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Heritability of brain volumes in older adults: the Older Australian Twins Study

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ABSTRACT

The relative contributions of genetic and environmental factors to brain structure change throughout the lifespan. Brain structures have been reported to be highly heritable in middle-aged individuals and younger; however, the influence of genes on brain structure is less studied in older adults. We performed a magnetic resonance imaging study of 236 older twins, with a mean age of 71.4 ± 5.7 years, to examine the heritability of 53 brain global and lobar volumetric measures. Total brain volume (63%) and other volumetric measures were moderately to highly heritable in late life, and these genetic influences tended to decrease with age, suggesting a greater influence of environmental factors as age advanced. Genetic influences were higher in men and on the left hemisphere compared with the right. In multivariate models, common genetic factors were observed for global and lobar total and gray matter volumes. This study examined the genetic contribution to 53 brain global and lobar volumetric measures in older twins for the first time, and the influence of age, sex, and laterality on these genetic contributions, which are useful information for a better understanding of the process of brain aging and helping individuals to have a healthy aging.

1. Introduction

The development of the human brain is under the influence of both genetic and environmental factors. The classical method to examine these influences is the twin design, as monozygotic (MZ) twins share all their genes, whereas dizygotic (DZ) twins share on average only 50% of their segregating DNA (Plomin et al., 1994). The twin design is used to estimate the "heritability" of a trait, which is the proportion of the observable differences between individuals that is because of genetic factors. Previous studies have reported heritability for a number of structural brain measures, which include brain volume (BV) (Kremen et al., 2010; Pfefferbaum et al., 2000; Thompson et al., 2001), brain surface complexity (Gatt et al., 2012; White et al., 2002), white matter fractional anisotropy, (Chiang et al., 2011; Kochunov et al., 2010) and cortical thickness (Gatt et al., 2012; Panizzon et al., 2009; Winkler et al., 2010). A recent meta-analysis of BV heritability (Blokland et al., 2012) reported that comparing the results of different studies was difficult because of the demographic or methodological differences. However, a collation of the published data showed the influence of genes on brain structures to be in the range of 73%–91% for intracranial volume (ICV), 46%–94% for BV, 64%–89% for cerebrum, 56%–82% for gray matter (GM), 80%–88% for white matter (WM), 26%–84% for the frontal lobe, 30%–86% for the parietal lobe, 55%–88% for the temporal lobe, and 32%–74% for the occipital lobe (Baare et al., 2001; DeStefano et al., 2009; Geschwind et al., 2002; Gilmore et al., 2010; Wallace et al., 2006; Yoon et al., 2010a). It should be noted however, that most of these studies were performed on individuals younger than 65 years.

We found only 7 studies that examined BV heritability in individuals aged older than 65 years (Carmelli et al., 2002;

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DeStefano et al., 2009; Geschwind et al., 2002; Pfefferbaum et al., 2000, 2001, 2004; Sullivan et al., 2001). These studies reported moderate heritability for key BVs, e.g. 64% heritability for cerebrum (Geschwind et al., 2002), 46% for total BV (DeStefano et al., 2009), 54% for total frontal, 47% for total parietal, 46% for total temporal, and 28% for total occipital lobes (Geschwind et al., 2002). However, these studies had a number of limitations: the study by DeStefano et al. (2009) was a family study which usually has a lower power compared with a twin design; the other 6 studies were twin designs but were all performed on male twins only; and the study by Pfefferbaum et al. (2001) had a small sample size (15 MZ and 18 DZ pairs). Moreover, these studies selected a rather narrow range of brain volumetric measures, and therefore they do not give a comprehensive picture of heritability across multiple brain regions. Pfefferbaum et al. (2000, 2001, 2004) studied the corpus callosum, lateral ventricles, and ICV; Geschwind et al. (2002) reported on right and left frontal, temporal, occipital and parietal lobes, and the hemispheres; Sullivan et al. (2001) reported on the hippocampus, corpus callosum, and ICV; and Carmelli et al. (2002) reported on the right and left frontal, temporal, occipital and parietal lobes, and 2 cerebrospinal fluid (CSF) measures. To address these limitations and gaps in the literature, the present study used the twin design, included a large number of male and female twins, and studied a considerable number of brain volumetric measures, including ICV, cerebrum, cerebellum, total GM, total WM, hemispheric volumes, right and left lobar, GM and WM volumes, and the frontal, temporal, occipital, parietal and cerebellar lobes. These structures show significant volume changes in late lifetime, and therefore studying the reason of their changes would shed light on a better understanding of the aging process.

Heritability of the brain measures might change over the lifespan. Although many brain phenotypes have been genetically studied, evidence for the changes of brain heritability with age comes mostly from the neuroimaging studies of brain volume. For example, increments of heritability of BVs during development and early adulthood have been illustrated (Lenroot et al., 2009; Wallace et al., 2006). On the other hand, although very few studies have examined the changes of BV heritability in late life, and as listed previously they might have some limitations, decrement of the heritability of BVs after reaching adulthood is suggested (Geschwind et al., 2002; Pedersen, 2000; Pfefferbaum et al., 2000). Changes in the genetics of brain cognition with age have also been observed in a review study (Lee et al., 2010). One possible reason for these changes is the interaction of genes and environment, which is able to alter the number and variety of active genes or change their level of activity (Chiang et al., 2011; Plomin et al., 1994; Sarah et al., 2007; Walsh, 1980). Aging is associated with a reduction of brain volume (Jernigan et al., 2001; Resnick et al., 2000; Scahill et al., 2003; Trollor and Valenzuela, 2001), impairments in brain diffusivity (Kochunov et al., 2011) and cortical thinning (Brans et al., 2010), and it is important to understand the relative influence of genetic and environmental factors on these changes (Kremen et al., 2012).

Many brain phenotypes have been observed to show different genetic influences in men and women, and examples include total BV (Everaerd et al., 2012; Faass et al., 2013; Posthuma et al., 2000), brain WM integrity (Chiang et al., 2011) and WM hyperintesity volume (Atwood et al., 2004), brain functional connectivity (Damoiseaux et al., 2012), and more phenotypes as reviewed previously (Vink et al., 2012). However, the studies that have investigated sex differences of genetic influences in specific brain regions are very rare. Such examples would include the observation of sex-specific messenger RNA expression levels in medial preoptic area and ventromedial hypothalamus (Faass et al., 2013), differential influences of the X chromosome on different brain regions (Lentini et al., 2012), and the sex-specific influences of brain-derived neurotrophic factor gene on hippocampus, frontal cortex, and hypothalamus in an animal study (Chourbaji et al., 2012). These preliminary reports suggest that brain regions might vary in the degree to which sex influences genetic expression.

In this study, we analyzed data from the Older Australian Twins Study (OATS) to investigate heritability of brain volume in late life. Fifty-three global and lobar brain volumetric measures were selected. Based on previous reports, we hypothesized that brain structures would be highly heritable in older adults (Geschwind et al., 2002; Pfefferbaum et al., 2004; Sullivan et al., 2001), that genetic influences would decrease with age (Pfefferbaum et al., 2000) and that heritability would be higher in men (Chiang et al., 2011) and in the left hemisphere (Eyler et al., 2012; Thompson et al., 2001). We also expected to find high genetic correlations between the volumetric measures (Glahn et al., 2007; Hulshoff Pol et al., 2006c; Schmitt et al., 2010). To the best of our knowledge, this study for the first time examined the genetic contribution to certain brain volumes in an older cohort of twins, and the influence of age, sex, and laterality on these contributions.

2. Methods

2.1. Participants

Participants were drawn from the OATS, a population-based study of twins aged 65 years or older (Sachdev et al., 2009a) living in the 3 eastern states of Australia (New South Wales, Victoria, and Queensland) and registered with the Australian Twin Registry (www.twins.org.au). Individuals who consented to participate were included if they had a consenting co-twin and were sufficiently competent in English to complete a neuropsychological assessment in that language. They were excluded if they were currently suffering from a life-threatening illness or a psychotic disorder. In addition, participants were excluded from the imaging component of the study if they had claustrophobia or a contraindication for magnetic resonance imaging (MRI) such as a cardiac pacemaker, a ferromagnetic foreign body, or an implanted device.

At the time of this analysis, a total of 285 individuals had been scanned in OATS. The exclusion of single twins (n = 17), siblings (n = 14), and opposite-sex DZ twins (n = 18), because of their confounding effects (Brun et al., 2009; Chou et al., 2009; Hulshoff Pol et al., 2006b; Yoon et al., 2011), resulted in 236 participants comprising 154 MZ and 82 DZ individuals (54 male MZ, 100 female MZ, 20 male DZ, and 62 female DZ). This sample had a mean age of 71.4 (±5.7) years (range 65–88 years, 1st quartile = 67, 3rd quartile = 73), Mini-Mental State Examination (Folstein et al., 1975) score of 28.71 (±1.40), Global Deterioration Scale (Sheikh and Yesavage, 1986; Yesavage et al., 1983) score of 1.60 (±2.90), handedness (Sachdev et al., 2009a) (right = 195, left = 25, mixed = 16), and 10.89 (±3.01) years of education. Notably, the MZ and DZ groups did not differ significantly (using "ttest2" function in MATLAB) in age (p-value = 0.38), Mini-Mental State Examination (p-value = 0.40), years of education (p-value = 0.33), handedness (p-value = 0.61) or Global Deterioration Scale (p-value = 0.52). There were more women (n = 164) than men (n = 72), and the men were slightly older (men mean age = 72.18 ± 4.9 (65–82 years; 1st quartile = 67; 3rd quartile = 76); women mean age = 70.19 ± 4.8 (65–88 years; 1st quartile = 66; 3rd quartile = 73); p = 0.0057). About 5% of the participants were classified as having mild cognitive impairment (MCI), but the