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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

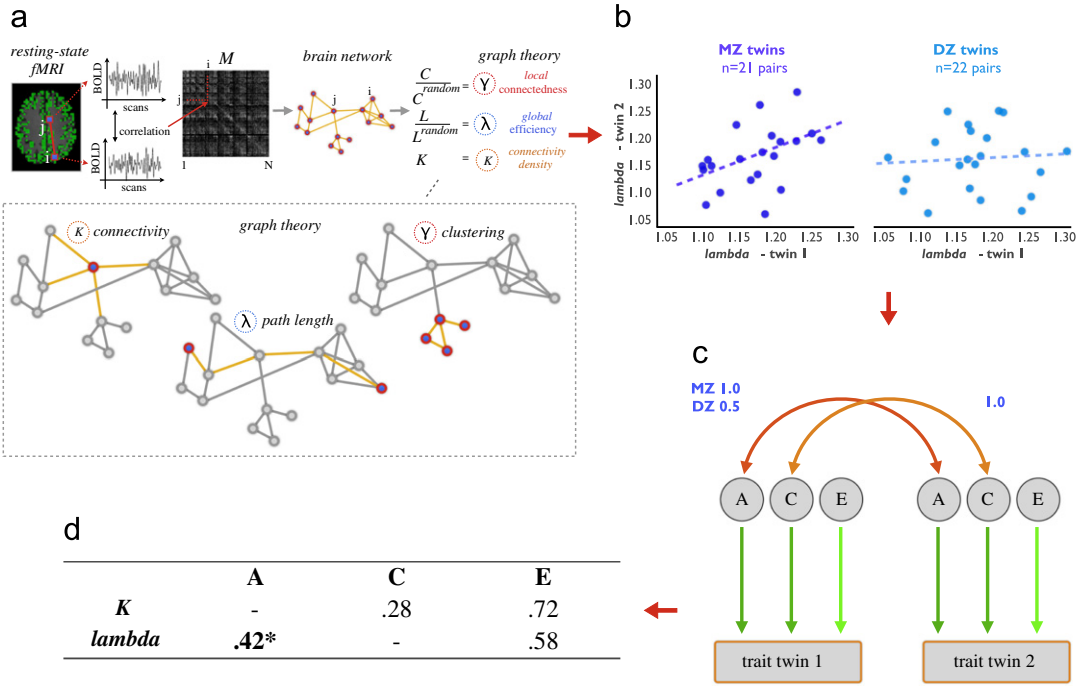
Resting-state functional MRI recordings were acquired (1.5T Philips Achieva, PRESTO, TE/TR=31.1/21.1, whole brain, 4 mm isotropic voxels, 9 min). Resting-state functional MRI time-series were preprocessed and normalized to standard MNI space (Van den Heuvel et al., 2008). The FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) 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,



	A	C	E
K	-	.28	.72
lambda	**.42***	-	.58

Figure 1 (a) Individual brain networks were reconstructed as the level of correlation between fMRI time-series between all gray matter voxels. Graph metrics were computed and compared by metrics of a set of comparable random networks (set of 20 networks). (b) Twin correlation of *lambda*, *gamma* and *K* metrics were computed. (c) Twin modeling; (d) ACE fit results, showing significant genetic control of *lambda*. $^{*}p<.05$.

Table 1 Estimates of means (SD) and correlations in Mono- and Dizygotic twin pairs.

	All twins (*N*=86)	MZ twins (*N*=42) (21 pairs: 9m/12f)		DZ twins (*N*=44) (22 pairs: 4m/4f/8dos)	
	Mean (s.d.)	Mean (s.d.)	rMZ (95% CI)	Mean (s.d.)	rDZ (95% CI)
Age, years	12.16 (.28)	12.08 (.18)		12.24 (.33)	
Lambda	1.17 (.06)	1.17 (.05)	**.49** (.05-.73)*	1.17 (.06)	.08 (−.31−.44)
K (log transformed)	891.58 (662.30)	812.93 (496.32)	−06 (−45 to .37)	966.66 (787.65)	.06 (−.31 to .41)
Gamma	2.70 (1.09)	2.68 (1.08)	.20 (−.03 to .59)	2.72 (1.12)	.32 (−.04 to .59)

$^{*}p<.05$.

maximum-likelihood estimates of heritability were obtained by genetic structural equation modeling (van Soelen et al., 2012).

3. Results

Normalized path length *lambda* MZ correlations (expressing the level of overlap of communication efficiency between twin pairs) were found to be higher than DZ correlations (Table 1 and Figure 1d). Genetic model fitting revealed a significant heritability of *lambda* (h^2=42%, $p<.05$ CI=(.05-.73), AE model). Twin resemblance of connectivity density *K* (expressing the level of coherence in number of connections across twin pairs) was not significantly different between MZ and DZ pairs, suggesting no significant contributions of genetic factors to overall brain connectivity. In addition, a mild influence of common environment on absolute brain connectivity was found at the trend level (p=.06, ns). Normalized clustering *gamma* (expressing the level of overlap in local clustering) was not found to correlate across twin pairs, suggesting that no significant influence of genetic or common environment factors to local clustering could be found.

4. Discussion

The heritability of functional brain network connectivity was examined in 12-year old monozygotic and dizygotic twin pairs using resting-state functional Magnetic Resonance Imaging. Our network findings suggest a significant heritability of normalized path length *lambda* (h^2 *lambda*=.42%), indicating a significant contribution of brain communication efficiency at this young age, irrespective of the total number of brain connections (connectivity density *K*). In addition, there were no indications of the influence of genes

or common environment on local clustering (as measured by the normalized clustering coefficient *gamma*). Our findings thus suggest the existence of a set of genes shaping the global architecture of functional brain communication, already early during brain development.

This study supports the notion of a significant heritability of functional brain connectivity (Smit et al., 2008; Glahn et al., 2010; Fornito et al., 2011). Extending these findings our study now shows that this heritability is present already early in childhood. Our findings suggest an influence of genes on global brain efficiency, but not on the number of brain connections, which is consistent with a recent study in adult twins showing genetic effects to be stronger for cost-efficiency than for other topological metrics (Fornito et al., 2011). In contrast to the findings in adult twins (.60), our heritability estimates are considerably lower (.42), possibly suggesting an increase in genetic control during aging. Both studies include, however, relative small sample sizes, which limits the interpretation of this direct comparison. Combining the findings from Fornito et al. (2011) with our current results in a small meta-analysis confirmed the genetic control of global brain efficiency ($p<.05$), further supporting our current findings of genetic control of global brain efficiency.

Recent advances in brain connectomics have revealed an efficient small-world and rich-club topology of the human brain, an organization crucial for healthy brain function (Bullmore and Sporns, 2009, 2012; van den Heuvel et al., 2009, 2012; Fornito et al., 2011; van den Heuvel and Sporns, 2011). Our findings now suggest that while the topology of brain communication appears to be under genetic control, the connectivity density—i.e., the number of functional connections in the network—is mostly influenced by environmental factors, not directly by genetic factors. Apparently, while in particular the strength of spontaneous functional brain connectivity appears to be mainly driven by environment, it is how these functional connections are organized that is controlled by genetic factors. Our findings thus suggest the existence of a distinct set of genes already active in early brain development controlling the underlying architecture of brain interactions, not pure (functional) connectivity itself. Rather than controlling specific functional connections between specific brain regions (Glahn et al., 2010), these genes may control general, in particular global, organizational principles of functional brain dynamics.

Recent studies have reported aberrant functional and structural brain network efficiency in brain developmental disorders, like schizophrenia (Collin et al., 2012; Lynall et al., 2010; van den Heuvel and Kahn, 2011; Fornito et al., 2012), as well as in neurodegenerative neurological diseases, such as Alzheimer's disease (Supekar et al., 2008; Buckner et al., 2009; Stam et al., 2009) and Amyotrophic Lateral Sclerosis (Verstraete et al., 2011). Reporting on genetic control of the topology of functional brain efficiency may therefore aid the search for finding new genetic biomarkers of disease. Recently, imaging genetics has become an increasingly popular approach (Tost et al., 2011) and through candidate gene approaches and genome-wide association studies (GWAS) several genes are now suggested to be associated with brain activity (Esslinger et al., 2009; Erk et al., 2011). Based on our heritability estimates it seems to be relevant to search for genes that are involved in the efficiency of functional brain connectivity in the human brain.

Some considerations should be taken into account when interpreting the findings of this study. First, this study was done in twins that were all 12 year old at the time of the MRI measurement. Thus, while our study provides accurate estimates of functional brain connectivity at this age, it provides no information on younger and older children or adults, limiting the comparison of heritability estimates to these groups, in particular adults (Smit et al., 2008; Fornito et al., 2011). It does, however, provide estimates of heritability of brain connectivity without age being a possible factor of influencing the stability of connectivity strength (Power et al., 2012), which is a clear advantage of our selected approach. Second, this study was done at 1.5 T field strength, which is known to have limited signal to noise ratios when compared to higher field strengths. More noise may influence the heritability estimates, which may result in an overestimation of the contribution of unique environmental factors and lower estimates for influences of genetic factors. Thus, we cannot excluded that the estimates reported in the current study representing a conservative measure and underestimating the actual heritability for efficiency of functional brain connectivity at the age of 12.

In conclusion, our findings are in support of a significant influence of the genome on the efficiency of functional brain connectivity in twins at 12 years of age. Our findings suggest that the architecture of functional brain communication is, at least in part, shaped by genes active already early in brain development.

Role of the funding source

The authors declare that the funding source had no influence on study design, interpretation of the results, neither in writing the manuscript, nor in the decision to submit the manuscript.

Contributors

MP and IS did the experiment and analyzed the data. MP, DB and HE designed the study. MP, IS, CS, RS, DB and HE wrote the manuscript.

Conflict of interest

The authors have no conflict of interest to report.

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