with post-hoc principal component analysis (3*)

[4] Two timepoints

[5] White matter hyperintensities were the only neuroanatomic variable reported

[6] PCA used, but to assess global, rather than structure-specific, eigenvalues

[7] Handedness only

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Table 2

Comparison of Qualitative Study Design Characteristics for Reports on Neuropathology Using MRI in Twins

Study	Condition of interest	Population	Structure of interest	Volumetric parcellation?	Morphological measures?	Voxel-level measures?
Casanova, 1990a	Schizophrenia	Adult	Corpus Callosum	N	N	N
Casanova, 1990b	Schizophrenia	Adult	Corpus Callosum	N	Y	N
Suddath, 1990	Schizophrenia	Adult	Ventricles, hippocampus	Y	N	N
Casanova, 1991	Schizophrenia	Adult	Corpus Callosum	N	Y	N
Weinberger 1991	Schizophrenia	Adult	Cerebral lateralization	Y	N	N
Weinberger, 1992a	Schizophrenia	Adult	Hippocampus Prefrontal cortex	Y	N	N
Weinberger, 1992b	Schizophrenia	Adult	Limbic structures	Y	N	N
Bartley, 1993	Schizophrenia	Adult	Sylvian fissure	Y	N	N
Kinnunen, 1993	Lupus	Adult	Clinical readings	N	N	N
Goldberg, 1994	Schizophrenia	Adult	Prefrontal Cortex, Hippocampus	Y	N	N
Thorpe, 1994	Multiple sclerosis	Adult	Clinical readings	N	N	N
Hyde, 1995	Tourette syndrome	Pediatric	Caudate	Y	N	N
Noga, 1996	Schizophrenia	Adult	Hemispheric volumes and other measures of hemisphere size	Y	Y	N
Jackson, 1998	Epilepsy	Adult	Hippocampus	Y	N	N
McNeil, 2000	Schizophrenia	Adult	Hippocampus	Y	N	N
Barré, 2001	**Schizophrenia**	**Adult**	**Multiple substructures**	**Y**	**N**	**N**
Briellmann, 2001	Epilepsy	Adult	Clinical Findings, Hippocampus	Y	N	N
Noga, 2001	Bipolar I	Adult	Mesial Temporal, Basal Ganglia	Y	N	N
Bridle, 2002	Schizophrenia	Adult	Subcortical	Y	N	N
Cannon, 2002	Schizophrenia	Adult	Voxel-level	N	N	Y
Kiseppä, 2002	Bipolar I	Adult	Cerebral lobar gray/white volumes ventricular volumes	Y	N	N
Narr, 2002a	**Schizophrenia**	**Adult**	**Corpus Callosum**	**Y**	**N**	**N**
Narr, 2002b	**Schizophrenia**	**Adult**	**Hippocampus**	**Y**	**N**	**Y**
Gilbertson, 2002	PTSD	Adult	Hippocampus			
Castellanos, 2003	ADHD	Pediatric	Caudate	Y	N	N
Järvenpää, 2004	Cognitive Dysfunction	Adult	Hippocampus	Y	N	N
Kates, 2004	Autism	Pediatric	Cerebral lobar and cerebellar gray/white volumes, ventricles	Y	N	N
May, 2004	PTSD	Adult	Septum Pellucidum	N	N	N
Van Erp, 2004	**Schizophrenia**	**Adult**	**Hippocampus**	**Y**	**N**	**N**
Van Haren, 2004	**Schizophrenia**	**Adult**	**Hippocampus**	**Y**	**N**	**N**
Hulshoff Pol, 2004	Schizophrenia	Adult	Whole brain volume, gray/white brain volumes	Y	N	N
Rijsdijk, 2005	**Schizophrenia**	**Adult**	**Whole brain, Hippocampus, Ventricles**	**Y**	**N**	**N**
Spaniel, 2005	Schizophrenia	Adult	Global T1/T2 Relaxation	N	N	N
Styner, 2005	**Schizophrenia**	**Adult**	**Corpus Callosum**	**Y**	**Y**	**N**
Terriberri, 2005	Schizophrenia	Adult	Corpus Callosum	N	Y	N
Hulshoff Pol, 2006	Schizophrenia	Adult	Voxel-based morphometry	N	N	Y
Levitt, 2006	PTSD	Adult	Cerebellar Vermis	Y	N	N
Ettinger, 2007	**Schizophrenia**	**Adult**	**Thalamus**	**Y**	**N**	**N**
de Geus, 2007	Anxiety and Depression	Adult	Voxel-based Morphometry	N	N	Y
van 't Ent, 2007	ADHD problems	Pediatric	Voxel-based Morphometry	N	N	Y

Note: This summary table excludes case reports and studies using twin samples to address nongenetic questions. Reports that include information on the genetics of typical neuroanatomy, usually because they provide statistics on control samples, are shown in **bold**.
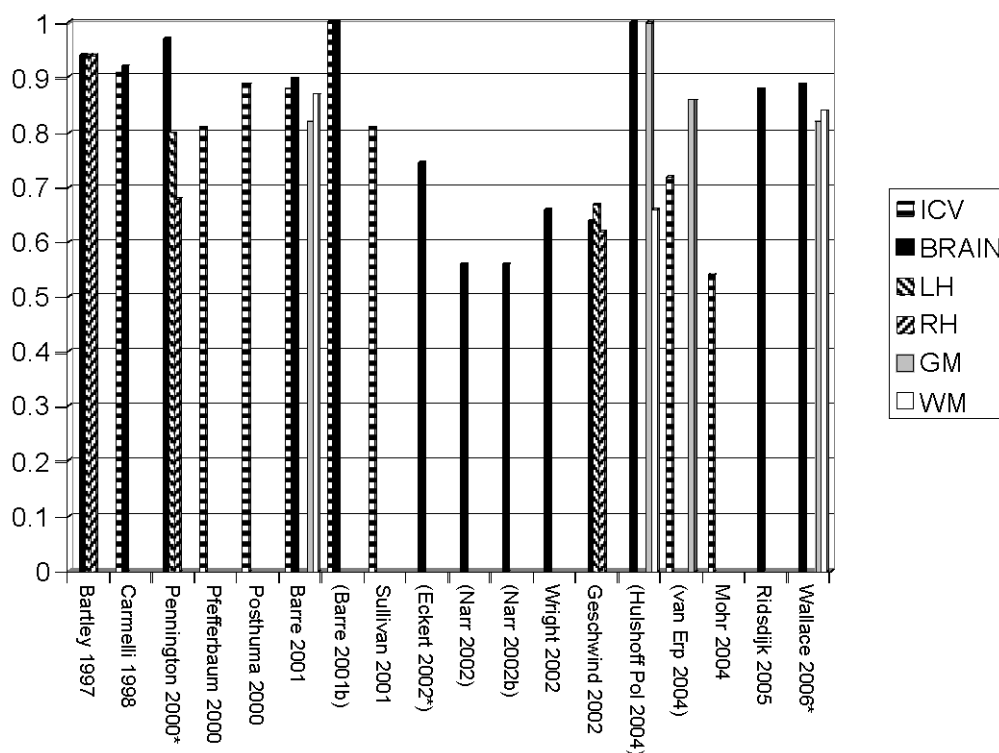
Figure 1

Summary of heritability estimates for volumes of large neuroanatomic structures.

Note: Reports are listed in parentheses if heritability is calculated via Falconer estimation, either by the authors of the study or post hoc based on correlations; the remaining studies use SEM.

* = Pediatric studies

ICV = intracranial volume

Brain = total brain or total cerebrum

LH = left hemisphere

RH = right hemisphere

GM = total gray matter

WM = total white matter

Voxel-Based Image Analyses

Rather than defining brain regions, an alternative approach is to analyze structure at the voxel level; analyses of these fundamental elements represent the highest level of magnification possible for a particular brain scan. A voxel-level approach has the advantage of vastly increased spatial resolution, as well as a lack of *a priori* constraints on the data. Disadvantages of voxel-level analyses include the more exploratory nature of the method (the inevitable flip side of effectively ignoring functional neuroanatomy), the necessity of many thousands of analyses and subsequent multiple testing issues that arise, and the potential for higher measurement error in these smaller measurements. Nevertheless, the technique offers great promise in identifying subtle effects of genetic factors on brain structure that may be obscured by more regional measures.

There have been only two published twin studies that report results in typical populations at high resolution, though voxel-level analyses are somewhat more common in neuropathological samples. In an influential paper, Thompson et al. examined gray matter density in 10 MZ and 10 DZ adult twin pairs and found that genetic factors strongly influenced language and executive processing centers. (Thompson et al., 2002). Probability maps suggested particularly strong genetic effects in middle frontal regions, and an asymmetry in Wernicke's region (the center for receptive speech), with the left side highly significant but not the right. More recently, Holshoff Pol et al. (2006) examined both gray and white matter density in a substantially larger sample of 258 individuals. Their analysis found several highly significant gray matter foci, including in the superior and middle frontal lobe, Heschl's gyrus, cingulate cortex, and portions of the occipital lobe. Additionally, these analyses discovered significant heritability in white matter tracts, including the superior occipitofrontal fascicle, corpus callosum, and corticospinal tracts.

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Morphometric Measures

The role of the genome on differences in brain shape appears to be significant, but more modest than its influence on volume. Though less well studied, twin findings on shape differences have been fairly consistent (Bartley et al., 1997; Biondi et al., 1998; Bonan et al., 1998; Eckert et al., 2002; Haidekker et al., 1998; Lohmann et al.,1999; Mohr et al., 2004; Steinmetz et al., 1994; White et al., 2002). In general, brain morphology appears to be significantly heritable, but to a lesser extent than volume. For example, raters are able to successfully match surface renderings of MZ pairs, even when there are striking qualitative differences; this finding suggests some familial influences, but also a role of the unique environment in the development of gyral patterns (Biondi et al., 1998). More quantitative measures have produced similar findings. A study by Bartley et al. (1997) found low heritability for gyral patterning, despite high heritability estimates for volumes in 10 MZ and 9 DZ pairs. Similarly, a study by White et al. (2002) on 24 MZ twin pairs reported that within-pair correlations on volumetric measures were substantially higher than surface measures of cerebral morphology. Lohmann also found an effect of genes on sulcal patterns in 19 pairs of MZ twins, with stronger pairwise correlations for deeper (and ontogenetically older) sulci (Lohmann et al., 1999). Other groups have replicated these findings using different metrics of cortical shape and gyral complexity (Haidekker et al., 1998; Mohr et al., 2004). Similar conclusions are found when examining the morphology of the central sulcus (Bonan et al., 1998; Le Goualher et al., 2000), the planum temporale (Eckert et al., 2002), or the corpus callosum (Styner et al., 2005; Terriberry et al., 2005) specifically, rather than global sulcal patterns.

Multivariate Analyses

Despite the critical importance of understanding the etiology of interregional neuroanatomic associations, there are only four reports that investigate questions of this nature. Baaré et al. (2001a) examined relationships between height, intracranial volume (ICV), total gray matter, total white matter, and lateral ventricular volumes in a sample of 54 MZ and 58 DZ adult twin pairs and 34 sibs of DZ pairs, via variance component analyses. Between gray and white matter, they found a genetic correlation of .68, a unique environmental correlation of .04, and no statistically significant evidence of genetic correlations between the lateral ventricles and other regions of interest. A principal components analysis by Pennington et al. (2000) on a sample of 34 MZ and 32 DZ late teen or young adult twin pairs (most pairs had one or more twins with reading disability) parcellated the brain into 7 cortical gray compartments and 6 noncortical structures (white matter, basal ganglia, brain stem, hippocampus, cerebellum, and the central gray nuclei, including the thalamus). While cerebral structures loaded pri-

marily on the first factor, all other structures loaded on the second (except central gray, which loaded equally on both). Both factors were significantly more correlated in MZ than in DZ pairs, suggesting a strong genetic component to each. The third extant multivariate volumetric study by Wright et al. (2002) parcellated the brain into regions with high spatial resolution. This study identified two putative supraregional principal components under genetic control. Specifically, a frontoparietal limbic/paralimbic factor and a factor related to audition (lateral temporal cortex, insula, occipitofrontal, and other frontal regions) were found; factor loadings, however, were quite low (< |0.25|). These findings would suggest that genes are involved in generating functional relationships between distant brain regions.

Recently, our group completed a multivariate analysis of six ontogenetically diverse volumetric ROIs (cerebrum, cerebellum, lateral ventricles, thalamus, corpus callosum, and basal ganglia) using a large pediatric sample and traditional behavioral genetic techniques (Schmitt et al., 2007). In general, the genetic correlations were quite high (Table 3). Further, the relationships between these structures were almost entirely determined by a single genetic factor shared between brain tissues. The lateral ventricles and the corpus callosum were notable exceptions; while the genetic influences on the ventricles were low, genes seem to play a strong role in generating variability in human corpus callosum area, but these effects are largely independent of other tissues. We also found genetic and environmental correlations for cerebral gray and white matter (.84 and −.04, respectively) similar to those Baaré et al. (2001a) found for total gray and white matter in their adult sample.

Longitudinal Studies

There is only one paper that reports longitudinal data on neuroanatomic structures and changes with age. It is based on two volumetric measurements with an interval of 4 years between them, using subjects recruited from the National Heart, Lung and Blood Institute (NHLBI) study on World War II veterans (Pfefferbaum et al., 2004). The subsequent analyses on 71 twin pairs suggest genetic stability in both the corpus callosum and lateral ventricular volumes over this time interval. This study also found evidence for environmental factors increasing the variability in both measures with time, suggesting ongoing changes in brain structure even in the 8th decade of life.

Relationships Between Brain and Behavior

Though numerous twin studies have investigated the relationships between atypical behavior and neuroanatomic endophenotypes (Table 2), there are relatively few that have attempted to understand how the genetic and environmental effects on typical cognitive and behavioral measures are mediated through brain morphology. Most of the existing work has been

Table 3

Genetic and Environmental Correlations for Six ROIs in a Pediatric Twin Sample

	Cerebrum	LV	CC	Thalamus	SC	Cerebellum
Cerebrum	1	.26 (.06 .43)	.37 (.17 .54)	.35 (.16 .51)	.23 (.03 .42)	.58 (.43 .70)
LV	.18 (−.33 .69)	1	−.05 (−.25 .15)	−.22 (−.40 −.03)	-.23 (−.41 −.03)	.29 (.10 .46)
CC	.30 (.05 .52)	.22 (−.54 .74)	1	.49 (32 .63)	.39 (.19 .55)	.10 (−.11 .30)
Thalamus	.97 (.83 1.0)	.00 (−.49 .65)	.42 (.11 .66)	1	.65 (.52 .75)	.07 (−.13 .27)
SC	.82 (.71 .92)	−.37 (−.80 .24)	.35 (.07 .64)	.91 (.81 .98)	1	.13 (−.07 .33)
Cerebellum	.82 (.59 1.0)	.20 (−.59 .71)	.12 (−.38 .57)	.79 (.44 1.0)	.63 (.29 .93)	1

Note: Genetic correlations are provided below the diagonal, with environmental correlations above (From Schmitt et al. 2007).

LV = lateral ventricles

CC = corpus callosum

SC = subcortical nuclei including caudate nucleus, putamen, and globus pallidus

95% confidence intervals are given in parentheses.

on cognition. The detection of brain–cognition correlations has been particularly elusive in typical twin samples. An initial study on full scale IQ and several brain volumes in a small twin sample of MZ twins failed to find a significant correlation with any structure (range −.04 to .20; Tramo et al., 1998).

Evidence suggests, however, that a small correlation does exist. Using voxel-based morphometry, Thompson found strong evidence that intelligence (defined as a combination of selected subtests of the WAIS-R) was significantly correlated with frontal gray matter in his sample of 40 twins, but did not attempt to parcellate the correlation into genetic and nongenetic components (Thompson et al., 2001). Spurred by this discovery, Posthuma et al. (2002) compared WAIS-IIIR IQ scores to total gray and white matter volumes in an extended twin design with 24 MZ pairs, 31 DZ pairs, and 25 siblings. They found a small, but significant correlation between IQ and neuroanatomic structures, with all of the covariance between IQ and brain anatomy associated with genetic factors. A follow-up study examining WAIS-III subtests produced similar results, with small brain-behavioral correlations dominated by genetic effects (Posthuma et al., 2003). Using higher resolution imaging methods, Hulshoff Pol et al. (2006) identified significant genetic correlations between the right medial frontal gyrus and PIQ and VIQ, and between PIQ and the right parahippocampal gyrus. It is noteworthy, however, that since both intelligence and large brain volumes are strongly genetically influenced, the proportion of genetic effects shared between these phenotypes is small, even though genetic factors appear to predominate in explaining their (small) observed covariance.

The only brain and behavior study on a typical pediatric twin population was by Pennington (Pennington et al., 2000), which found WISC-R full scale IQ measures to be correlated with total cerebral volume (.42 in their reading disabled sample, .31 in a control group). The genetic correlation between these measures in the combined sample was .48.

The remaining studies on cognition are from the NHLBI, an all male geriatric population (Carmelli et al., 2002b; Carmelli et al., 2002a; Carmelli et al., 1999). Of these, one presents a systematic analysis of two cognitive factors (verbal memory and executive function; Carmelli et al., 2002b). These two factors were based on principal components analyses on data from several tests (Trails A and B, Stroop, California Verbal Learning Test, the Iowa Screening Battery for Mental Decline, and the WAIS Digit symbol substitution subtest), and were highly heritable (.62 and .64, respectively). Executive function was found to be positively correlated with frontal and temporal regions, and negatively correlated with lateral ventricular volume (magnitude of correlations approximately .20). A similar, slightly weaker pattern was found with brain–verbal memory correlations. However, out of all measures, only lateral ventricular volumes and executive function shared common genetic origins to a significant level (genetic correlation = −.25). Other studies from the NHLBI focus on the relationships between cognitive and physical performance, and white matter hyperintensities in the elderly (Carmelli et al., 2002a; Carmelli et al., 1999).

Functional Imaging

Functional MRI experiments on twin samples are extraordinarily rare. To our knowledge there are only three reports published, with two examining aspects of schizophrenia in very small samples (Karlsgodt et al., 2007; Spaniel et al., 2006). The remaining study examined the neural substrates of sadness in 8-year-olds; 47 MZ and 57 DZ twin pairs were included in the study (Côté et al., 2007). Despite the large sample size (by the standards of fMRI research), this study found no genetic influences on the relationships between sadness and brain activation in two areas of the brain (medial prefrontal cortex and ventrolateral prefrontal cortex) previously correlated with the subjective experience of sadness; rather, these relationships were dominated by unique environmental effects.

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Other Reviews

There is only one other comprehensive review of the twin MRI literature (Peper et al. 2007). Although it is unusual for reviews to cite reviews, this paper is noteworthy for several reasons. First, it represents an independent evaluation of the literature. Second, it provides more detail on several aspects of volumetric neuroimaging. Third, like nearly all other studies reported here, it is not published in a genetics journal and therefore may have escaped the notice of many interested readers.

Limitations of Current Research

Despite the promise of these methods, numerous limitations of the field are readily apparent. First is a relative dearth of work and lack of replication in this novel field for all but the largest brain structures, exacerbated by the limited sample sizes of the great majority of existing studies (Figure 2). The information that can be gleaned from control groups from pathological studies suffers this problem to an even greater extent (Figure 3). Small samples lead to low confidence in parameter estimates, which is certainly responsible for much of the observed discrepancies between studies. Further, many studies restrict their samples exclusively to MZ twins,

which prevents them from distinguishing genetic effects from those of the shared environment (Biondi et al., 1998; Mohr et al., 2001; Mohr et al., 2004; Reed et al., 2002; Steinmetz et al., 1995; Tramo et al., 1998). Of the papers on typical development that include MZ and DZ pairs in order to disentangle genetic and shared environmental effects most are based either on the NIMH pediatric imaging study, an adult sample acquired by the Netherlands Twin Registry, or on the male geriatric sample from NHLBI. Fortunately, these studies also are among the largest extant; nevertheless, there is a critical need for replication at all stages of the life cycle. Thus far, many of the structures demonstrate high familiarity, with MZ correlations of .9 or more. As (all other things being equal) large correlations have smaller standard errors than for smaller ones, the MZ correlations are relatively precisely known. However, the smaller DZ correlations — which often have been obtained from smaller samples — are particularly in need of additional data to increase their precision, and that of variance components estimates obtained from them.

The variety of image processing methodologies, anatomical parcellation strategies, and statistical analyses used are also likely contributors to non-replication. In general, studies that employ state of the art
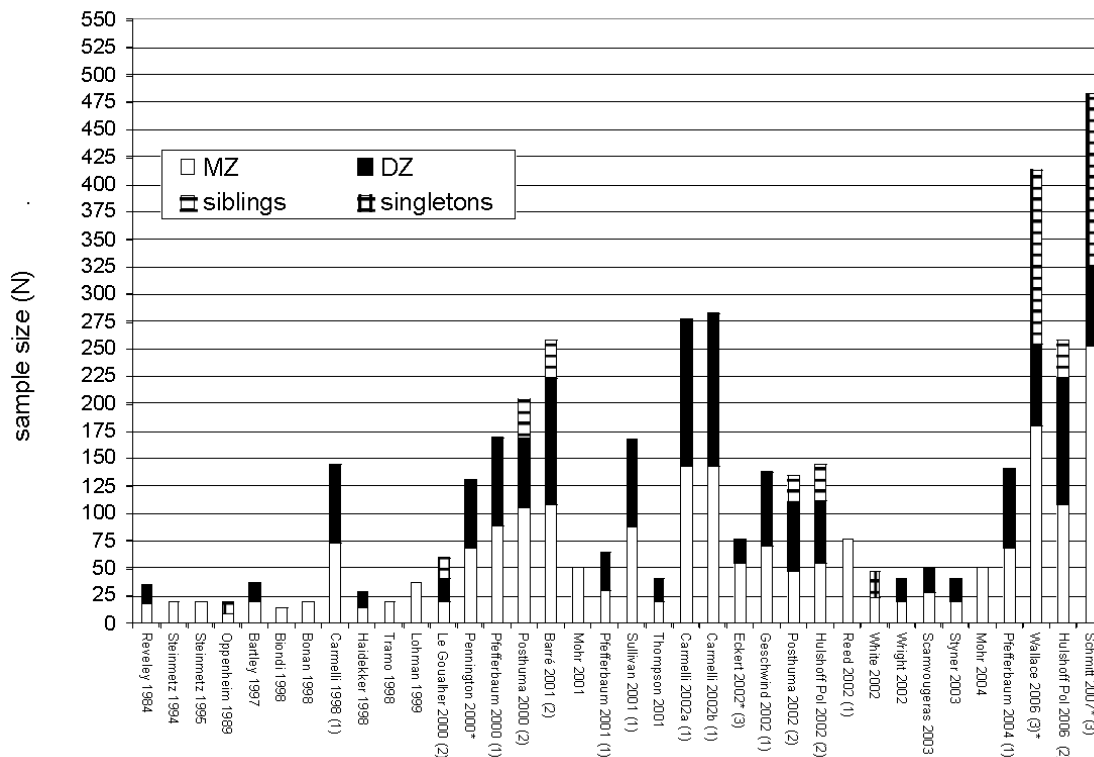

Figure 2
Sample characteristics of the extant MRI twin studies on typical populations.

Note: To facilitate comparisons with singleton and sibling subsamples, individual twins are counted rather than twin pairs. Several reports share overlapping samples, either derived from the National Heart, Lung, and Blood Institute sample (1), the Netherlands Twin Registry (2), or NIMH's longitudinal pediatric imaging study (3).

   * = reports based on data from pediatric populations.

image processing techniques rarely use advanced statistical genetic methodologies, and vice versa. Of the studies that demonstrate advanced methodological approaches in both domains, many (e.g., Wright et al.) are limited by extraordinarily small samples. Some of the newer studies (e.g., Holshoff Pol et al., 2006) set new standards for the rigorous combination of neuroimaging, quantitative genetics, and statistical power that will be required in order to provide definitive answers to most important neurogenetic questions.

The Role of MRI in Twin Research and Prospects for the Future

Even though the field is in its infancy, the synthesis of imaging and twin research already has produced some intriguing findings. In addition to confirming our expectations that volumes of large brain structures are highly heritable, studies at higher resolution suggest that regions of the brain involved in language, executive function, multimodal association, and emotion may have particularly strong genetic determinants. There is limited, but tantalizing evidence of genetically mediated relationships between cognition and brain structure, and prominent genetic correlations between diverse neuroanatomical regions.

A recent special edition of *Human Brain Mapping* on genetics and imaging (Volume 28, Issue 8) reflects the increasing interest in fusing these sciences within the neuroimaging community. Combining genetics and imaging is hardly novel; since the emergence of MRI, for example, the functional anatomy of neurogenetic disease has been of great interest (Reiss et al., 2000). What seems different now is the sheer increase in scale for investigation of the genetics of typical neurodevelopment, with several large twin studies just beginning to report their initial findings. Several more large projects (e.g., the Vietnam Era Twin Study of Aging, and the Brisbane Twin Imaging Study) are well on their way towards gathering large samples by the standards of conventional brain imaging. With these samples, much more subtle questions can be asked, such as how genetic effects change over neurodevelopment and aging, how different neuroanatomic structures share common genetic determinants, how genetic effects on behavior are mediated through cortical networks, and whether individual differences in functional neuroanatomy are genetically mediated. Further, as many of these studies are longitudinal and population-based, the ability to measure brain structure in subjects before and after the development of common psychiatric conditions (e.g., ADHD, dementia) is a likely possibility.
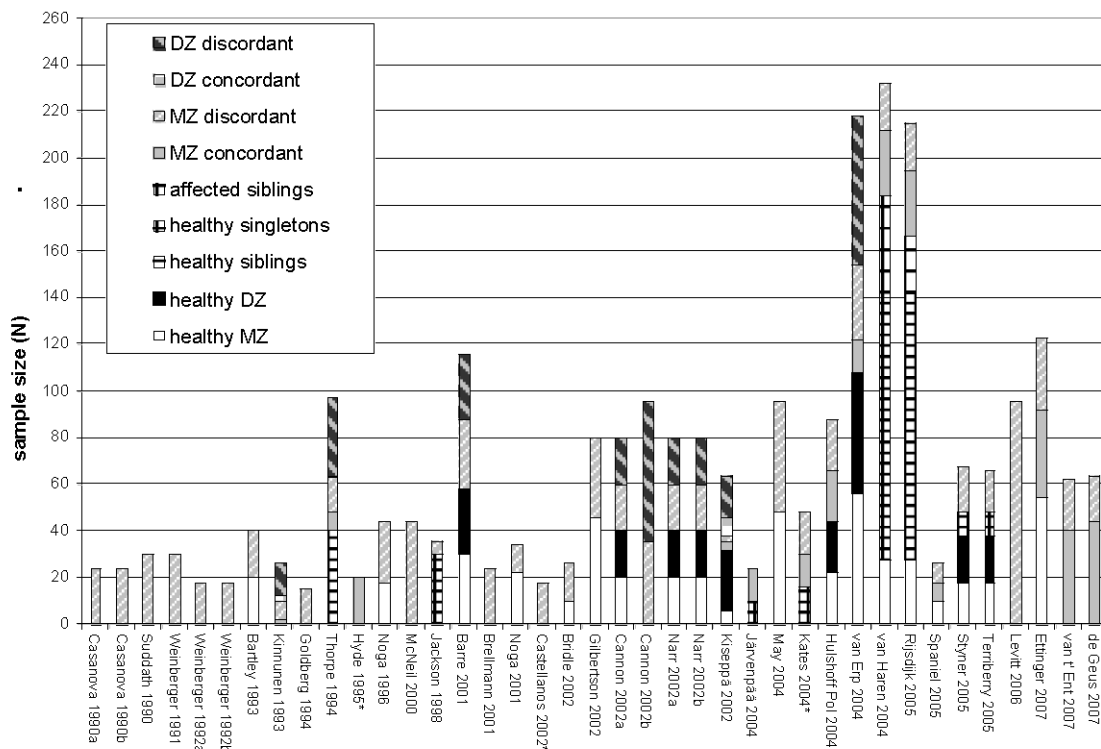

Figure 3

Sample characteristics of the extant MRI twin reports on neuropathology.

Note: Control twins are shown as solid colors (MZ white, DZ black). Qualitative characteristics of these studies are provided in Table 2.

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The next decade promises to be an exciting time for individuals interested in the genetics of neurobiological phenotypes. It will also represent a critical moment in the evolution of behavioral genetics, a moment in which the field must decide how best to integrate these new techniques into its rigorous tradition of quantitative analysis. Simply ignoring neurobiological measures could have serious detrimental effects, as rapid advances in neurogenetics and subsequent changes in the scientific landscape are inevitable. On the other hand, scientists unfamiliar with neuroimaging should avoid being too mesmerized by the technological aspects of the methods. Rather, we must critically evaluate how best to bring these powerful tools together in a meaningful and productive manner.

Acknowledgments

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