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UDC 159.91:612.821 **doi**: 10.21702/rpj.2020.2.2 ***Systematic review***

Behavioral Genetic Studies of Structural Brain Characteristics

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Abstract
Introduction. This paper provides an overview of current research in individual differences in structural brain characteristics. The impact of individual differences in structural brain characteristics on individual differences in psychological characteristics is considered within the concept of endophenotypes, which represent an intermediate link between the gene and the complex phenotypic characteristic.
Theoretical Basis. This paper analyzes the impact of genetic and environmental factors on individual differences in structural brain characteristics measured by magnetic resonance imaging and diffusion tensor imaging. The review presents the results of twin studies, genome-wide association studies, and candidate genes studies.
Results and Discussion. In general, genetically informative studies of structural brain characteristics indicate that a small number of structures (i.e., corticospinal pathways or the volume of the lateral ventricles) have moderate heritability estimates varying from 20 to 50 %. In contrast, the heritability estimates are over 50 % for the majority of structural characteristics. The contribution of genetic factors to individual differences in structural brain characteristics changes during ontogenesis. A general genetic contribution to individual differences in structural brain characteristics and behavioral phenotypes is examined using multivariate analysis methods. The review (a) presents the results of new types of molecular genetic studies, primarily using the genome-wide association analysis, which examines hundreds of thousands of DNA markers simultaneously, (b) discusses studies of such genetic factors as copy number variations as well as whole-genome studies, and (c) shows that the current transition process to the format of multicenter consortia and the associated growth of the studied samples provides new opportunities for studying the contribution of genetic factors to individual differences in structural brain characteristics.

Keywords
behavioral genetics, twin method, GWAS analysis, candidate genes, heritability, tomographic methods, brain volume, endophenotype, intelligence, schizophrenia

Highlights
- Genetic factors make an important contribution to all the structural brain characteristics.
- At the genetic level structural brain characteristics are associated with a number of behavioral characteristics (intelligence, schizophrenia, bipolar disorder, etc.).

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▸ The transition from twin studies to the large-scale studies based on international collaborations helps identify new genetic mechanisms that underlie individual differences in structural brain characteristics.

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Introduction

Genetically informative research represents one of the most important sources of information about the nature of individual differences. Despite the fundamental importance, the high cost and laboriousness were limitations for studies of this type for a long time. The development of data analysis methods and new technologies for studying brain activity, as well as the formation of large-scale research collaborations that unite large groups of researchers from different laboratories and countries, lead to an increasing interest in such studies.

In 1972, I. Gottesman (Gottesman & Shields, 1972) proposed the concept of endophenotypes. In classical genetics, a phenotype is any observable or measurable variable characteristic (i.e., height, weight, eye color, personality traits, learning abilities). The endophenotype refers to such characteristics, which individual differences are formed under the influence of genetic factors and are associated with psychological characteristics in the normal state or in mental disorders. Endophenotypes are considered as an intermediate link between genes and human behaviors. In other words, this is a link in the 'gene – endophenotype – psychological characteristic' chain. A wide range of different characteristics – from brain morphology to electrophysiological phenomena – can be endophenotypes for either behavioral characteristic (Malykh, Egorova, & Meshkova, 2008).

A variety of characteristics which are recorded using various neuroimaging methods, such as magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), etc. are used as endophenotypes of psychological characteristics in genetically informative studies (i.e., those studies that take into account the impact of genetic factors on the studied characteristics) of structural brain characteristics. The most popular method for studying the etiology of individual characteristics of the human brain morphology is the MRI method, which helps obtain three-dimensional images of internal structures based on differences in nuclear-resonance properties in different tissues of the body. Diffusion tensor imaging (Glahn et al., 2012; Brun et al., 2009; Kochunov et al., 2010) is another method for analyzing brain morphology. This method helps fix the bundles of nerve fibers connecting various brain regions as well as associations between the axons of the white matter. The diffusion tensor imaging (DTI) method was proposed to evaluate the anisotropy (direction) in the diffusion of water molecules in the brain tissue (Chiang et al., 2009).

Despite the fact that the role of structural brain characteristics as endophenotypes of psychological characteristics has been questioned in recent years (Iacono, Malone, & Vrieze, 2017), a combined analysis of structural MRI of 21199 individuals showed that structural characteristics

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of the brain are important predictors of a number of mental illnesses, first of all schizophrenia, bipolar disorder, and attention-deficit/hyperactivity disorder (Thompson et al., 2020). Moreover, a number of studies have shown that structural characteristics of the brain are associated with individual differences in psychological phenotypes such as intelligence (Hilger, Ekman, Fiebach, & Basten, 2017), emotional sphere (Marstaller, Burianová, & Reutens, 2016; Adrián-Ventura, Costumero, Parcet, & Ávila, 2019) and even demographic characteristics (Llera, Wolfers, Mulders, & Beckmann, 2019).

This review analyzes genetically informative studies of individual characteristics of the structural brain characteristics associated with various psychological phenotypes.

Theoretical Basis

Tomographic studies of structural brain characteristics using the twin method

To assess the relative contribution of genetic and environmental factors to the individual differences of neurophysiological characteristics, specialists in behavioral genetics use methods to study family members with varying degrees of genetic similarity (Malykh, Kovas, & Gaisina, 2016). One of the most informative methods is to compare data obtained using neuroimaging methods when examining monozygotic (MZ) and dizygotic (DZ) twins. The method is based on the difference in genetic similarity between MZ twins growing from a single fertilized egg (100 % of similarity) and DZ twins developing from two different eggs fertilized at the same time. Comparison of MZ and DZ within-pair correlations helps evaluate the role of hereditary and environmental factors in the individual differences of a studied characteristic. If genetic factors contribute to individual differences in a particular characteristic, then correlation between MZ twins should be higher than those between DZ twins. The term 'heritability' is often used to describe the contribution of genetic factors to the variability in a characteristic. The twin method is also used to assess the etiology of associations between various characteristics on the basis of multidimensional models that help assess the contribution of genetic and environmental factors to the covariance of several phenotypic variables (Malykh et al., 2008).

A significant contribution of genetic factors to individual differences in the structural brain characteristics was already shown in one of the first studies on the lateral ventricular volume in healthy MZ and DZ twins (Basser, Mattiello, & Lebihan, 1994). Subsequent studies documented high rates of heritability for such general brain characteristics as intracranial volume (h^2 > 81 %) and total brain volume (66–97 %) (Baaré et al., 2001; Bartley, Jones, & Weinberger, 1997; Wright, Sham, Murray, Weinberger, & Bullmore, 2002; Carmelli et al., 1998; Pfefferbaum, Sullivan, Swan, & Carmelli, 2000). An important role of genetic factors (over 82 %) was also shown in the first family study of individual differences in the total volume of cerebral white and gray matter, which comprised both twins and siblings (Reveley, Reveley, Chitkara, & Clifford, 1984). Other studies have shown that 65 % of the volume of each hemisphere is determined by genetic factors (Geschwind, Miller, DeCarli, & Carmelli, 2002; Malykh et al., 2016); the heritability of the cerebellum volume was 88 % (Posthuma et al., 2000), the corpus callosum – 79–94 % (Pfefferbaum et al., 2000; Scamvougeras, Kigar, Jones, Weinberger, & Witelson, 2003).

A high level of heritability (up to 83 %) is also shown for gray matter density in Broca's and Wernicke's areas, frontal cortex, Heschl's gyrus, left occipital and left parietal lumbar regions, middle temporal cortex and tonsil (Cannon et al., 2006; Hulshoff Pol et al., 2006; Thompson et al., 2001). A number of works accentuate the importance of genetic factors in the individual

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characteristics of the thickness of the cortex, especially in the frontal and parietal areas (Joshi et al., 2011; Lenroot et al., 2009; Rimol et al., 2010; Yoon, Fahim, Perusse, & Evans, 2010). The highest genetic contributions (up to 93 %) are observed for individual differences in the white matter density of the corticospinal tract, corpus callosum, superior longitudinal and occipitofrontal fascicles (Thompson et al., 2001; Peper, Zwiers, Boomsma, Kahn, & Hulshoff Pol, 2009).

Some studies involving elderly people (69–80 years) (Carmelli, Swan, DeCarli, & Reed, 2002) and children (Wallace et al., 2006) showed a significant influence of genetic factors on the dispersion of structural brain characteristics. Considering that twins share a smaller number of common environmental factors (i.e., live separately), the data obtained from these studies may be interpreted in the context of stabile genetic control of the volume of the studied brain structures.

In addition to MRI studies, an important contribution of genetic factors was also shown in studies using diffusion tensor imaging (DTI). Thus, a DTI study involving twins and other siblings provided data on a significant role of heritability in the asymmetry of the inferior fronto-occipital fascicle (33 %), anterior thalamic region (37 %), and the uncinate fascicle (20 %). The contribution of common environmental factors was also shown: 10 % for occipital forceps and 15 % for the corticospinal tract (Jahanshad et al., 2010). Other twin studies employing DTI also showed significant heritability estimates for the corpus callosum (Brun et al., 2009; Pfefferbaum et al., 2000), the occipital lobes (Brun et al., 2009), as well as for the lateral orbitofrontal gyrus, the cerebellum, a number of subcortical structures, the brainstem and the uncinate gyrus, the right temporal white matter, and the superior frontal gyrus (Yoon, Perusse, Lee, & Evans, 2011).

A 2012 meta-analysis of 62 genetically informative studies of the morphology of brain structures showed that, in general, genetic factors contribute significantly to individual differences in general parameters, including intracranial volume, total brain volume, cerebral cortex volume, total and local volumes of gray and white matter, etc. (Blokland, de Zubicaray, McMahon, & Wright, 2012). Moreover, according to the meta-analysis results, there is a significant variability in the heritability estimates of the subcortical structures, the ventricles of the brain, characteristics of the corpus callosum, the cerebellum volume, etc.

In general, the genetic analysis of structural brain characteristics shows that moderate heritability (20 to 50 %) is characteristic of a small number of structures (i.e., corticospinal pathways or the lateral ventricular volume), while the heritability estimates are over 50 % for the majority of structural characteristics (Strike et al., 2015). The construction of multidimensional twin models also makes it possible to assess the severity of genetic correlations showing the contribution of genetic factors to the covariance of characteristics at the phenotypic level. Thus, pronounced genetic correlations between the characteristics of gray and white matter of different areas of the cerebral cortex were observed for the following brain structures: correlations from 30 to 60 % – for connections of the occipital regions with other areas of the cortex, from 80 to 95 % – for the volume of gray and white matter in the frontal, parietal, and temporal areas (Schmitt et al., 2008). A common genetic factor was determined for the subcortical structures, which explained up to 60 % of phenotypic covariance (Schmitt et al., 2010). The presence of high genetic correlations between the characteristics of various brain structures may indicate that the same genetic factors may be associated with the variability of a wide range of characteristics in the brain.

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Age-related changes in the heritability of structural brain characteristics

Age-related brain changes occur throughout life. Thus, MRI studies in a wide age range (from 4 to 20 years) showed an increase in the volume of cerebral gray and white matter in the period from 4 years to early adolescence. In early adolescence, the volume of gray matter starts to decrease (except for gray matter in the temporal region, which increases until late adolescence), while the volume of white matter continues to increase (Paus et al., 1999; Durston et al., 2001). By the age of six, the total brain volume of a child reaches 95 % of the adult brain volume (Paus et al., 1999). Thus, despite the fact that by the age of 6 years, the total brain size almost reaches its constant volume, the ratio of gray and white matter varies from adolescence to adulthood (Paus, 2005; Toga & Thompson, 2005; Raz et al., 2004). In adulthood, a decrease in the total brain volume is associated with a decrease in the volume of gray matter (Bartzokis et al., 2001). At the same time, the volume of white matter continues to increase up to 45 years.

Interestingly, in a portion of the sample of healthy subjects, total brain volume increases up to the age of 40 (van Haren et al., 2008). In general, adulthood is associated with the following significant changes in the structural features of the brain: an increase in the volume of white matter, a nonlinear pattern of a decrease in the total volume of the brain, as well as the volume and density of gray matter.

Behavioral genetic studies show that genetic influences may vary at different ages. For example, heritability of intelligence increases during development (Plomin & Craig, 1997; Haworth et al., 2009). The ratio of genetic and environmental factors of the variability of brain structures may also change during ontogenesis. In the first year of life the heritability estimate of total brain volume is 69 % (Gilmore et al., 2010), increasing to 94 % by 9 years (Peper et al., 2009), and to 96 % by 96 years (van Soelen et al., 2010). Such high estimates are observed until the age of 27 years (Bartley et al., 1997) and decrease to 90 % by 30 years (Baaré et al., 2001), to 69 % by 49 years (Winkler et al., 2010), and up to 46 % by 64 years (DeStefano et al., 2009). The genetic contribution to cerebellar size variability also increases from 70 % at 8 years (Yoon et al., 2011) to 89 % at 11 years (Wallace et al., 2006) and 96 % at 12 years (van Soelen et al., 2012). After a maximum at 12 years, the role of genetic factors decreases: up to 80 % at 17 years (Bartley et al., 1997), and up to 52 % at 47 years (Batouli, Trollor, Wen, & Sachdev, 2014). A similar pattern is observed for heritability of the volume of gray and white matter, intracranial volume, some brain lobes, and ventricular volume. Figure 1 shows research results.

The DTI studies evaluating fractional anisotropy (characterizing the number and orientation of the conducting pathways (paths) of brain white matter) also demonstrated age-related differences. Thus, a large-scale genetically informative study (705 twins and their siblings, adolescents, and adults) showed that the contribution of genetic factors to the variability of white matter characteristics was more pronounced in adolescents than in adults (Chiang et al., 2011).

We should note that at the moment, the results of studies of the volume of other brain structures in different years of life are contradictory, which may be explained by measurement errors in these small-sized areas (Batouli et al., 2014).

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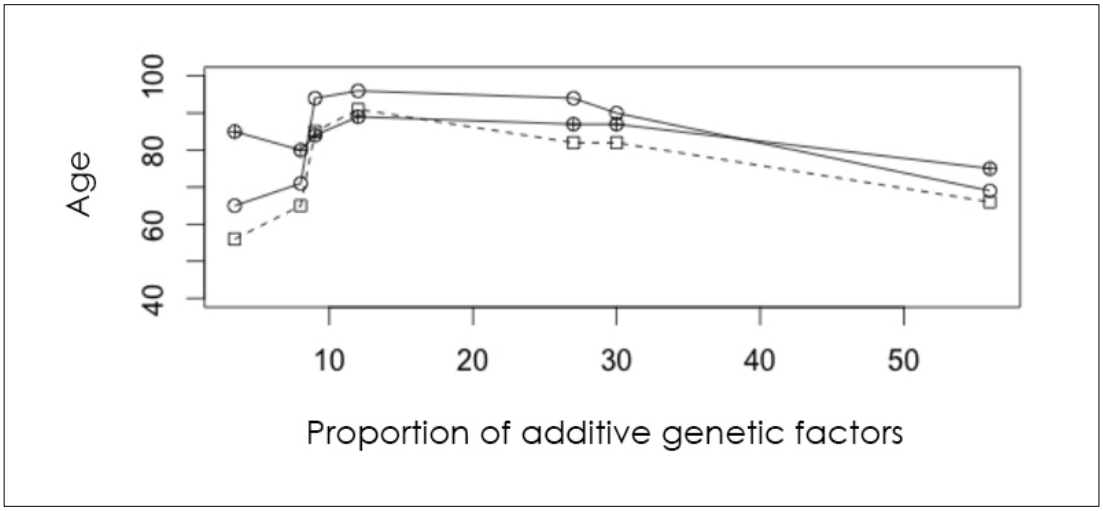

Figure 1. Change in the contribution of additive genetic factors to the variability of the total brain volume and the volume of gray and white matter (modified data of Batouli et al., 2014)

Legend: round hollow dots correspond to the total brain volume; square dots correspond to the gray matter volume; round dots with crosses correspond to the white matter volume.

Molecular genetic studies of structural brain characteristics

Despite the fact that for a large number of structural brain characteristics the contribution of genetic factors to individual differences was established in a series of twin and family studies, the specific molecular genetic mechanisms that contribute to this variability are still not fully understood (Brans et al., 2008). Currently, more and more genetically informative studies are aimed at identifying specific genes that contribute to the variability of neurophysiological characteristics. These characteristics are associated with a large number of genetic factors with small effect sizes (the so-called Quantitative Trait Loci). To date, there are methods for mapping of genome regions associated with quantitative characteristics using molecular markers (i.e., single-nucleotide polymorphisms, SNPs). This method represents the analysis of genetic associations to determine associations between one or many DNA polymorphic variants and any (i.e., neurophysiological) characteristic (Malykh et al., 2016).

One of the approaches to the analysis of genetic associations is the selection of candidate genes isolated on the basis of theoretical biological mechanisms of studied characteristics. To date, researchers identified a number of candidate genes associated with differences in brain structural characteristics. BDNF, APOE, MECP2, HFE, MTFHR, NRG1 genes are among the most often studied ones.

The brain-derived neurotrophic factor (BDNF) plays a crucial role in the development of the central nervous system, participating in the proliferation and synaptic growth of brain neurons, as well as in the modulation of synaptic signals (for example, in the case of long-term potentiation of hippocampal neurons). A valine-to-methionine substitution at codon 66 (Val66Met allele) in the BDNF gene is associated with changes in the structural and functional characteristics of the hippocampus, which, in turn, affects human working memory. Another important participant in the metabolic processes associated with the growth, degeneration, and regeneration of nerve cells is plasma apolipoprotein E (apo E). It is associated with the normal catabolism of triglyceride-rich

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lipoproteins. The ApoE4 allele has been shown to be associated with genetic risks of Alzheimer's disease (Lu et al., 2011). Different variants of the MTHFR gene are associated with pathological development of the neural tube. There are MTHFR alleles that are associated with increased plasma homocysteine levels, as well as nervous tissue damage and brain atrophy (Brans et al., 2008). The HFE gene regulates the absorption of iron ions.

Jahanshad et al. (2012) showed that the integrity of nerve fibers, as measured by DTI-derived fractional anisotropy, is associated with variations in this gene. These data may indicate the important role of iron ion metabolism in the development and degeneration of nerve tissue. The MECP2 gene encodes a protein related to methylated DNA and is involved in cell differentiation processes during embryonic development. Joyner et al. (2009) showed the presence of an association between this gene and cortical surface area (not thickness). The neuregulin gene (NRG1) and the neuregulin receptor gene (ErbB4) are associated with a wide range of manifestations of pathogenesis in patients with schizophrenia and bipolar disorder. It is assumed that at the structural level, these processes are associated with changes in the integrity of the white matter in the anterior limb of the internal capsule (ALIC). Changes in the NRG1–ErbB4 signaling pathway detected in groups of subjects with different symptoms are encoded by the s4673628 (Zuliani et al., 2011), rs6994992 (McIntosh et al., 2007), and rs839523 alleles (Konrad et al., 2009).

It is probable that structural brain characteristics are associated with the combined effect of a large number of genes. Thus, there are data indicating that certain genes make the greatest contribution to the variability of the temporal cortex volume (Kohannim et al., 2012).

When studying structural brain characteristics, a large number of studied genes lead to the problem of multiple comparisons and the high probability of type I errors. Special corrections and statistical procedures are used to solve this problem (i.e., Family-Wise Error Rate – FWER, Worsley et al., 1996; and False Discovery Rate – FDR, Genovese, Lazar, & Nichols, 2002). Modeling based on real genetic data shows that the use of corrections for multiple comparisons can reduce the number of type I errors to 5 % (Meyer-Lindenberg et al., 2008). However, the need remains for replication of the obtained data in independent studies. Thus, a number of studies indicate an association of the FOXP2 gene, associated with the evolution of human speech, and the characteristics of various brain structures (foremost, the inferior frontal gyrus, caudate nucleus, and cerebellum). However, initial data were obtained in MRI studies in groups of 14 to 96 subjects. However, data replication in a sample of 1301 individuals did not indicate an association between the variability of neuroanatomical parameters and the SNP FOXP2 (Hoogman et al., 2014). There are evolutionary and experimental prerequisites to consider genes associated with primary microcephaly (ASPM, MCPH1, CDK5RAP2, and BRCA1 genes) the basis for individual differences in brain size in a normal population as well as linguistic and cognitive abilities. However, a study involving 1776 subjects from 789 twin families showed no association between these genes and the characteristics under investigation (Bates et al., 2008).

Due to certain limitations of the candidate gene method, in recent years, genome-wide association analysis (GWAS) has been used in genetically informative studies of brain structure, which examines hundreds of thousands of DNA markers simultaneously in their associations with various characteristics. GWAS studies focus on the study of single-nucleotide polymorphisms (SNPs) – a type of variability in the DNA sequence in different individuals associated with the substitution of one nucleotide by another in a specific DNA locus (for example, adenine (A) for thymine (T)) and characterized by the presence of different alleles (usually two) in the population (for example,

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allele A and allele T). Given these effect sizes, large samples of subjects are required to obtain statistically significant results.

Currently, the most complete meta-analysis of associations between structural brain characteristics and specific genes was carried out by a team of researchers from the ENIGMA consortium (Thompson et al., 2020). In the initial work of the consortium, the data for 30717 subjects from 50 cohorts were analyzed. The entire sample was divided into 2 equal parts for conducting a genome-wide (GWAS) analysis of associations between certain loci and the structural characteristics of brain regions. The mathematical model of associations was tested in a subsample of 13171 subjects and verified in a second subsample of 17546 subjects. The study revealed 8 main loci associated with the volume of such structures as the caudate nucleus, the hippocampus, the putamen lenticular nucleus, as well as with the intracranial volume. Significant relationships identified in the study explained from 0.17 to 0.52 % of phenotypic variability of volumes in various brain regions. Interestingly, the analyzed loci were associated with individual structures, and not with multiple effects on various brain regions. The effect size of the KTN1 gene was maximum for differences in the putamen volume. This gene encodes a kinectin receptor protein that binds kinesin and is also involved in organelle transport processes. Expression of the DCC gene in the brain is most pronounced during the first two trimesters of prenatal development, which suggests its connection with the regulation of the volume of brain structures in the early stages of nervous system growth. It is known that the DCC gene (rs62097986; 18q21.2; n = 28.036; $P = 1.01 * 10^{-13}$) encodes netrin (a receptor associated with axon growth and migration, as well as with the growth of the striatum). The expression of BCL2L1 is maximum at 24–38 weeks after conception, during the period of the most active apoptosis in the putamen. BCL2L1 (rs6087771; 20q11.21; n = 25.540; $P = 1.28 * 10^{-12}$) encodes an antiapoptosis factor that inhibits the programmed death of immature neurons in the brain. DLG2 is maximum active in the middle of intrauterine development during the growth of the striatum. The DLG2 gene (rs683250; 11q14.1; n = 26.258; $P = 3.94 * 10^{-11}$) encodes the density of protein 93 in the post-synaptic region (Hibar et al., 2015). Genetic variants in this locus are associated with learning processes and cognitive flexibility (in some studies also with schizophrenia).

In later studies, the data collected by the ENIGMA consortium were combined with data from two other large-scale projects: the CHARGE consortium and the UK biobank. Thus, the researchers were able to identify more than 200 individual loci that contribute to the variability of characteristics of 70 different brain structures (Thompson et al., 2020). Moreover, despite the fact that the contribution of a single locus to the total phenotypic variability ranged from 0.1 % to 1 %, the combination of the detected loci into one model made it possible to explain up to 20 % of the total variance. In general, for genetic loci associated with brain morphology, there is an association with regulatory genes, as well as with regulatory elements specific for humans compared to other mammals. To access the data obtained by the ENIGMA team, an interactive site https://enigma-brain.org/enigmavis/ has been created, which provides researchers with more detailed information about brain structures and the contribution of specific genetic loci.

Results and Discussion

Structural brain characteristics as endophenotypes of behavioral phenotypes

Within the concept of endophenotypes, structural brain characteristics may be considered both as intermediate characteristics associated with mental illness and in the context of the study of

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normal psychological characteristics. For example, according to modern meta-analytical studies, the total brain volume and the volume of gray and white matter are associated with general intelligence (Gignac & Bates, 2017). Certain studies of associations between intelligence and the total volume of gray and white matter, indicate moderate (r = ±0.30) phenotypic correlations. The use of multidimensional models in genetically informative studies help establish common genetic contribution in such characteristics as individual differences in brain volume and test scores for verbal and nonverbal intelligence (Posthuma, 2002; Malykh et al., 2016), as well as gray matter volume covariance of the frontal lobes and intelligence (Strike et al., 2015; Carmelli et al., 2002). In addition, the identified general genetic factors are observed in the covariance of verbal and nonverbal intelligence with such brain structures as gray matter of the frontal, occipital, and parahippocampal regions, as well as the white matter fascicles of the superior occipital-frontal fasciculus and corpus callosum (Hulshoff Pol et al., 2006). At the same time, twin studies also provide information on the role of environmental factors in the individual differences of the characteristic. For example, general environmental influences were found for individual differences in the characteristics of control functions and the volume of the frontotemporal regions of the brain (Carmelli et al., 2002). Meanwhile, we should take into consideration that the effects of environmental and genetic factors may be multidirectional, thereby reducing phenotypic correlations (Strike et al., 2015).

Table 1 shows the results of the main genetically informative studies of the covariance between intelligence and structural brain characteristics.

Table 1
Genetically informative studies on associations between structural brain characteristics and cognitive abilities (IQ)

Covariance of phenotypes	MZ/DZ sample	Age	r_p	r_g	r_e	Article
Total cortical volume and FSIQ	25/23	>12 years	–	0.48	–	Pennigton et al., 2000
Cortical gray matter volume and factor g Cortical white matter volume and factor g	24/31	19–69	0.25 0.24	0.29 0.24	– –	Posthuma, 2002
White matter of corpus callosum and verbal intelligence (VIQ) Parahippocampal white matter and PIQ	54/58	19–69	0.14 0.23	0.15 0.40	– –	Hulshoff Pol et al., 2006

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Covariance of phenotypes	MZ/DZ sample	Age	r_p	r_g	r_e	Article
Cortical gray matter volume and Raven's progressive matrices	48/64	9	0.22	0.36	–0.16	van Leeuwen et al., 2009
Cortical thickness in the LH medial frontal regions and the RH occipital regions and the FSIQ	77/84	30	0.8 0.34	0.56 1	–0.66 0.22	Brans et al., 2010
Total brain volume and the FSIQ Cortical white matter volume and the VIQ	11/21	19–56	0.27 0.29	0.50 1	–0.17 –0.41	Brouwer et al., 2014
Cortical thickness in the LH paracentral lobule and the FSIQ Cortical thickness of the cuneus and the FSIQ	23/28	12	–0.29 –0.28	–0.32 –1	–0.24 0.39	Brouwer et al., 2014

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Table 1
Genetically informative studies on associations between structural brain characteristics and cognitive abilities (IQ)

Covariance of phenotypes	MZ/DZ sample	Age	r_p	r_g	r_e	Article
Putamen volume, thalamus volume, and the FSIQ	50/56	19–55	0.01 0.26	0 0.29	0.08 0.08	Bohlken et al., 2014
Gray matter thickness, cortical surface area, and general cognitive abilities	131/96	51–60	0.08 0.21	0.09 0.24	0.10 0.21	Vuoksimaa et al., 2015

Note: FSIQ (full scale intelligence) – general intelligence*; VIQ* (verbal intelligence) – verbal intelligence*; PIQ* (performance intelligence) – non-verbal intelligence*;* r_p – phenotypic correlations*;* r_g – genetic correlations*;* r_e – environmental correlations.

In addition to genetic and environmental factors as such, a genotype-environmental interaction may play an important role in the formation of individual differences. A number of studies indicate an interaction of socio-economic status (SES) and genetic factors that affect the integrity of fibers of the white matter measured using the diffusion tensor imaging: heritability estimates were higher among participants with a higher SES (Malykh et al., 2016). Another example of a genotype-environmental interaction is represented by the studies of differences in the heritability of the DTI indices in participants with different IQ levels. According to the results obtained by Blockland et al. (2012), over 80 % of the observed individual differences in fractional anisotropy in the posterior limb of internal capsule, corpus callosum, radiate crown, and thalamus were associated with genetic factors in a group of high-IQ participants. At the same time, the contribution of genetics did not exceed 40 % in low-IQ participants. Despite the fact that the specific mechanisms of this interaction are still unclear and require further study, the association of individual differences in SES and intelligence with the heritability of structural brain characteristics may depend on the expression of certain genes. For example, it is known that the expression of the brain-derived neurotrophic factor BDNF gene associated with neuronal growth and cognitive function may change under the influence of learning (Kesslak, So, Choi, Cotman, & Gomez-Pinilla, 1998). Genetic factors may also play an active role in the transformation of the physical and social environment, which can be manifested in the effect of genetic correlations (Hoogman et al., 2019). In particular, due to the contribution of genes that affect individual differences in the characteristics of white matter, the axonal conductivity

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of neural signals in the thalamus and corticospinal tract may change, which may indirectly affect the development of intelligence. Thus, genetic effects may be mediated by other characteristics, such as gender, age, SES, and IQ, etc. (Hackman & Farah, 2009; Zavala et al., 2018).

Genetically informative studies are also actively used in investigating the etiology of psychopathological characteristics. In a number of studies exploring the brain mechanisms of schizophrenia, patients demonstrated a progressive decrease in the volume of the frontal and temporal lobes of the cerebral cortex and a decrease in the total brain volume. It turned out that in the covariance between the risks of schizophrenia and changes in the structural brain characteristics, additive genetic effects play a pronounced role (66 % for the total brain volume, 76 % for frontal lobes, and 79 % for temporal lobes) (Batouli et al., 2014; Malykh et al., 2016). The general genetic factor obtained from multidimensional modeling by structural equations also explains a significant amount of the variability of associations between schizophrenia and the concentration of gray matter in the frontal and temporal regions (Brans et al., 2008). A decrease in the volume of white matter is associated with a genetic risk of bipolar disorder (77 %), despite the fact that the specific genetic mechanisms of such an association require further analysis (Gershon, Alliey-Rodriguez, & Liu, 2011). Modern large-scale studies of associations between structural brain characteristics and psychopathology have determined neurophysiological profiles of subcortical brain structures characteristic of individuals with such diseases as schizophrenia, bipolar disorder, ADHD, and major depressive disorder (MDD). The findings from 21199 individuals showed that schizophrenia, bipolar disorder, and major depressive disorder are associated with a decrease in the volume of the hippocampal regions, ventricles of the brain, thalamus, amygdala, and the nucleus accumbens. In so doing, the severity of changes is maximum for schizophrenia, approximately half that for bipolar disorder and four times less for major depressive disorder (Mufford et al., 2019). Changes in the amygdala and the nucleus accumbens are also characteristic of ADHD; a decrease in the volume of the putamen and the caudate nucleus is also observed (more detailed data are presented on the interactive site of the ENIGMA project).

The transition to the format of multicenter consortia provides new opportunities for modern researchers. Thus, by increasing the studied samples, there were obtained data on new groups of psychopathology, such as Tourette's syndrome (Mufford et al., 2019), insomnia (Grasby et al., 2020) or anorexia (Walton et al., 2019). Moreover, the SNP studies were extended by the studies of copy number variations as risk factors for the development of psychopathology and individual differences in the characteristics of both cortical and subcortical brain structures (Thompson et al., 2020). Currently, there is a gradual transition from genome-wide studies to whole-genome ones, which take into account even rare genetic variants (Medland, Jahanshad, Neale, & Thompson, 2014).

Conclusion

An increase in the number of genetically informative studies of brain structures and functions, as well as a significant increase in the studied samples are the most important trends in research at the intersection of genetics and neuroscience in recent years. The results of twin studies convincingly indicate a significant role of genetic factors in the formation of individual differences in many structural brain characteristics (total brain volume, thickness and surface area of the cerebral cortex, volume of gray and white matter, etc.). At the same time, the development of

molecular genetic methods helps approach the analysis of associations between neurophysiological characteristics with specific polymorphic variants of various candidate genes. An integrated approach to the study helps trace the path from genes to psychological phenotypes through individual differences mediating structural and functional characteristics of the brain. The transition to new types of molecular genetic studies, including studies of such genetic factors as copy number variations, genome-wide and whole-genome studies, offers new possibilities for determining the molecular-genetic mechanisms that underlie individual differences in structural brain characteristics and psychological characteristics.

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No conflict of interest