

Genetic contributions to human brain morphology and intelligence

While showing an impressive growth prenatally, the human brain is not completed at birth. There is considerable brain growth during childhood with dynamic changes taking place in the human brain throughout life, probably for adaptation to our environments.

Evidence is accumulating that brain structure is under considerable genetic influence [Peper et al., 2007]. Puberty, the transitional phase from childhood into adulthood, involves changes in brain morphology that may be essential to optimal adult functioning. Around the onset of puberty gray matter volume starts to decrease, while white matter volume is still increasing [Giedd et al., 1999].

Recent findings have shown, that variation in total gray and white matter volume of the adult human brain is primarily (70–90%) genetically determined [Baare et al, 2001] and in a recent magnetic resonance imaging (MRI) brain study with 45 monozygotic and 61 dizygotic 9-year-old twin-pairs, and their 87 full siblings also high heritabilities have been found [Peper et al, in preparation]. Thus, while environmental influences may play a role in later stages during puberty, around the onset of puberty brain volumes are already highly heritable.

Genetic influences and functional relevance

Twin studies have also shown that genetic effects vary regionally within the brain, with high heritabilities of frontal lobe volumes (90–95%), moderate estimates in the hippocampus (40–69%), and environmental factors influencing several medial brain areas.

However, the mechanisms by which interaction between genes and environment occur throughout life as well as dynamics of brain structure and its association with brain functioning still remain unknown. Twin and family studies and newly evolving genetic approaches start to give us a glimpse as to which genes and (interacting) environmental influences are shaping our brains.

Brain structure – measured macroscopically using MRI – and the dynamic changes therein, have a functional relevance.

Studies revealed that total brain volume is positively correlated with general intelligence. In healthy subjects, the level of intellectual functioning has been positively associated with whole brain, gray, and white matter volumes [Thompson et al, 2001; Posthuma et al, 2002]. More focally, several brain areas were found to be correlated with intelligence. Interestingly, it was also shown that the trajectory changes in cortical thickness throughout adolescence are associated with the level of intelligence.

Furthermore, a common set of genes may also cause the association between brain structure and cognitive functions. However, in elderly twins, the associations between frontotemporal brain volumes and executive function were found to be because of common environmental influences shared by twins from the same family [Carmelli et al., 2002]. These results point to the possibility that overlapping sets of genes or common environmental influences cause variation in two distinct phenotypes. It might be, for example, that a higher level of cognitive functioning leads a person to select an environment that also increases brain size. The genetic influence on brain size then simply reflects the genetic influences on cognition. Thus, the specific mechanism, pathways, and genes that are involved in human brain morphology and its association with cognitive functions remain elusive.

Although genetic effects on morphology of specific gray matter areas in the brain have been studied, the

heritability of focal white matter was unknown until recently. Similarly, it was unresolved whether there is a common genetic origin of focal gray matter and white matter structures with intelligence. In our study involving 54 monozygotic and 58 dizygotic twin pairs and their 34 singleton siblings, verbal, and performal intelligence were found to share a common genetic origin with an anatomical neural network involving the frontal, occipital, and parahippocampal gray matter and connecting white matter of the superior occipitofrontal fascicle, and the corpus callosum [Hulshoff Pol et al., 2006]. For the genetic analyses, structural equation modeling and voxel-based morphometry were used. To explore the common genetic origin of focal gray matter and white matter areas with intelligence, cross-trait/cross-twin correlations were obtained in which the focal gray matter and white matter densities of each twin are correlated with the psychometric intelligence quotient of his/her cotwin.

The results of this study indicate that genes significantly influence white matter density of the superior occipitofrontal fascicle, corpus callosum, optic radiation, and corticospinal tract, as well as gray matter density of the medial frontal, superior frontal, superior temporal, occipital, postcentral, posterior cingulate, and parahippocampal cortices. Moreover, the results show that intelligence shares a common genetic origin with superior occipitofrontal, callosal, and left optical radiation white matter and frontal, occipital, and parahippocampal gray matter (phenotypic correlations up to 0.35).

These findings point to a neural network that shares a common genetic origin with human intelligence. Thus, it seems that the individual variation in morphology of areas involved in attention, language, visual, and emotional processing, as well as in sensorimotor processing are strongly genetically influenced.

In addition, unique environmental factors influenced vast gray matter and white matter areas surrounding the lateral ventricles (up to 0.50). This finding coincides with the significant environmental influences on lateral ventricle volume [common (0.58) and unique (0.42) with no significant contributions of genes] that was reported previously in this twin sample [Baaré et al., 2001].

Clinical implications

Considering the high heritabilities for global brain volumes and particular focal brain densities and thicknesses, the search for genes that are involved in brain growth, aging, and brain structure maintenance is important. Such knowledge can help us understand normal developmental and age-associated changes in individual variation in brain functioning. Moreover, it enhances our knowledge of individual variation in brain functioning and facilitates the interpretation of the morphological changes found in psychiatric disorders such as schizophrenia [van Haren et al., 2007]. Also, it allows future efforts to find particular genes responsible for brain structures to be concentrated in areas that are under considerable genetic influence [Hulshoff Pol et al., 2006].

A genetic approach to find genes involved in brain structure that has been applied in several studies is that of diseases with a clear genetic etiology such as Huntington's disease, Down syndrome, Williams syndrome, and Velocardiofacial syndrome. A review reveals for these diseases besides disease specific brain changes, decreases in total brain, white matter, and hippocampus volumes, irrespective of the genes and/or chromosomes involved. This suggests that many genes are probably involved in the individual variation of these measures [Peper et al., in press].

It is important to investigate which environmental factors have an influence on the expression of genes (as found in DNA-methylation). Additionally, the study of interaction between genes and environmental factors is warranted. Furthermore, the simultaneous effects of multiple genes and possibly the interaction among genes, also needs investigation as the high heritability of a complex quantitative phenotype such as brain volume cannot be explained by a single-gene polymorphism

Conclusion

MRI studies in twins indicate that, given the basic additive genetic model, overall brain volume in adulthood is highly heritable.

To test for influences of genetic, common, and unique environmental factors or interactions between genetic and environmental influences, twin studies carried out in large and more homogenous samples, analyzed with advanced quantitative genetic methods are needed.

To investigate the stability of genetic and environmental influences onto functional neural networks in human brain longitudinal twin studies in childhood as well as in adulthood are needed since brain volume changes dynamically throughout life.

New brain-imaging methods, such as DTI-fiber tracking and resting state functional MRI, allow to study the heritability of neural networks underlying brain functioning.

These new methods, in coherence with new genetic approaches, will enable us to further disentangle which genes and environmental factors and interactions therein influence human brain structure throughout life.

Source: European College of Neuropsychopharmacology

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