NeuroImage 106 (2015) 154–160

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Does degree of gyrification underlie the phenotypic and genetic associations between cortical surface area and cognitive ability?

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ARTICLE INFO

Article history:
Accepted 18 November 2014
Available online 26 November 2014

Keywords:
Gyrification
Cortical folding
Cognitive ability
Heritability
Twin
Aging

ABSTRACT

The phenotypic and genetic relationship between global cortical size and general cognitive ability (GCA) appears to be driven by surface area (SA) and not cortical thickness (CT). Gyrification (cortical folding) is an important property of the cortex that helps to increase SA within a finite space, and may also improve connectivity by reducing distance between regions. Hence, gyrification may be what underlies the SA–GCA relationship. In previous phenotypic studies, a 3-dimensional gyrification index (3DGI) has been positively associated with cognitive ability and negatively associated with mild cognitive impairment, Alzheimer's disease, and psychiatric disorders affecting cognition. However, the differential genetic associations of 3DGI and SA with GCA are still unclear. We examined the heritability of 3DGI, and the phenotypic, genetic, and environmental associations of 3DGI with SA and GCA in a large sample of adult male twins (N = 512). Nearly 85% of the variance in 3DGI was due to genes, and 3DGI had a strong phenotypic and genetic association with SA. Both 3DGI and total SA had positive phenotypic correlations with GCA. However, the SA–GCA correlation remained significant after controlling for 3DGI, but not the other way around. There was also significant genetic covariance between SA and GCA, but not between 3DGI and GCA. Thus, despite the phenotypic and genetic associations between 3DGI and SA, our results do not support the hypothesis that gyrification underlies the association between SA and GCA.

Introduction

The formation of cortical folding is highly reproducible within species, with minor individual variations (Rakic, 2009). Yet the purposes of cortical folding across the lifespan are still unknown. The degree of gyrification of the human brain has historically been believed to reflect a need to increase SA without disproportionately increasing head size (e.g., Armstrong et al., 1995; Reillo et al., 2011). Various theories have been posited to explain patterns of cortical folding. It may, for example, be a way of improving connectivity by reducing distance between regions (for a review of gyrification and connectivity, see Zilles et al., 2013) or the reduction of axonal length between cortical areas (Van Essen, 1997; for a review see White and Hilgetag, 2011). It also seems likely that improved connectivity provides a means of allowing for increased cognitive capacity. Primate research seems consistent with this hypothesis. For example, studies of primates have indicated that larger brains have increased folding relative to smaller brains (e.g., Rilling and Insel, 1999), and among more recently evolved primates, convolution has been found to have increased at a faster pace than has brain size (Zilles et al., 1989). Consequently, degree of gyrification might reflect cognitive changes most distinctive to human primates, and may modulate intelligence in humans.

Abbreviations: AFQT, Armed Forces Qualification Test; CT, cortical thickness; GCA, general cognitive ability; GI, gyrification index; 3DGI, 3-dimensional gyrification index; SA, surface area; VETSA, Vietnam Era Twin Study of Aging.

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http://dx.doi.org/10.1016/j.neuroimage.2014.11.040
1053-8119/

Folding, and consequent surface expansion of the cerebral cortex, appears to be an important factor in influencing mammalian cognitive abilities (for a review, see Sun and Hevner, 2014). Overall, there are converging lines of evidence consistent with differential expansion being a mechanism for gyrification; the idea of connectivity as the primary function of gyrification has generally not been supported (Sun and Hevner, 2014; Ronan et al., 2014; for studies modeling increased cortical thickness without gyrification, see Murre and Sturdy, 1995 and Ruppin et al., 1993). Of the small number of gyrification studies published to date, the phenotype has been studied largely in relation to neuropsychiatric disorders such as Alzheimer's disease, autism, velocardial facial syndrome, and schizophrenia (Liu et al., 2012; Wallace et al., 2013; Schaer et al., 2006, 2013; Kates et al., 2009; Palaniyappan and Liddle, 2012; Nanda et al., 2013). Wallace et al. (2013) reported that while autism-spectrum cases did not differ from controls in SA, they exhibited significant posterior gyrification increases bilaterally. This group made the case that lack of gyrification–SA association may reflect developmentally dissociable phenotypes, and that gyrification increases could lead to certain cognitive abilities observed in people with autism-spectrum disorders. Gyrification has also been negatively associated with psychosis and 22q11 deletion syndrome (e.g., Palaniyappan and Liddle, 2012; Nanda et al., 2013; Schaer et al., 2006), both genetic conditions notable for multiple cognitive deficits (reviews by Elvevag and Goldberg, 2000; Green et al., 2004; Eisenberg et al., 2010). An examination of Alzheimer's disease cases found that global gyrification and sulcal width differentiated mild Alzheimer's cases from healthy controls (Liu et al., 2012). Mild cognitive impairment has also been associated with greater than normal reductions in gyrification in late-life (Liu et al., 2013). The latter findings suggest that gyrification might be very relevant to cognitive aging.

Other research has examined the relevance of gyrification to normative aging. A study by Zilles et al. (1988) manually measured 3DGI postmortem in the brains of 61 adults ages 16–91. This early study of a gyrification index, similar to the index derived currently using our MRI methods, manually measured degree of gyrification using multiple histological brain slices. Manual measurement of postmortem brain is very labor-intensive, and in that study it required the measurement of only every fourth slice of the brain. They found no significant relationship between 3DGI and age. Using different types of measures, Magnotta et al. (1999) observed reduced gyrification with age in the brains of 148 adults aged 18–82 years based on measures of sulcal and gyral curvature. Hogstrom et al. (2013) reported results from an MRI study of 322 adults ages 20–85, and found that 3DGI decreased with age (Hogstrom et al., 2013). This study used the same index of gyrification as in the present study, one that is based on the entire cortex.

Some research suggests that genetic factors have a strong influence on sulci and gyri during neurodevelopment (Piao et al., 2004). Evaluating gyral patterns in monozygotic (MZ) twins, Lohmann et al. (1999) observed that deeper and developmentally earlier sulci of the brain are more highly correlated between twins than are the surface sulci. They concluded that more superficial sulci, developing after birth, may be more affected by environmental influences.

These two early studies are limited by the fact that they each included only about 20 twin pairs. These are considered to be very small sample sizes for twin analysis, something that may substantially increase the risk of unreliable results (Neale and Cardon, 1992; Martin et al., 1978). In addition, Lohmann et al. (1999) included only MZ twins. Without including dizygotic (DZ) twins, analyses cannot fully disentangle genetic influences from those due to the common environment (Neale and Cardon, 1992). The development of semi-automated techniques has made it possible for subsequent MRI twin studies to have substantially larger sample sizes. That, in turn, has made it possible to obtain more reliable estimates of the amount of variance in gyrification that is accounted for by genetic and environmental influences.

It is important to note, in addition, that our index of gyrification is different from the gyrification that has been examined in these twin studies. They were examining gyral patterns. In the present study, we examined degree of gyrification. The difference is analogous to shape versus volume of brain structures. Gyral patterns reflect the extent to which the patterns (or exact locations) are the same. We are measuring degree of gyrification such that one can have the same amount of gyrification without the gyri and sulci being in the same location. Heritability of the former is likely to be lower than heritability of the latter; it is probable that gyral patterns are less heritable than degree of gyrification.

In 515 middle-aged twins in the Vietnam Era Twin Study of Aging (VETSA; Kremen et al., 2006, 2013), we previously examined the genetic covariance among total SA, mean CT, and GCA (Vuoksimaa et al., in press). SA, rather than CT, drove the phenotypic and genetic associations between cortex and GCA. As noted, previous research suggests that gyrification is positively phenotypically associated with cognitive ability and negatively phenotypically associated with Alzheimer's disease and mild cognitive impairment. These findings raise the possibility that gyrification could be the underlying source of our observed SA–GCA relationships. We are unaware of any genetically informative studies of degree of gyrification or of the relationship between gyrification and cognitive ability. The goals of the present study were to: 1) estimate the heritability of gyrification; 2) examine the phenotypic and genetic associations between gyrification and SA, given that gyrification is related to SA; and 3) test whether gyrification underlies the relationship between SA and GCA.

Materials and methods

Participants

Brain imaging and cognitive data at age 51–60 years were obtained for men enrolled in the Vietnam Era Twin Study of Aging (VETSA; Kremen et al., 2006, 2013). The VETSA sample is representative of community-dwelling U.S. men within their age range based on sociodemographic and health characteristics (Kremen et al., 2006, 2013; Schoeneborn and Heyman, 2009). All participants had been in prior military service at some time between 1965 and 1975, and most (~80%) had not been exposed to combat. In other words, these were Vietnam era, not necessarily Vietnam war, veterans. Of 534 who were scanned, 512 had analyzable 3DGI data: 132 MZ twin pairs, 92 DZ twin pairs, and 64 unpaired twins. Participants chose a study site at either the University of California San Diego or Boston University. If they chose to do the study at Boston University, participants were brought to Massachusetts General Hospital for scanning procedures. All participants gave written informed consent to participate. The Institutional Review Board at each participating institution approved the study protocol.

Representativeness of the VETSA sample has been reported in detail elsewhere (Kremen et al., 2006, 2013). Overall, the prevalence for health conditions is consistent with population data for American men in this age range as reported from the 2004–2007 National Health Interview Survey by the Centers for Disease Control and Prevention (Schoeneborn and Heyman, 2009). In this sample, years of education $M(SD) = 13.8\ (2.1)$, body mass index $M(SD) = 28.8\ (4.2)$, the Center for Epidemiological Studies of Depression Scale (CES-D; Radloff, 1977) current depression $M(SD) = 8.2\ (8.1)$, median = 6.0. In this sample, 24% were current smokers, 9% had diabetes, and 59% had hypertension. As cited previously, the VETSA MRI sample did not differ from the rest of the VETSA sample on any of these variables (Panizzon et al., 2009). The VETSA sample is also comparable to the general population in this age range with respect to AFQT score variance. The average AFQT score for this sample is equivalent to an IQ score of 104–105 (Kremen et al., 2011). Variances of brain measures in this sample are similar to other samples in the literature, including samples in other twin studies. Socio-economic status in this sample was normally distributed and heterogeneous, with the broadest range of scores possible ($M = 5.5$, $SD = 1.8$, sample range = 0–9). Demographic and psychiatric information is presented in Table 1.