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SHORT COMMUNICATION

Genetic control of functional brain network efficiency in children

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Abstract
The human brain is a complex network of interconnected brain regions. In adulthood, the brain's network was recently found to be under genetic influence. However, the extent to which genes influence the functional brain network early in development is not yet known. We report on the heritability of functional brain efficiency during early brain development. Using a twin design, young children underwent resting-state functional magnetic resonance imaging brain scans (N=86 from 21 MZ and 22 DZ twin-pairs, age=12 years). Functional connectivity, defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions, was explored using graph theory and its heritability was examined using structural equation modeling. Our findings suggest that 'global efficiency of communication' among brain regions is under genetic control (h^2 *lambda*=42%), irrespectively of the total number of brain connections (connectivity density). In addition, no influence of genes or common environment to local clustering (*gamma*) was found, suggesting a less pronounced effect of genes on local information segregation. Thus our findings suggest that a set of genes is shaping the underlying architecture of functional brain communication during development.

1. Introduction

Brain regions continuously interact through means of complex organized structural and functional connections (Sporns et al., 2005; Bullmore and Sporns, 2009; van den Heuvel and Sporns, 2011). Functional connectivity between

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brain regions at the level of co-activation of spontaneous functional MRI time-series are believed to represent functional communication between brain regions (Bullmore and Sporns, 2009; van den Heuvel and Hulshoff Pol, 2010). A growing number of studies have applied advanced graph analysis techniques to resting-state fMRI data (Lynall et al., 2010; Fornito et al., 2011; Liu et al., 2008; Van den Heuvel et al., 2008), revealing insights in the general organization of functional brain networks. In particular, studies have suggested that the efficiency of communication between brain regions plays an important role in healthy cognitive functioning (Bassett et al., 2009; van den Heuvel et al., 2009). Conversely, aberrant network organization has been suggested to underlie a wide range of psychiatric and neurological brain disorders (Stam et al., 2009; Lynall et al., 2010; van den Heuvel et al., 2010).

While several structural and functional aspects of the brain are known to be highly heritable (Brans et al., 2008; Koten et al., 2009; Peper et al., 2009; Glahn et al., 2010; Smit et al., 2008), to which extent genes and environmental factors influence these functional neural networks remains largely unknown. A recent study in adults have suggested that a large proportion of inter-individual variance of the balance between communication efficiency and cost of functional wiring is attributable to additive genetic effects (Fornito et al., 2011). As the efficiency of communication between brain regions has been suggested to evolve during brain development (Boersma et al., 2010), the examination of these genetic factors during brain development is of fundamental interest. To this end, we investigated the genetic control of functional brain networks in young twins, aged 12 years, to obtain better understanding of which parts of brain communication are driven by 'nature' (genetics) and which are influenced by 'nurture' (environment), early in development.

2. Experimental procedures

2.1. Participants

Twin families were recruited from the Netherlands Twin Register (NTR (Boomsma et al., 2006)), and represent an epidemiologically sample from the Dutch population. Children were invited to participate in a large longitudinal twin study to explore the genetic and environmental influences on brain maturation (Peper et al., 2009). Exclusion criteria for participation included, having a pacemaker, any metal materials in the head including dental braces chronic use of medication, a known major medical or psychiatric history, and participation in special education. Written informed consents were obtained from all subjects and their parents. The study was approved by the Dutch Central Committee on Research involving Human Subjects (CCMO). Parents were financially compensated for travel expenses and the children received a small gift each. Zygosity was determined based on DNA polymorphisms. Resting-state functional magnetic resonance brain imaging (MRI) scans were obtained from the twin-pairs at age 12 years. After exclusions based on scan quality, scans from 86 children (21 MZ (9m/12f) and 22 DZ (4m/4f/8dos) pairs) could be included in the study.

2.2. Image acquisition and processing

Resting-state functional MRI recordings were acquired (1.5T Philips Achieva, PRESTO, TE/TR=31.1/21.1, whole brain, 4 mm isotropic voxels, 9 min). Resting-state functional MRI time-series were preprocessed and normalized to standard MNI space (Van den Heuvel et al., 2008). The FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) software package was used for gray/white matter segmentation (Fischl et al., 2004). Functional connectivity between brain voxels was computed as the level of correlation between their spontaneous fMRI BOLD signals. For each subject, a binary functional brain network was reconstructed on the voxel-level, with the network consisting of ~9000 voxels of gray matter with functional connections between those regions that showed a level of correlation between their voxel-wise resting-state time-series higher than a set threshold ($T>.4$) (Figure 1a) (Van den Heuvel et al., 2008; van den Heuvel et al., 2009).

2.3. Graph theory

Graph theory was used to examine the topology of the functional brain networks (Bullmore and Sporns, 2009; van den Heuvel and Hulshoff Pol, 2010). The level of connectivity was expressed by the number of binary connections *K*. Global efficiency of brain networks, estimated by computing the normalized path length *lambda*, was computed as the average number of steps that are needed to travel from one place in the network to any of the other regions (normalized to the path length of a set of 20 random networks with an identical degree sequence). (van den Heuvel et al., 2009). As such, shorter (normalized) path lengths express higher levels of communication efficiency across the network. In addition, connectivity density (i.e. the number of binary connections) was examined, together with the normalized clustering-coefficient *gamma* computed as the ratio of closed and connected triplets around each node, averaged over all nodes in the network (normalized to the clustering coefficient of a set of random networks). As such, higher *gamma* values express the tendency of nodes in a network to be more locally connected (Bullmore and Sporns, 2009) (Figure 1a). For a mathematical and a more detailed description of these commonly used graph metrics see (van den Heuvel et al., 2009; Van den Heuvel et al., 2008).

2.4. Genetic analysis

A twin design was applied to explore to which extent functional brain networks are heritable in children. Twin studies is a powerful methodology to quantify to what extent genetic and environmental factors influence brain morphology. Within a twin design, a genetic ACE model can estimate the additive genetic contribution (A) of a specific trait, together with the contributions of 'common' (C) and 'unique' (E) environment (for a detailed description on twin modeling see van Soelen et al. (2012). Twin pair similarity was used to examine the genetic and environmental factors underlying the graph network metrics (*lambda*, *gamma*, *K*) using structural equation modeling (van Soelen et al., 2012). Monozygotic (MZ) twin pairs are genetically identical and share (nearly) 100% of their genetic material, while dizygotic (DZ) twin pairs and full siblings share on average 50% of their segregating genes. By comparing the MZ and DZ correlations in a twin design, one can estimate the relative influences of genes and environment on variation of that phenotype (Figure 1b). Additive genetic influences (A) represent the influences on the phenotype of multiple alleles at different loci on the genome that act additively and the proportion of the observed variance in a trait that can be attributed to genetic factors is termed heritability. Common environmental influences (C) include all similar environmental sources of variance that twins experience during development. Environmental influences that are unique to an individual and not shared with other family members are included in the factor of unique environmental influences (E), also including the factor of measurement error in the model (Figure 1c). Sex was added as a covariate to the analysis. For phenotypes that were characterized by higher MZ than DZ correlations,