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Topology of genetic associations between regional gray matter volume and intellectual ability: Evidence for a high capacity network

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ABSTRACT

Intelligence is associated with a network of distributed gray matter areas including the frontal and parietal higher association cortices and primary processing areas of the temporal and occipital lobes. Efficient information transfer between gray matter regions implicated in intelligence is thought to be critical for this trait to emerge. Genetic factors implicated in intelligence and gray matter may promote a high capacity for information transfer. Whether these genetic factors act globally or on local gray matter areas separately is not known.

Brain maps of phenotypic and genetic associations between gray matter volume and intelligence were made using structural equation modeling of 3 T MRI T1-weighted scans acquired in 167 adult twins of the newly acquired U-TWIN cohort. Subsequently, structural connectivity analyses (DTI) were performed to test the hypothesis that gray matter regions associated with intellectual ability form a densely connected core.

Gray matter regions associated with intellectual ability were situated in the right prefrontal, bilateral temporal, bilateral parietal, right occipital and subcortical regions. Regions implicated in intelligence had high structural connectivity density compared to 10,000 reference networks ($p = 0.031$). The genetic association with intelligence was for 39% explained by a genetic source unique to these regions (independent of total brain volume), this source specifically implicated the right supramarginal gyrus.

Using a twin design, we show that intelligence is genetically represented in a spatially distributed and densely connected network of gray matter regions providing a high capacity infrastructure. Although genes for intelligence have overlap with those for total brain volume, we present evidence that there are genes for intelligence that act specifically on the subset of brain areas that form an efficient brain network.

Introduction

Distinct regions of the cerebral cortex show consistent associations with general intellectual ability, as shown in brain imaging studies measuring brain structure, and activity (Haier et al., 2004; Gray and Thompson, 2004; Jung and Haier, 2007; Narr et al., 2007; Colom et al., 2009; Barbey et al., 2012; Schnack et al., 2014). These regions include early information processing areas of the temporal (fusiform gyrus, Wernicke's area) and occipital lobes (extrastriate cortex) as well as higher associative processing areas of the parietal (supramarginal gyrus, angular gyrus and superior parietal gyrus) and frontal lobes (dorsolateral prefrontal cortex, inferior frontal gyrus and orbitofrontal cortex). Also, subcortical areas such as the hippocampus, caudate nucleus and thalamus show positive associations with intelligence (MacLullich et al., 2002; Frangou et al., 2004; Haier et al., 2009; Bohlken et al., 2014a; Grazioplene et al., in press). The consistency of these findings across the literature has led to network models of intelligence, stating that cortical and subcortical gray matter regions rely on efficient communication through white matter fiber bundles to support intelligence (Jung and Haier, 2007; Deary et al., 2010; Colom et al., 2010). Indeed, network analyses have revealed that individuals with a higher intelligence have more efficient brain networks (Li et al., 2009; van den Heuvel et al., 2010; Langer et al., 2012; Fischer et al., 2014). However, the extent to which brain networks for intelligence are shaped through genes and environment is not known.

Gray matter volume and intelligence share common genetic variance (Thompson et al., 2001; Baaré et al., 2001; Posthuma et al., 2002; Toga and Thompson, 2005). Importantly, genetic factors implicated in intelligence and gray matter are found in specific regions, pertaining

Abbreviations: A, additive genetic; C, common environmental; CFARI, Crossing Fiber Angular Resolution of Intra-Voxel structure; DNA, deoxyribonucleic acid; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; DZ, dizygotic; E, unique environmental; EPI, echo-planar imaging; FA, fractional anisotropy; INFACT, INtravoxel Fiber Assegnment by Continuous Tractography; IQ, intelligence quotient; MZ, monozygotic; MRI, magnetic resonance imaging; ROI, region of interest; SD, standard deviation; SEM, structural equation modeling; SMG, supramarginal gyrus; STV, summed total volume; TB, total brain volume; WAIS, Wechsler adult intelligence scale.

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primarily to the medial/superior frontal, occipital and parahippocampal cortices and the thalamus (Hulshoff Pol et al., 2006; Brans et al., 2010; Bohlken et al., 2014b). There is evidence for considerable differences in the degree to which cortical and subcortical regions are shaped through genes (Wright et al., 2002; Kremen et al., 2010; Rimol et al., 2010; Blokland et al., 2012; Chen et al., 2012). Although, overall shared genetic influences (i.e. through total brain volume) seem to out weight region-specific genetic influences (Giedd et al., 2007). These findings raise the question to what extent the genetic correlation between regional gray matter and intellectual ability is mediated through a general overlapping genetic factor (i.e. total brain volume) or through region specific genetic influences. Therefore, the first aim of this study was to investigate the influence of environmental and genetic factors on the association between local gray matter volume and intellectual ability by use of a multivariate twin design, incorporating total brain volume. Associations with intelligence subtests were also explored to test for regional variation according to distinguishable cognitive abilities.

Interregional connectivity may be the key to the neural processes that give rise to intelligence (Gray and Thompson, 2004; Jung and Haier, 2007; Deary et al., 2010; Bullmore and Sporns, 2012). Although genetic influences on white matter microstructure and functional connectivity have been found to overlap with cognitive ability (Chiang et al., 2009; Koten et al., 2009), it remains to be investigated whether genetic influences on gray matter regions implicated in intelligence could be related to underlying connectivity patterns. We hypothesized that the gray matter areas implicated in intelligence form a densely connected network to facilitate efficient information transfer. Therefore, the second aim of this study was to characterize the connectivity of gray matter regions that associate with intellectual ability using diffusion tensor imaging. This was accomplished by comparing the density of the structural connectivity underlying the gray matter areas implicated in intelligence with a distribution of reference networks.

Methods

Participants

In this study, 167 adult twins participated. Participants were all part of the U-Twin cohort, which was acquired between 2009 and 2013 (Bohlken et al., 2014b). The sample consists of 45 complete monozygotic (MZ), 35 complete dizygotic (DZ) twin pairs and 7 individuals from incomplete (1 MZ, 6 DZ) pairs of whom a magnetic resonance imaging (MRI) brain scan and intelligence quotient (IQ) were obtained. Of the DZ twins, five pairs were of opposite sex (DOS). All participants were between the age of 18 and 67 years (mean = 32.7, SD = 13.6 years). Zygosity was determined by resemblance for polymorphic DNA markers. Upon participation, all subjects gave their written informed consent. This study was approved by the Medical Ethical Committee of the UMC Utrecht and the experiments were in accordance with the Declaration of Helsinki. Two DZ twins and one MZ twin did not complete the WAIS III intelligence test; therefore an evaluation of intellectual ability was obtained in 164 participants. Two DZ twins did not complete the MRI part of the study. Therefore a complete structural (T1-weighted + DWI (diffusion weighted imaging)) MRI dataset was acquired in 165 participants.

Assessment of intellectual ability

An evaluation of intellectual ability was obtained by means of a shortened version of the WAIS III general intelligence test, consisting of five subtests: Digit Symbol Substitution, Block Design, Arithmetics, Digit Span and Information. All five subtests were used to calculate a proxy for the full-scale IQ, which will be referred to as IQ from now on.

Brain image acquisition and processing

MRI scans were acquired on a Philips Achieva scanner operating at 3 T, using an eight-channel SENSE head-coil. A T1-weighted 3D fast-field echo scan was acquired from each participant. Scan acquisition was performed using the following parameters: 220 0.8 mm contiguous slices; echo time (TE) 4.6 ms; repetition time (TR) 10 ms; flip angle 8°; in-plane voxel size 0.75×0.75 mm^2.

Cortical volume of 34 anatomically delineated cortical ROIs and the volume of 7 subcortical ROIs was extracted in each hemisphere using the FreeSurfer 5.1.0 structural imaging pipeline (Fischl et al., 2004; Kremen et al., 2010). Also, a measure of total brain volume (TB) was calculated by summing the total gray matter volume, the cortical white matter volume and the cerebellar volume.

The DWI scan consisted of a single shot EPI-DTI with 30 diffusion weighted volumes ($b = 1000$ s/mm^2) with non-colinear gradient directions and five diffusion-unweighted volumes ($b = 0$ s/mm^2), TR/TE = 7035/68 ms, FOV 240 mm, matrix 128/128, 75 slices at 2 mm thickness, no gap, SENSE factor 3, no cardiac gating. Two DWI datasets were acquired in the transverse plane per subject using the same parameters but with reverse k-space readout, allowing for correction of susceptibility artifacts and increasing signal to noise ratio.

Preprocessing of the DWI scans was performed with the diffusion toolbox of Andersson et al. (Andersson and Skare, 2002; Andersson et al., 2003) and in-house developed software (Mandl et al., 2010). First, susceptibility artifacts were corrected by calculating a distortion map based on the two $b = 0$ images acquired with reversed k-space readout. Subsequently it was applied to the two sets of 30 direction-weighted images. This resulted in a corrected DWI set consisting of a single $b = 0$ image and 30 corrected weighted images, thereby avoiding the need for non-linear registration approaches to the T1-weighted images (Andersson et al., 2003). The DWI set was corrected for Eddy-current distortions and small head movements by realigning all scans to the diffusion-unweighted image (Andersson and Skare, 2002).

Tensor fitting was performed using a constrained compressed sensing algorithm called Crossing Fiber Angular Resolution of Intra-Voxel structure (CFARI) (Landman et al., 2012). CFARI models the diffusion profile in each voxel as a finite mixture of discrete and independent compartments, defining the diffusivity within each compartment separately. This has the advantage that it provides a robust framework for identifying intra-voxel structure and is able to estimate fiber tracts in areas of high fiber complexity (e.g. crossing fibers) despite the limited number of 30 orientations in which the DWI data were acquired. CFARI is implemented in the Java Image Science Toolkit and is publicly available (http://www.nitrc.org/projects/jist) (Lucas et al., 2010).

Tractography was performed using an approach called INtravoxel Fiber Assegnment by Continuous Tractography (INFACT) (Landman et al., 2012), which is a continuous tracking method based on the FACT algorithm (Mori and van Zijl, 2002). All voxels with fractional anisotropy (FA) > 0.3 were used as starting seeds for tractography. Tracing was ended when a voxel with FA < 0.1 was encountered or when the turning angle exceeded 45°. A Runge–Kutta solver was used for determining tract continuation. After tractography was completed, all fibers shorter than 10 mm were discarded, as they were deemed spurious. Finally, all remaining fibers were linearly extended by 5 mm in the orientation prior to termination to maximize the probability of penetration into the gray matter. The presence of a white matter connection between two gray matter regions was determined by labeling each streamline with the gray matter areas it connects based on the anatomical segmentation mask. The anatomical segmentation mask was registered to the DWI scan using a six-parameter rigid body transformation. A total of six scans needed to be excluded from further DTI/network analysis due to unreliable measurements.

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