NeuroImage 129 (2016) 356–366

Contents lists available at ScienceDirect

NeuroImage

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

Is bigger always better? The importance of cortical configuration with respect to cognitive ability

Eero Vuoksimaa [a,b,c,*], Matthew S. Panizzon [a,b], Chi-Hua Chen [a,b,d], Mark Fiecas [a,b], Lisa T. Eyler [e,a], Christine Fennema-Notestine [a,d], Donald J. Hagler Jr. [d], Carol E. Franz [a,b], Amy J. Jak [a,f], Michael J. Lyons [g], Michael C. Neale [h], Daniel A. Rinker [a,d,i], Wesley K. Thompson [a], Ming T. Tsuang [a,b], Anders M. Dale [d,j], William S. Kremen [a,b,f,**]

[a] Department of Psychiatry, University of California, San Diego, La Jolla, CA 92093, USA
[b] Center for Behavioral Genomics Twin Research Laboratory, University of California, San Diego, La Jolla, CA 92093, USA
[c] Department of Public Health, and Institute for Molecular Medicine (FIMM), University of Helsinki, Helsinki, Finland
[d] Department of Radiology, University of California, San Diego, La Jolla, CA 92093, USA
[e] Mental Illness Research Education and Clinical Center, VA San Diego Healthcare System, San Diego, CA, USA
[f] Center of Excellence for Stress and Mental Health, VA San Diego Healthcare System, La Jolla, CA 92093, USA
[g] Department of Psychological and Brain Sciences, Boston University, Boston, MA 02215, USA
[h] Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University School of Medicine, Richmond, VA 23220, USA
[i] Imaging Genetics Center, Institute for Neuroimaging and Informatics, University of Southern California, Los Angeles, CA, USA
[j] Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093, USA

ARTICLE INFO

Article history:
Received 12 August 2015
Accepted 22 January 2016
Available online 29 January 2016

Keywords:
Cortical surface area
Cortical thickness
General cognitive ability
Twin research
Neurodevelopment

ABSTRACT

General cognitive ability (GCA) has substantial explanatory power for behavioral and health outcomes, but its cortical substrate is still not fully established. GCA is highly polygenic and research to date strongly suggests that its cortical substrate is highly polyregional. We show in map-based and region-of-interest-based analyses of adult twins that a complex cortical configuration underlies GCA. Having relatively greater surface area in evolutionary and developmentally high-expanded prefrontal, lateral temporal, and inferior parietal regions is positively correlated with GCA, whereas relatively greater surface area in low-expanded occipital, medial temporal, and motor cortices is negatively correlated with GCA. Essentially the opposite pattern holds for relative cortical thickness. The phenotypic positive-to-negative gradients in our cortical-GCA association maps were largely driven by a similar pattern of genetic associations. The patterns are consistent with regional cortical stretching whereby relatively greater surface area is related to relatively thinner cortex in high-expanded regions. Thus, the typical "bigger is better" view does not adequately capture cortical-GCA associations. Rather, cognitive ability is influenced by complex configurations of cortical development patterns that are strongly influenced by genetic factors. Optimal cognitive ability appears to be driven both by the absolute size and the polyregional configuration of the entire cortex rather than by small, circumscribed regions.

Introduction

There is a long history of scientific curiosity about the neural underpinnings of individual differences in intelligence or general cognitive ability (GCA). Elucidating those brain-behavior relationships, including their genetic and environmental underpinnings, is important for understanding normal and pathological development and aging, and neuropsychiatric disorders.

Studies of associations between GCA and neocortical (hereafter referred to as cortical) gray matter size are growing in number. There are more studies of cortical thickness (CT) than of cortical surface area (SA). Studies of CT have been mixed, with reports of positive, negative, and no associations with GCA (Vuoksimaa et al., 2015). Although there are fewer studies of SA–GCA relationships, those have consistently shown significant positive SA–GCA associations (Vuoksimaa et al., 2015). Although there is some evidence in support of the predominant view that "bigger is better" when it comes to cortical-GCA associations, it seems likely that the cortical underpinnings of GCA are not so simple. A fundamental conundrum, for example, is the fact that men do not have higher average GCA than women despite having larger brains

* Correspondence to: E. Vuoksimaa, Department of Public Health, University of Helsinki, P O Box 20 (Tukholmankatu 8 2B), FI-00014 University of Helsinki, Finland.
** Correspondence to: W. S. Kremen, Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive (MC 0738), La Jolla, CA 92093, USA.
E-mail addresses: eero.vuoksimaa@helsinki.fi (E. Vuoksimaa), wkremen@ucsd.edu (W.S. Kremen).

http://dx.doi.org/10.1016/j.neuroimage.2016.01.049
1053-8119/

and larger cortex. Our view is that we need to think in terms of complex configurations of SA and CT in order to develop a more complete picture of the cortical underpinnings of GCA. At a minimum, this would seem to require a combined examination of both SA and CT (see Schnack et al., 2015; Vuoksimaa et al., 2015), but that has been rare in studies of cortical-GCA associations.

At the global level, SA and CT are genetically independent (Panizzon et al., 2009), and SA appears to be the primary driver of the phenotypic and genetic association between cortex size and GCA (Vuoksimaa et al., 2015). However, there is also evidence that there are some, generally inverse SA–CT associations in some subregions (Panizzon et al., 2009). The relationship between regional SA and CT may be affected by the phenomenon of cortical stretching whereby cortical thinning is presumed to be caused by regional areal expansion. This phenomenon is seen throughout adulthood (Hogstrom, Westlye, Walhovd, & Fjell, 2013) and is most pronounced in some prefrontal regions (Hogstrom et al., 2013; Panizzon et al., 2009); also when looking at the relative SA and CT (Winkler et al., 2010). Further evidence for the importance of looking at both relative SA and relative CT comes from studies of gyrification (Tallinen, Chung, Biggins & Mahadevan, 2014; Jalil Razavi, Zhang, Liu & Wang, 2015). Gyrification of the cortex, an important characteristic of the human brain, is positively correlated with SA but negatively with CT (Hogstrom et al., 2013). A recent work suggests that gyrification patterns are a function of relative cortical expansion and relative thickness (Tallinen et al., 2014). In the presence of tangential expansion, thinner cortex buckles and folds more easily than thicker cortex, which results in more gyrification (Zilles et al., 2013). In short, studying both cortical SA and CT is needed for greater understanding of brain morphometry and its behavioral correlates such as cognitive ability.

Both animal and human studies have demonstrated an anterior–posterior (A–P) gradient of genetic effects on cortical areal expansion. The same genes that cause anterior SA expansion also cause posterior contraction and vice versa (Bishop, Rubenstein, & O'Leary, 2002; Chen et al., 2011; Chen et al., 2012; Chen et al., 2013; O'Leary, Chou, & Sahara, 2007). We have also demonstrated that, relatively orthogonal to the A–P gradient of areal expansion, there is a dorsal–ventral (D–V) gradient of genetic influences on CT in the human brain indicating that the same genetic effects that make cortex relatively thicker in dorsal regions also make cortex relatively thinner in ventral regions and vice versa (Chen et al., 2013). In animal and human studies, these gradients from positive to negative correlations are observed only after global effects are taken into account, i.e., total SA and mean CT, respectively. Otherwise, the gradients simply shift from more strongly positive to less strongly positive: i.e., the same genetic effects that cause SA expansion in one region also cause SA expansion in other regions, and the same genetic effects that make cortex thicker in one region also make cortex thicker in other regions (Eyler et al., 2012). In order to elucidate relative regional effects, it is necessary to examine regional values in the context of global size. However, studies of the relationship between GCA and either SA or CT have not accounted for total SA or mean CT (reviewed by Vuoksimaa et al., 2015).

One recent finding regarding SA is the observation that better visuospatial reasoning ability was associated with greater areal expansion in prefrontal, lateral temporal, and inferior parietal cortices (Fjell et al., 2015). The authors pointed out that these are regions that have undergone the greatest expansion during evolution and human postnatal development. Indeed, it seems that the highly non-uniform areal expansion of the cortex follows the same pattern across species (humans versus non-human primates) and within human development (Chaplin, Yu, Soares, Gattass, & Rosa, 2013; Fjell et al., 2015; Hill et al., 2010). Moreover, in humans the relatively high-expanded cortical regions also tend to be lightly and later myelinated, whereas relatively low-expanded regions tend to include regions that are more heavily and early myelinated (Glasser & Van Essen, 2011). Highly expanded/lightly myelinated regions include prefrontal, lateral temporal and inferior parietal cortices; relatively low-expanded/heavily myelinated regions include occipital and medial temporal cortices as well as regions in and around the central sulcus (Fjell et al., 2015; Glasser & Van Essen, 2011; Hill et al., 2010).

GCA is highly polygenic trait (Davies et al., 2011) and increased GCA has been positively selected in human evolution (Joshi et al., 2015). The patterning of cortical SA in humans also differs as a function of regions that are more strongly influenced by single nucleotide polymorphisms in more versus less evolutionarily conserved regions of the genome (Chen et al., 2015). However, the links among patterns of expansion/myelination, GCA, SA and CT have not yet been examined in combination, particularly with respect to genetic influences. In the current study, we took the novel approach of examining the cortical maps of the relationship between GCA and both CT and SA while taking global size into account. Specifically, in line with the animal literature and our own earlier work, we scaled regional SA in relation to total SA and regional CT in relation to mean CT in order to investigate if the configuration of high-expanded and low-expanded regions relative to global size is related to GCA. We then statistically compared these maps to maps of regions with high- versus low-expansion/light- versus heavy-myelination. Finally, we used the power of our twin design to examine the contribution of genetic and environmental factors in the observed cortical-GCA associations.

We hypothesized that cortical-GCA relationships would be determined by the configuration of the cortex such that we would observe both positive and negative correlations in relation to global effects of total SA and mean CT when examining SA and CT, respectively. Thus, cortical-GCA relationships would not simply be consistently positive (i.e., "bigger is better"). Specifically, we hypothesized that: 1) the gradients from positive to negative correlations between relative SA and GCA would be consistent with the non-uniform cortical expansion patterns across evolution and human development (i.e., high-expanded regions having positive correlation with GCA and low-expanded regions having negative correlations with GCA); 2) relatively thinner cortex in high-expanded regions would be associated with better GCA; and 3) genetic factors would play a significant role in regional cortical-GCA associations.

In short, the current evidence of A–P and D–V gradients (Chen et al., 2011, 2013) and of the dynamics between relative SA and CT in the configuration of the cortex (Tallinen et al., 2014) suggests that investigating relative SA and CT in combination can shed light onto the fundamental characteristics of cortical development. However, no studies have used the approach of looking at both relative SA and CT in the context of cognitive abilities. We use the term relative regional effects to indicate associations based on regional values relative to global size (e.g., the ratio of the SA at a vertex or a region of interest [ROI] to total SA).

Materials and methods

Participants

Brain imaging and cognitive data at ages 51–60 were obtained for 534 men from the Vietnam Era Twin Study of Aging (VETSA 1: 2002–2008) (Kremen et al., 2013). Of those, 513 had analyzable MRI data for creating continuous cortical maps: 130 monozygotic (MZ); 96 dizygotic (DZ) twin pairs; and 61 unpaired individual twins. DNA-based zygosity was available for 92% of the pairs; for others it was determined by questionnaire and blood group. The VETSA sample is representative of U.S. men in their age range based on sociodemographic and health characteristics (Kremen et al., 2006; Schoenborn & Heyman, 2009). All had prior military service, but most (78%) were not exposed to combat (Eisen, True, Goldberg, Henderson, & Robinette, 1987; Henderson et al., 1990).

Data were collected at two sites: University of California, San Diego and Boston University. Brain imaging in Boston was done at the Massachusetts General Hospital. All participants gave written informed