Quantitative genetics of human brain structure and function

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Preface and contributions of authors

As the first authors of the three manuscripts presented in chapters 3 to 5, I took the lead role in the design and execution of the proposed experiments. This included data preprocessing, quality control, statistical analysis, visualization of the results, interpretation of the results and writing of the manuscripts. For each of these steps, I also received valuable help from the co-authors.

For co-authors who at the time were part of the laboratory of Dr. Alan C. Evans at McGill University, in alphabetical order, the breakdown was as follows:

1. Gleb Bezgin: visualization and interpretation of the results in Chapters 4 and 5.
2. Alan C. Evans: Overall supervision of the Ph.D. Thesis.
3. Yasser Iturria-Medina: Design and interpretation of the analyses in Chapter 4 and and writing of the manuscript.
4. Budhachandra Khundrakpam: Design and interpretation of the analyses and writing of the manuscripts in Chapters 3, 4, and 5.
5. John Lewis: Data preprocessing, quality control, interpretation of the results and writing of the manuscripts in Chapters 3,4, and 5.
6. Mona Omidyeganeh: Analysis of the results in Chapter 4.
7. Andrew Reid: Data preprocessing, quality control, visualization and interpretation of the results in Chapter 3 and 4.
8. Pierre Rioux: Data preprocessing and statistical analysis in Chapters 3, 4, and 5.
9. Paule-Joanne Toussaint: Interpretation of the results and writing of the manuscript in Chapter 4.
10. Robert Vincent: Visualization of the results in Chapter 4.

11. Lu Zhao: Analysis and interpretation of the results in Chapter 3.

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2. Yassine Benhajali: quality control of the data used in Chapter 4.
3. Sherif Karama: Quality control of the data interpretation of the results and writing of the manuscripts in Chapters 3 and 5.
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The original contributions to scientific knowledge of the works presented in this thesis are:

1. The demonstration of an interaction between age and polygenic influences (GxA) on regional cortical thickness over adulthood and early ageing.
2. The introduction of a novel “jackknife”-based method for the clustering of traits indexing brain structure.
3. The mapping of heritability and GxA interactions at the connection level across the entire resting-state functional connectome.
4. The mapping of shared genetic influences among resting-state functional connections.
5. The demonstration of a link between the distribution of additive genetic variance in the functional connectome and the evolutionary history of the brain’s functional systems.
6. The mapping at high resolution of shared genetic influences between brain structure and intelligence.
7. The demonstration of the differential sensitivity of measures of brain structure for the detection of genetic influences on different subscales of cognitive function.

Other related publications

Co-authored publications

Iturria-Medina Y, Carbonell F.M, Sotero R.C, **Chouinard-Decorte F**, Evans A.C, Alzheimer's Disease Neuroimaging Initiative. Multifactorial causal model of brain (dis) organization and therapeutic intervention: Application to Alzheimer's disease. Neuroimage 2017; 152:60-77.

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Khundrakpam B.S, Lewis J.D, Reid A, Karama S, Zhao L, **Chouinard-Decorte F**, Evans A.C, Brain Development Cooperative Group. Imaging structural covariance in the development of intelligence. Neuroimage 2017; 144:227-240.

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Babbs, R.K, Sun X, Felsted J, **Chouinard-Decorte F**, Veldhuizen M.G, Small D.M. Decreased caudate response to milkshake is associated with higher body mass index and greater impulsivity. *Physiology & behavior* 2013; 121:103-111.

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Chouinard-Decorte F. Genetic variance in resting-state functional connectivity. *MICCAI 2016 Tutorial: advances in fMRI*. Athens, Greece, October 21st, 2016.

Chouinard-Decorte F. Heritability of functional connectivity. *Montreal Resting-State fMRI Workshop*, Montreal, Canada, May 29th, 2014.

Chouinard-Decorte F. & Evans A.C. Gene x Age interactions in cortical thickness networks. New Horizons in Human Brain Imaging, Oahu, Hawaii, USA, March 4-6th, 2013.

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Chouinard-Decorte F, Rioux P, Lewis J.D, Kent J.W, Carless M.A, Curran J.E, Dyer T, Göring H, Olvera R, Fox P.T, Almasy L, Duggirala R, Blangero J, Bellec P, Glahn D.C, Evans A.C. Genetic clustering of the human functional connectome. Annual Meeting of the Organization for Human Brain Mapping. Vancouver, British Columbia, Canada, June 25-29, 2017.

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Benhajali Y, **Chouinard-Decorte F**, Ferre P, Perusse D, Orban P, Bellec P. Heritability of brain activation subtypes in a language task - an fMRI twin study. Quebec Brain Imaging Network. Montreal, Quebec, Canada. February 10, 2017.

Chouinard-Decorte F, Rioux P, Lewis J.D, Kent J.W, Carless M.A, Curran J.E, Dyer T, Göring H, Olvera R, Fox P.T, Almasy L, Duggirala R, Blangero J, Bellec P, Glahn D.C,

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derivatives. 19th Annual Meeting of the Organization for Human Brain Mapping, Seattle, WA, USA, June 16-20, 2013.

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Abstract

The human brain is an incredibly complex organ that can be described and measured in many different ways. Whichever way we choose, no two brains are exactly the same. The general focus of this thesis will be to understand the causes of this inter-individual variability, how different aspects of the brain are affected, how these effects vary over time and space, and how this can ultimately further our understanding of cognition, behavior and neurological disorders.

In Chapter 1, a more detailed introduction to these concepts and to the structure of the thesis is provided. Chapter 2 first provides an overview of the anatomy of the brain from the perspective of structure and function, which introduces the measures that will be used to describe the brain in the following chapters. This is followed by a short account of the inter-species differences found, at the macroscopic level, between human and primate brains. This emphasizes that inter-individual variation in quantitative traits is most relevant and that genetic variation is necessarily an important cause of this inter-individual variability. The second section of Chapter 2 then provides an overview of the structure and function of the human genome along with the types of genetic variation that can be found within. Given the importance of quantitative variation, a complete account of how discrete genetic factors can account for the inheritance of quantitative traits is then provided, followed by a description of the methods used to estimate this effect and the definition of the specific parameters of interest for this thesis.

Chapter 3 then takes a first look at the quantitative genetics of brain structure, specifically from the perspective of age-related changes in the genetic influences over cortical thickness. Chapter 4 then looks at the quantitative genetics of brain function from

the perspective of resting-state functional connectivity. This includes the complete mapping of heritability, age-related interactions and genetic correlations across the entire functional connectome. The results are then further analyzed and interpreted in view of the evolutionary history of the brain's functional systems. Finally, Chapter 5 moves beyond the analysis of structure and function to show how the results from the previous two chapters could be used to inform other traits related to cognition, behavior and disease. The focus is placed on the genetics of intelligence and the identification specific brain areas where measures of cortical structure are influenced by these same genetic factors.

Taken together, these results demonstrate that genetic variation is an important cause of inter-individual variation in measures of brain structure and function in the population. They also show that the detailed investigation and proper interpretation of these influences could offer valuable insight into the genetics of cognition, behavior, and neurological disorders, and perhaps even into the evolution of the human brain.

Résumé

Le cerveau humain est un organe incroyablement complexe qui peut être décrit et mesuré de nombreuses façons. Peu importe le moyen choisi, aucun cerveau n'est identique. L'objectif général de cette thèse sera de comprendre les causes de cette variabilité interindividuelle, comment différents aspects du cerveau en sont affectés, comment ces effets peuvent varier spatialement et à travers le temps, et comment ceci pourra ultimement améliorer notre compréhension des processus cognitifs, comportementaux et des maladies neurologiques.

Le premier chapitre fournit une introduction plus détaillée de ces concepts et de la structure de cette thèse. Le second chapitre offre d'abord un survol de la neuroanatomie structurelle et fonctionnelle du cerveau, ce qui introduit les traits qui seront utilisées pour mesurer le cerveau dans les chapitres suivants. Ces sections sont suivies d'un court résumé des différences inter-espèces qui sont observées, au niveau macroscopique, entre le cerveau humain et celui des primates. Ceci met l'emphase sur l'importance de l'étude des traits quantitatifs au niveau interindividuel et sur le fait que des variations génétiques sont nécessairement une cause importante de cette variation interindividuelle. La seconde section de ce chapitre offre donc un survol de l'organisation structurelle et fonctionnelle du génome, ainsi que des types de variations génétiques qui peuvent y être trouvées. Vu l'importance des traits quantitatifs, une description détaillées des mécanismes par lesquels la variance des traits quantitatifs peut être héritée est fournie, suivie d'une description des méthodes statistiques qui permettent d'estimer cet effet et des paramètres d'intérêt qui en découlent.

Ensuite, the troisième chapitre jette un premier regard sur la génétique quantitative de la structure du cortex cérébral, spécifiquement du point de vue des interactions entre l'âge et les influences génétiques sur l'épaisseur corticale. Le quatrième chapitre s'attarde aux influences génétiques au niveau fonctionnel, spécifiquement du point de vue de la connectivité fonctionnelle au repos. Ceci inclut la cartographie complète de l'héritabilité, de ses interactions avec l'âge et des corrélations génétiques à travers le connectome fonctionnel en entier. Les résultats sont ensuite analysés et interprétés en rapport à l'histoire évolutive des systèmes fonctionnels du cerveau. Finalement, le cinquième chapitre dépasse l'analyse seule des aspects structurels et fonctionnels pour démontrer comment les résultats des chapitres précédents peuvent être utilisés dans l'étude d'autres traits liés aux aptitudes cognitives, au comportement et aux maladies. Le focus est placé sur la génétique de l'intelligence et sur l'identification de régions du cerveau où les mesures corticales sont sous l'influences des mêmes facteurs génétiques.

Dans l'ensemble, ces résultats démontrent que la variation génétique est une cause importante de variation interindividuelle dans les mesures structurelles et fonctionnelles du cerveau. Ils démontrent aussi que l'étude détaillée et la juste interprétation de ces influences pourrait nous fournir d'importantes informations sur la génétique des traits cognitifs, comportementaux, des maladies neurodégénératives et peut-être même sur l'évolution du cerveau humain.

Chapter 1: Introduction.

> *"They are in you and me; they created us, body and mind; and their preservation is the ultimate rationale for our existence. They have come a long way, those replicators. Now they go by the name of genes, and we are their survival machines. […] Survival machines that can simulate the future are one jump ahead of survival machines that can only learn of the basis of trial and error. […] The evolution of the capacity to simulate seems to have culminated in subjective consciousness. Why this should have happened is, to me, the most profound mystery facing modern biology."*

Richard Dawkins, *The selfish gene*, 1976.

This excerpt from one of the most famous contemporary works in evolutionary biology summarizes in its own way the topics and fields of research that the current thesis intersects with. First are the replicators, the genes, which have been hard at work for hundreds of millions of years. Second is this capacity to simulate, the ability to not only learn from what we have experienced but from what we imagine could happen. Functions which, unambiguously, belong to the brain. Last is the interplay between the two: the fact that over millions of years of replication the genes have evolved to encode, among other things, this wonderful organ that is the brain.

Regarding the genes, it has been a relatively short 151 years since Mendel understood the rules of their inheritance (Mendel, 1866) and an even shorter 16 years

since we first sequenced the human genome in its entirety (Venter et al., 2001). Regarding the brain, though we have had access to it for centuries, studying it has historically been a rather invasive process. It has been less than 50 years since the introduction of CAT scans and NMR imaging allowed detailed images of the brain to be taken non-invasively (Filler, 2009). We therefore find ourselves at a historical crossroads, where we have finally gained access to these key parts of the human survival machine. We now have the opportunity to understand these intimately linked components, explore their structure and functioning, and unravel their evolutionary history.

The scientific study of the interplay between the genome and the brain is a doubly complicated endeavor. As will be detailed in Chapter 2, the organization of the brain must be understood not only in terms of its structure but also of its function (Sections 2.1.1 and 2.1.2). Moreover, what is known of the evolution of the human brain indicates that it has relied mostly on the selection of alleles influencing quantitative traits (Section 2.1.3). Based on this, the second section of Chapter 2 begins by providing a description of the structure and function of the human genome (Section 2.2.1). This leads to a description of the different types of genetic variation that can be found therein and of the mechanisms through which they can affect the human phenotype (Section 2.2.2). Given the central role of the genetic contribution to quantitative traits, Section 2.2.3 then provides a detailed account of how discrete genetic factors inherited in a Mendelian fashion can ultimately account for the non-Mendelian inheritance of inter-individual variation in quantitative traits. This includes the definition of the concept of additive genetic variance, of the methods through which this variance can be estimated and of the population parameters of interest which rely upon it.

The most common of these parameters is the heritability, which describes the contribution of additive genetic variation to the full variation observed in a trait (Falconer & Mackay, 1996). More advanced parameters can estimate the degree to which genetic influences are shared between traits and whether or not these genetic influences change depending on environmental conditions (Almasy, Dyer, & Blangero, 1997; Blangero, 1993). The estimation and correct interpretation of these parameters is critical to improve our understanding of the quantitative genetics of the human brain, and to clarify the potential misunderstandings of these measures (Visscher, Hill, & Wray, 2008). In line with this, the specific goals of the three studies presented in the subsequent chapters are as follows:

1. Chapter 3: (1) to replicate previous findings on the heritability of cortical thickness and (2) to extend our understanding of how these genetic influences may vary over adulthood and early ageing (i.e. GxA interaction).
2. Chapter 4: (1) to provide a complete mapping the heritability of functional connectivity, (2) to map shared genetic influences across the functional connectome, and (3) to provide evidence supporting a reinterpretation of the heritability functional connectivity in line with the evolution of the brain's functional systems.
3. Chapter 5: (1) to map genetic influences on different measures of cortical structure and cognitive function and (2) to explore how the use of different quantitative traits can inform us about shared genetic influences between brain structure and cognition.

These results are then summarized and discussed in Chapter 6. The analyses reported in each Chapter are also discussed from a more general perspective as an analytical framework that could be applied to a great number phenotypes beyond those derived from Magnetic Resonance Imaging. Finally, although the emphasis is placed on evolution in terms of interpretation, discussion is also provided on the implications of this general framework for the study of common disorders and quantitative traits in human populations.

Chapter 2: Background.

This chapter is divided into two main sections that summarize the core concepts behind the analyses presented in this thesis. The first focuses on the human brain and provides an overview of its structural and functional anatomy, which introduces the traits that will be used to measure the brain. Using these definitions, an overview of the evolutionary differences that characterize the human brain is then given, which helps to define the type of inter-individual variation we will focus on and introduces the following section. The second section focuses on the human genome and begins, as with the brain, with a short account of its structure and function. This provides some context for the definition of the concept of genetic variation and the mechanisms through which it can affect the brain. Finally, a detailed account is provided of how genetic variation can influence quantitative traits and how these influences can be measured.

2.1 The human brain.

Anatomy provides a natural starting point both for the definition of the traits that will be used in this thesis and the interpretation of the results. However, the following sections do not intend to provide a full account of structural and functional neuroanatomy. Instead, section 2.1.1 focuses on the definition of the main structural landmarks of the cortical and subcortical gray matter, while section 2.1.2 outlines the broad strokes of their functional organization. These definitions and examples are then used in section 2.1.3, which looks at the evolution of these areas and networks of the brain. This leads to the argument that most of the differences found between human brains and their closest relatives are

quantitative rather than qualitative in nature. This, in turn, stresses the importance of considering quantitative variation when looking at inter-individual variation in human populations.

2.1.1 Structural neuroanatomy.

It is difficult to reference each statement on the basics of human neuroanatomy in a detailed manner, in part because much of this knowledge can be traced back for hundreds of years (Eustachi, 1714). The Atlas of Human Anatomy by Frank H. Netter is therefore used as a general reference for this section (Netter, 2010). In practice, the contents of this section were learned in the classroom and dissection room under the tutelage of Dr. David Ragsdale, Dr. Edith Hamel, Dr. Fraser Moore and Dr. Geoffroy Noel. In turn, the more practical perspective of dissection offers a good starting point for the description of structural neuroanatomy. From the external aspect, once the brain has been removed from the cranial cavity and stripped of the meninges, the largest and most evident part is the cerebral cortex. The cortex is a sheet of gray-matter, ranging from two to four millimeters in thickness, that can be mapped according to its folds and fissures. The most prominent of these is the longitudinal fissure, which separates the left and right hemispheres. Each hemisphere can be further subdivided into four main lobes, each composed of multiple gyri, defined by the sulcal landmarks.

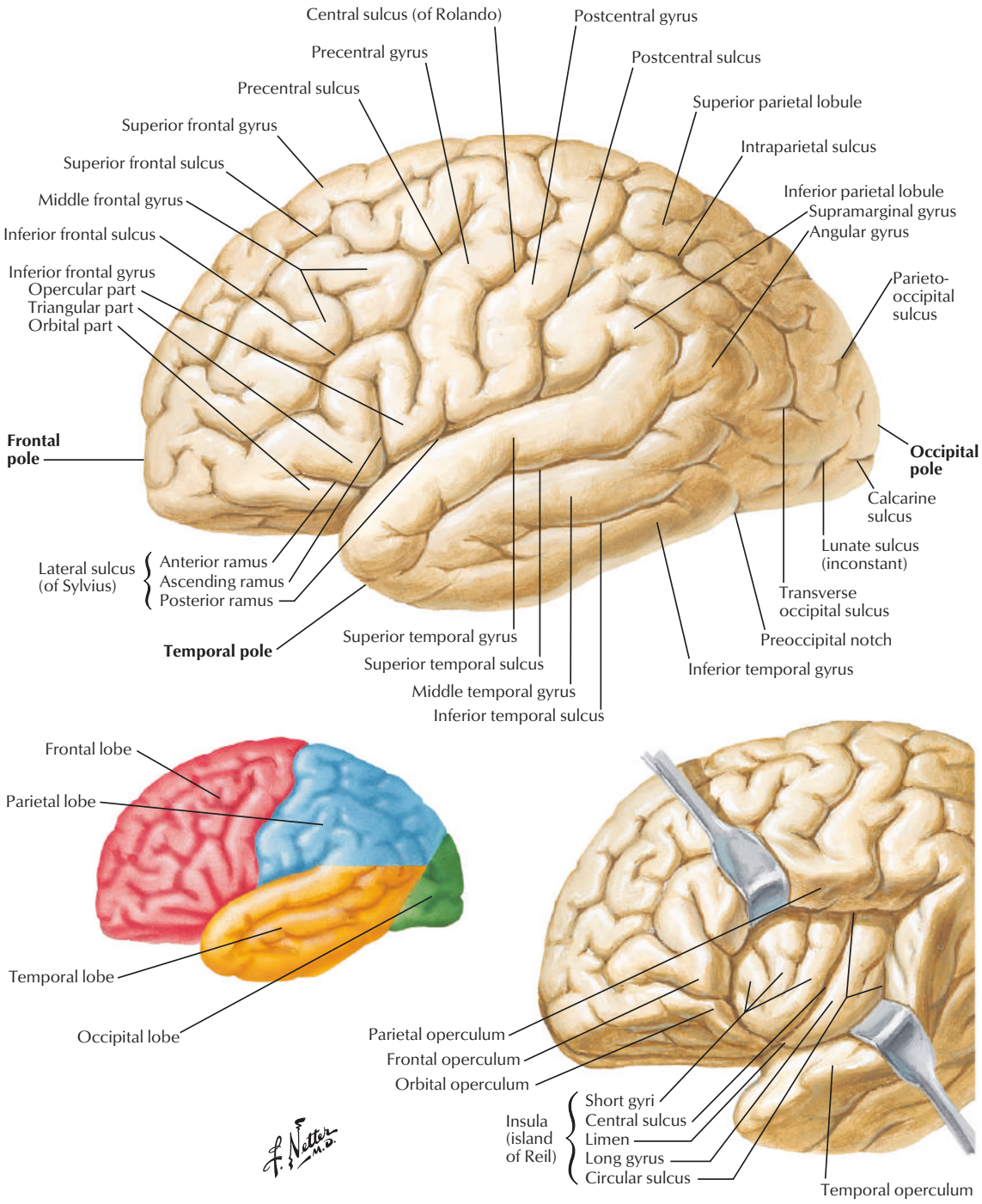


Figure 2.1: Sulcal landmarks of the lateral surface of the brain.

Main landmarks of the lateral surface of the cerebral cortex as referred to in the text. Note the definition of the parieto-occipito-temporal junction at the bottom left.

From: Netter, 2010.

The frontal lobe is delimited caudally by the central sulcus and ventrally by the lateral sulcus. It includes the precentral gyrus, located between the central and precentral sulci, as well as the superior, middle, and inferior frontal gyri, delimited by the superior and inferior frontal sulci. Located on the other side of the central sulcus is the parietal lobe. Rostrally, the parietal lobe includes the postcentral gyrus, which is delimited by the central and postcentral sulci. Caudally, it also includes the superior and inferior parietal lobules which are separated by the intraparietal sulcus. The inferior parietal lobule is further subdivided into the supramarginal and angular gyri. The aforementioned sulci and gyri can be seen in Figure 2.1.

On the medial surface, the parietal cortex also includes the precuneus which is delimited rostrally by the marginal sulcus and caudally the parieto-occipital fissure. This fissure also forms the anterior boundary of the occipital lobe. The occipital lobe includes cuneus and the lingual gyrus, which are respectively located on the dorsal and ventral banks of the calcarine sulcus (see Figure 2.2). On the lateral surface, its anterior boundary is drawn as a line going from the termination of the parieto-occipital fissure down to the preoccipital notch. This is also the caudal boundary of the temporal lobe, while the lateral sulcus forms its dorsal boundary. On the lateral aspect, the temporal lobe is subdivided into the superior, middle and inferior temporal gyri by the superior and inferior temporal sulci (see Figure 2.1). On the ventral aspect, the inferior temporal gyrus is separated from the fusiform gyrus by the occipitotemporal sulcus, which is in turn separated from the parahippocampal gyrus by the collateral sulcus (see Figure 2.3). Two additional areas must be mentioned since they do not fall into the aforementioned categories: the cingulate gyrus, which is located on the medial surface, wraps around the corpus callosum and is

bordered dorsally by the cingulate sulcus (see Figure 2.2), and the insula, which is buried deep within the lateral sulcus (see Figure 2.1).

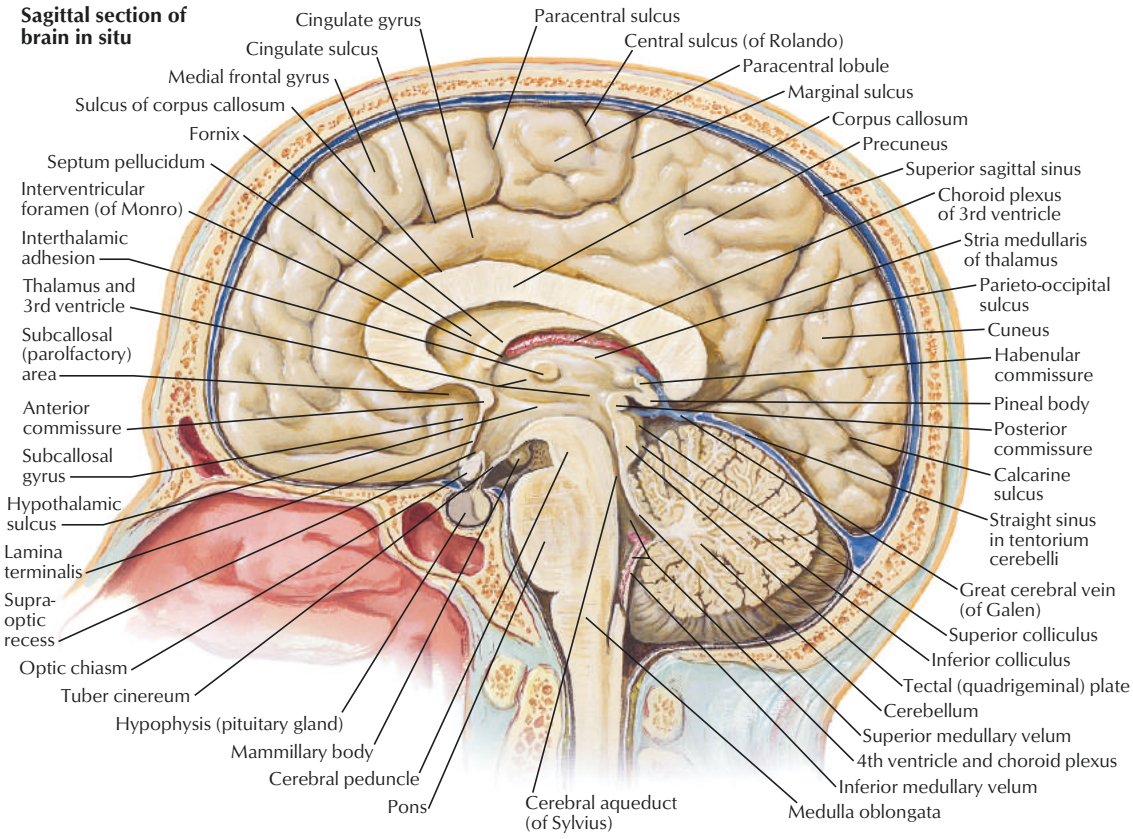


Figure 2.2: Sulcal landmarks of the medial surface of the brain.

Main anatomical landmarks of the medial surface of the human brain. In the text, the emphasis is placed on the cingulate gyrus, precuneus and occipital lobe. Note also that the thalamus and cerebellum are visible.

From: Netter, 2010.

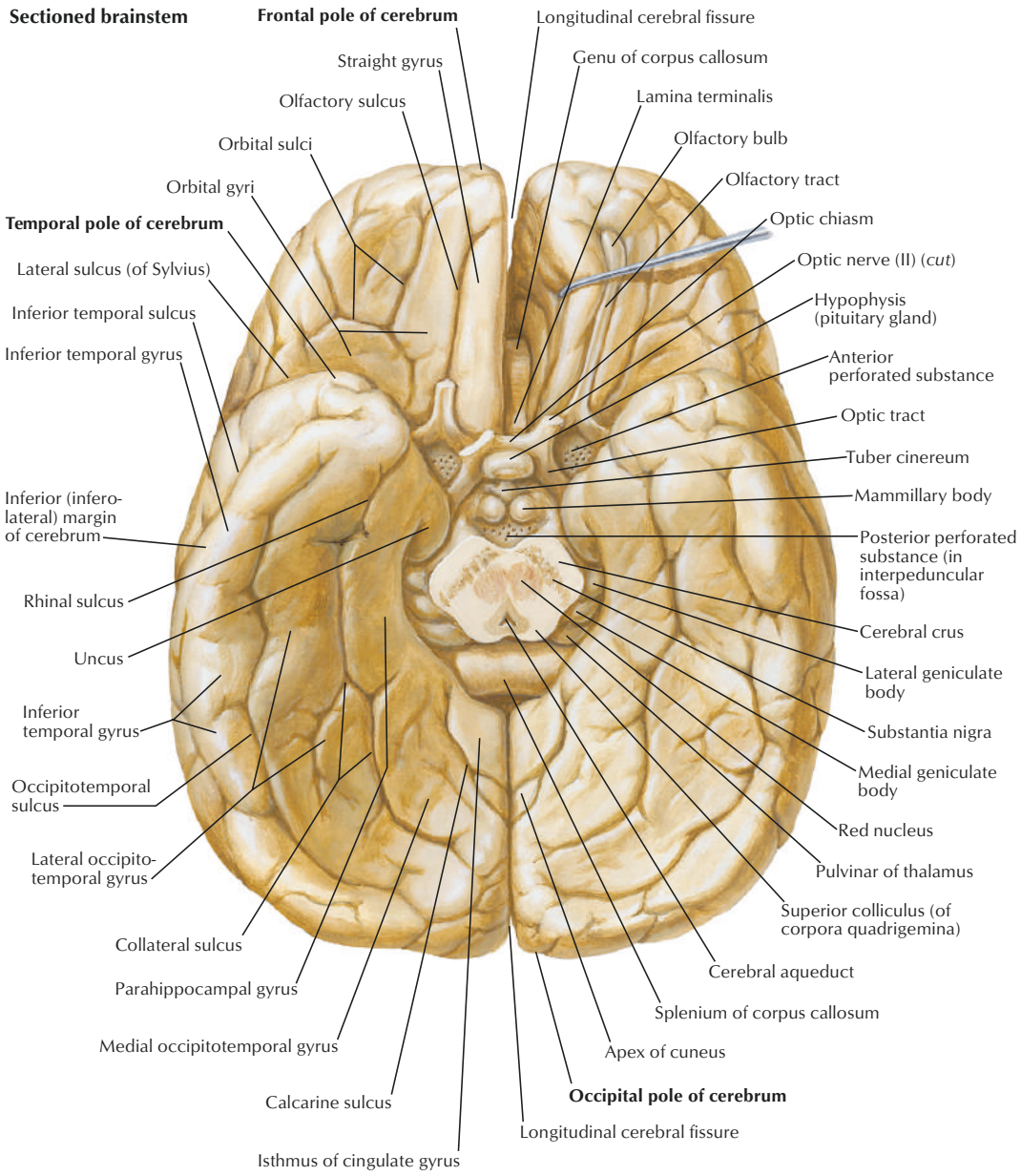


Figure 2.3: Sulcal landmarks of the ventral surface of the brain.

Main anatomical landmarks of the ventral surface of the cerebral cortex. In the text, the emphasis is placed on the temporal lobe. Note that here the brainstem and cerebellum have been resected to expose these areas.

From: Netter, 2010.

Sitting beneath the occipital lobe, the cerebellum is attached to the brainstem by the cerebellar peduncles and is completely dissociated from the cerebral hemispheres. As its name suggests, it forms a “small brain” that includes a very thin cortex, tightly folded into folia, as well as its own deep gray matter nuclei (see Figure 2.2). In addition, some gray-matter structures also lie buried in the white matter of the cerebral hemispheres. The largest, which will be most relevant here, are the basal ganglia, the thalamus, the hippocampus, and the amygdala. The basal ganglia include the caudate nucleus, putamen and globus pallidus. The caudate nucleus forms the lateral wall of the lateral ventricles and follows their curvature from the anterior to the temporal horn. The putamen and globus pallidus are located approximately between the insula and the thalamus, slightly anterior to the latter. The thalamus is a rounded structure, located medially at the level of the third ventricle. The hippocampus is a medial structure of the temporal lobe which forms the floor of the temporal horn of the lateral ventricle (see Figure 2.4). Rostral to the hippocampus, the amygdala is a small “almond” shaped gray matter structure of the anterior temporal lobe.

These structures form the main landmarks that will be used for the interpretation of the results found in the following sections, but their description also serves another important purpose. While (nearly) all human beings possess a cerebellum, basal ganglia, central sulcus, etc., there also exists a great amount of inter-individual variability in brain structure. These are readily found in MRI databases and some fairly common patterns including gyral duplications have been described, notably in the dorsal temporal lobe (Tzourio-Mazoyer & Mazoyer, 2017). Since the cortex is essentially a two-dimensional

sheet of tissue, such large-scale variations as well as more minute differences in the relative sizes of each area can both be captured by the same measures. Namely, these are the surface area, thickness and volume of the cortex.

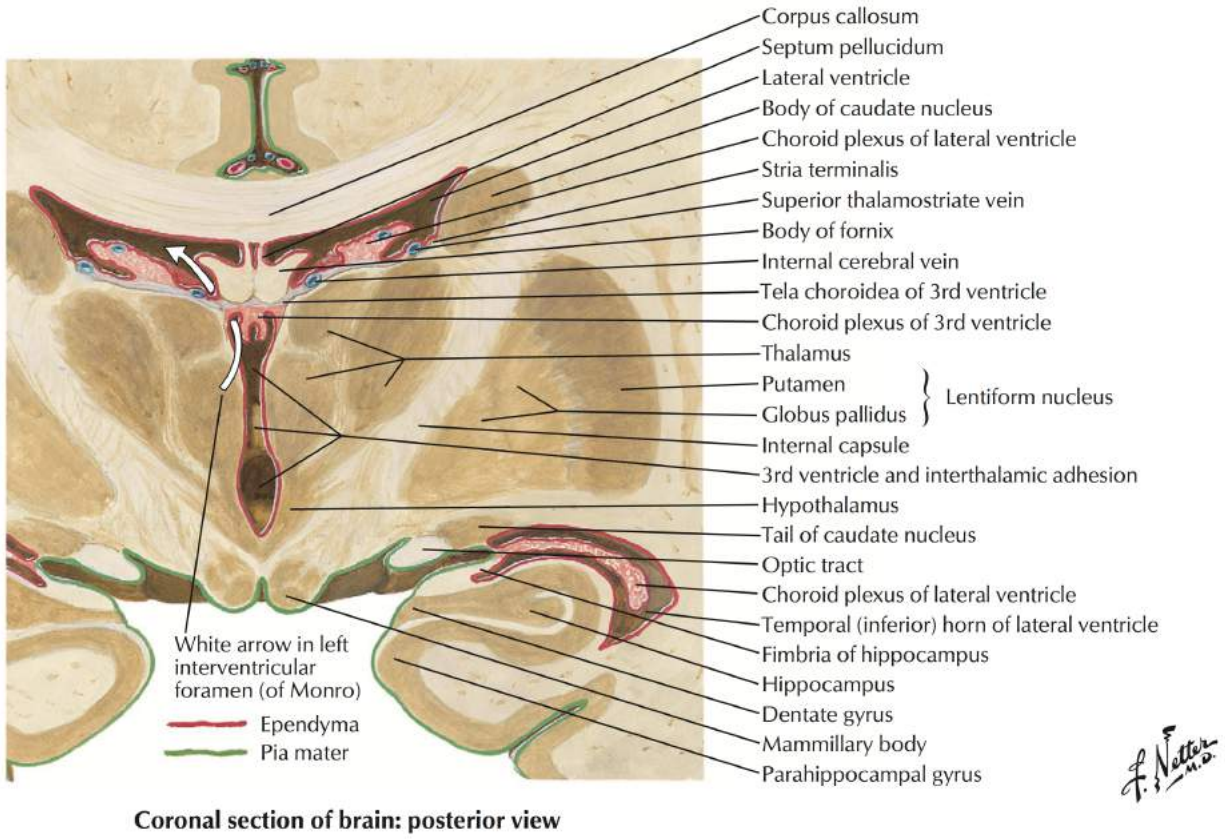


Figure 2.4: Subcortical gray matter structures.

Coronal section showing the principal deep gray matter structures detailed in the text. Note that here the amygdala and thalamus are absent. It should be kept in mind that these form complex tridimensional structure beyond what is seen here.

From: Netter, 2010.

2.1.2 Functional neuroanatomy.

The anatomy of the brain can also be described in terms of its functional rather than structural organization. Functional areas tend to correspond fairly well to those defined based on cytoarchitecture, but functional subdomains are often still present within these. In addition, functional anatomy highlights the fact that all parts of the brain are interconnected and function as an integrated whole. This section provides a few examples to illustrate this point, which will also serve as a foundation for the next section and the work presented In Chapter 4.

A first example is the cortical motor system. Most areas that are involved in the generation of the motor output are housed in the precentral gyrus and the caudal part of the prefrontal cortex (Rizzolatti & Luppino, 2001). As can be seen in Figure 2.5, the organization of these areas is more complex and does not precisely follow the simple subdivisions made by the superior, middle and inferior frontal gyri. In addition, these areas are densely interconnected with somatosensory areas located in the postcentral gyrus and rostral parietal cortex. While this relationship is logically required for the proper generation and adjustment of motor response, it is interesting to note that these processes also involve the basal ganglia, thalamus and cerebellum (Apps & Garwicz, 2005; Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo, 2014). This functional relationship is highlighted notably by Huntington's disease, where the degeneration of inhibitory connections from the striatum to the thalamus result in unwanted or uncontrolled motor outputs (Galvan, André, Wang, Cepeda, & Levine, 2012).

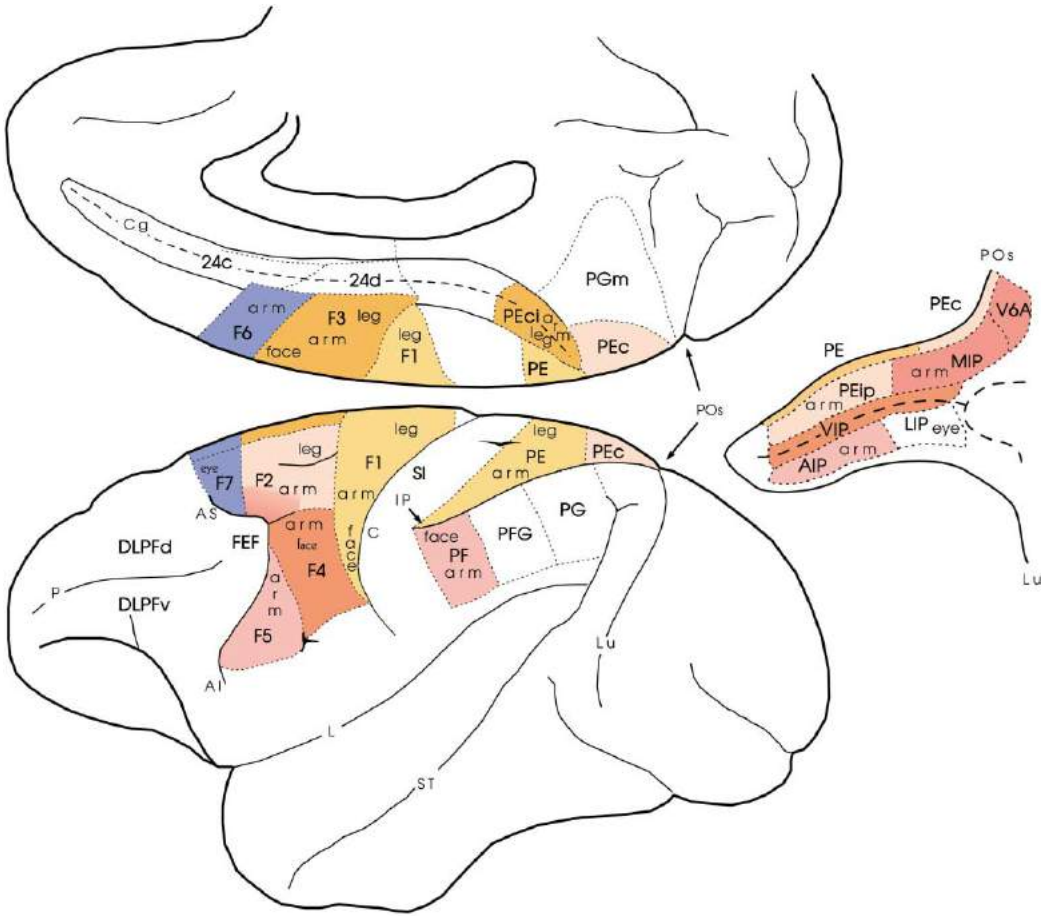


Figure 2.5: The cortical motor system.

Overview of the cortical areas involved in motor function. Areas shown here are involved in the generation of the motor output, planning of the motor output and sensory feedback related to the generation and execution of the motor output. Note that while these are shown for the macaque brain, a homologous complement of areas is found in humans. From: Rizzolatti & Luppino (2001).

Another example is the visual network, which is centered around the occipital lobe (Gilbert & Li, 2013). The primary visual cortex (V1), which contains a retinotopic map of the information initially sensed by the eye, is located on the banks of the calcarine sulcus. From there, the processing of visual information is carried on through a chain of interconnected areas which initially surround V1 in the occipital cortex, but quickly diverge into the dorsal and ventral “streams”. These two pathways involve a number of areas found in the superior parietal lobule and the ventral temporal lobe (Figure 2.6). Conceptually, the dorsal stream decodes the “where” in terms of location and movement, while the ventral stream decodes the “what” in terms of recognized form and color. In addition, most of these areas also receive input from the frontal cortex, which are involved in the attentional control of visual information processing (Gilbert & Li, 2013).

Many more networks could be mentioned and all could be described in more detail: the dorsal temporal lobe includes many areas involved in auditory processing (Scott, 2005), the medial temporal lobe includes structures involved in the processing of memory and emotions (Bird & Burgess, 2008), while more rostral frontal areas are involved in higher order cognitive processes including decision-making, working memory and attention (Miller & Cohen, 2001). What these examples show is that while functional organization overlaps in some ways with structural anatomy, it also offers a distinct perspective on the regional and network organization of the brain. This network organization can now be studied using resting-state functional Magnetic Resonance Imaging (rs-fMRI). Specifically, rs-fMRI allows these functional networks to be identified based on the degree of coherence of their functional timecourses, referred to as functional

connectivity. Inter-individual variation is readily found in functional connectivity, making this the fourth phenotype of interest of this thesis (Mueller et al., 2013).

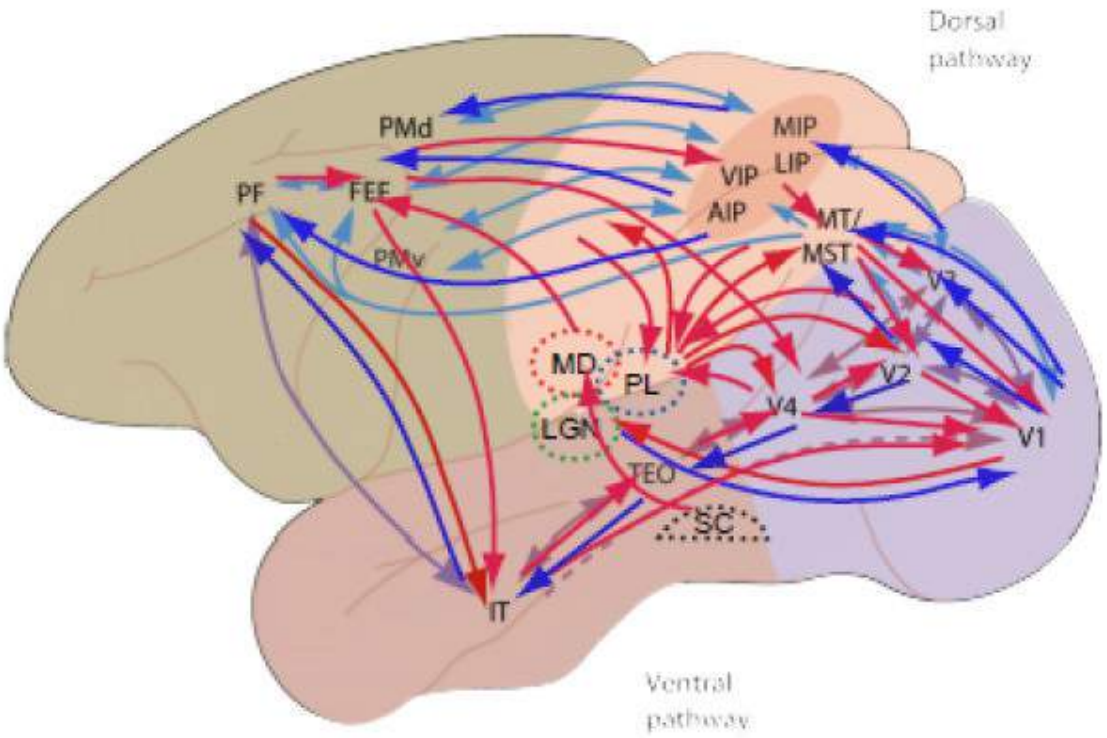


Figure 2.6: The cortical visual system.

Overview of the cortical areas involved in visual function. This includes the perception and decoding of visual information as well as feedback mechanisms related to attention as well as the control of eye movements.

From: Gilbert & Li (2013).

2.1.3 On the evolution of the human brain and the nature of inter-individual differences.

The previous sections defined some of the areas and networks that can be found in the human brain. Yet, as is reflected in figures 2.5 and 2.6, much of the underlying research has been carried out on non-human primates. This already suggests that there is a great degree of homology between the human and primate brains. Still, we would intuitively expect the human brain to have evolved some recent, defining characteristics that set it apart from its closest relatives. If we consider the brain as a set of interconnected areas, then perhaps we can expect to find new areas in the human brain to explain our distinctive cognitive and behavioral characteristics.

In this regard, the visual and sensorimotor systems discussed above are a good starting point because they have been described and studied across a broad range of extant species. On the other hand, this hints at their older phylogenetic age and thus higher degree of conservation. Indeed, functional homologs can be found for most known areas of the cortical visual network in humans and primates. More specifically, this includes areas V1 and V2, which are also shared with the more distant tree shrews and rodents (Kaas, 2008) and Area V3, which forms the outer border of V2 in all primates (Lyon & Kaas, 2002). Higher order areas V4, V5 (MT), V6 (DM), MST, FST and IT also have their homologs in monkeys and even prosimians (Kaas, 2012). While this is based on cytoarchitectonic data, functional mapping using fMRI has also yielded a homologous set of visual areas in humans and macaques (Kolster, Peeters, & Orban, 2010). Thus, it seems safe to say that the architecture of the visual network is conserved in most primates, including humans (Kaas, 2005). The situation is similar for the sensorimotor

network: Brodmann areas 1, 2, 3a and 3b, which make up the postcentral gyrus, can be found in New World Monkeys, Old World Monkeys and Humans (Kaas, 2004). Area M1 and the dorsal premotor cortex can also be identified in rodents and tree shrews (Remple, Reed, Stepniewska, & Kaas, 2006). The more recently evolved frontal eye fields, supplementary motor areas and cingulate areas can also be found in prosimians (Wu, Bichot, & Kaas, 2000). Thus, it again seems safe to say that the cortical architecture of the sensorimotor network has also been conserved in humans and primates.

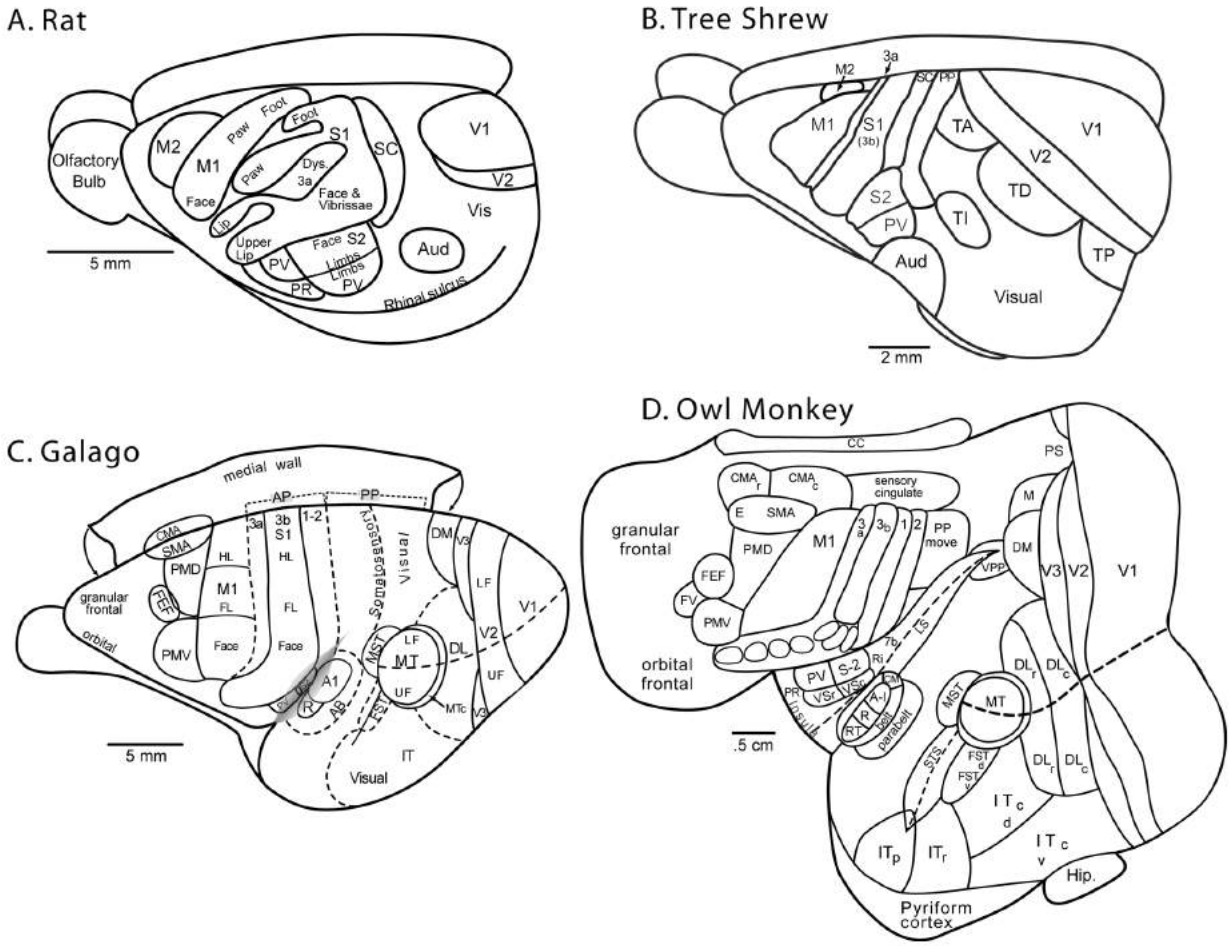


Figure 2.7: Comparative anatomy of the sensory and motor areas of the cortex.
This figure details the homology of the brain areas involved in various functional networks (i.e. mainly somatosensory, motor, visual and auditory) across four mammalian species. While more areas are visibly present in primates compared to rodents, most if not all areas found in the human brain have their homologs in primates.
From: (Kaas, 2008)

In contrast, frontal and parietal cortices are thought to have expanded significantly in humans, making them more likely candidates to house new areas (Kaas, 2004). In the case of the lateral prefrontal cortex however, the data does not seem to support this hypothesis. Using cytoarchitectonic mapping, (Petrides & Pandya, 2002) identified a full complement of homologous regions in both human and macaques. Also, regarding language more specifically, homologs have been found for Broca's area (Petrides & Pandya, 1999; Preuss & Goldman-Rakic, 1991) and Wernicke's area (T. M. Preuss & Goldman-Rakic, 1991a) in both monkeys and prosimians. Surprisingly, perhaps, there are therefore no new areas to be found in the prefrontal cortex. The one part of the brain that shows some promise for the identification of newly evolved brain regions is the parietal cortex. In monkeys, the parietal cortex is divided into Brodmann areas 5 and 7 by the intraparietal sulcus while in humans, these two areas are found together in the superior parietal lobule (Karnath, 2001). The regions of the inferior parietal lobule, Brodmann areas 39 and 40, are apparently virtually impossible to identify in non-human primates (T. M. Preuss & Goldman-Rakic, 1991a) and have been discussed as uniquely human (Karnath, 2001). Functional data has so far supported this claim and shown that

they are likely involved in complex “three-dimensional structure-from-motion processing” (Vanduffel et al., 2002). One interesting theory is that the evolution of the inferior parietal lobule could be related to the capacity to make and use tools (Frey, 2007). In spite of this, some authors argue that the inferior parietal lobule could simply be an expansion or specialization of the posterior temporal cortex rather than a novel area.

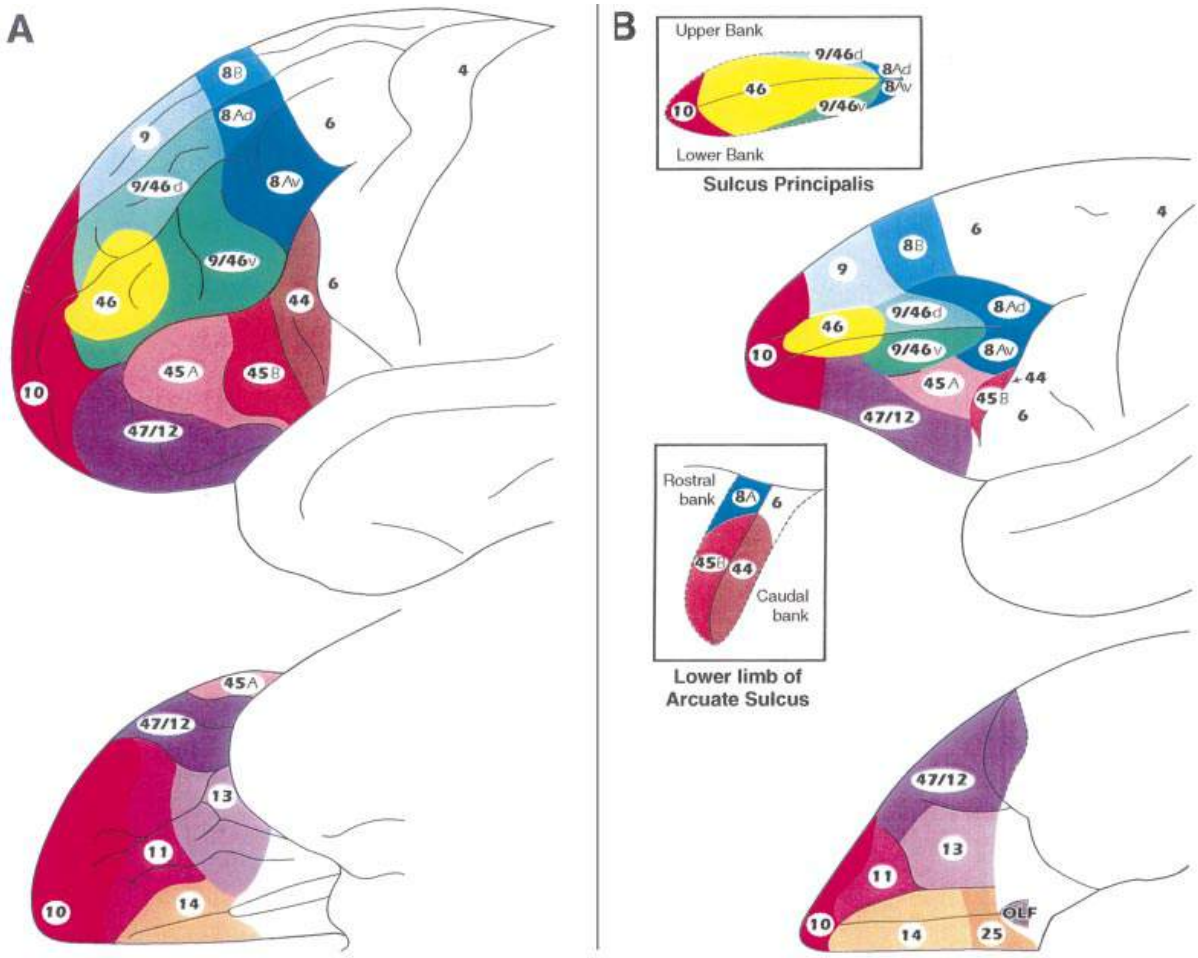


Figure 2.8: Comparative anatomy of the frontal cortex.

This figure details the homology of cytoarchitectonic areas of the frontal cortex between humans (A) and macaques (B). Homologs are again found for all human areas. Note, however, the marked differences in the relative sizes and shapes of each area.

From: (M. Petrides & Pandya, 2002)

Thus, while some authors warn that large regions of the cortex remain to be explored (Preuss, 2011), the current data seems to show that nearly all human brain areas have non-human homologues (Striedter, 2005). How then can we explain the marked cognitive and behavioral differences between humans and primates? A few observations can help guide us in the right direction. In the case of language for instance, while areas seem to be conserved, humans exhibit direct cortical projections from tongue and larynx devoted areas to the brainstem nuclei involved in orofacial motor function (Jürgens & Alipour, 2002). This has been hypothesized to play a role in human “vocal dexterity” (Striedter, 2005). This shows that a reorganization of connectivity, rather than the addition of new regions, might explain some human specializations.

From another point of view, the presence or absence of regions and connections represent qualitative differences between different brain. Such qualitative differences at the macroscopic level are visible few. That is not the case when it comes to differences in quantitative traits. The fossil record clearly shows that the size of the brain has increased markedly in the human lineage (Bruner, 2016). This was driven mainly by the expansion of the neocortex (Finlay & Darlington, 1995), hinting at the fact that many of the areas mentioned above have been differentially enlarged (Buckner & Krienen, 2013).

This brings us to a critical concept: most of the differences found between the human and primate brain, at the macroscopic level, seem to be quantitative rather than qualitative in nature. In some way, this is echoed in a citation by Charles Darwin, saying that “the differences in mind between man and the higher animals, great as it is, is certainly one of degree and not of kind” (Darwin, 1871). Since the process of evolution, which gave rise to these inter-species differences, relies on the selection of inter-individual differences, it follows that adopting a quantitative approach to their study is especially relevant. In turn, it must now be shown how genetic variation can influence such traits, so that the selection of quantitative traits can result in evolution.

2.2 The human genome.

In the previous section, we defined four phenotypes related to brain structure and function and emphasized the importance of using such quantitative traits. In this section, we will now move on the genome and again begin by defining its structure and function. This will then help to understand the different types of genetic variation and how they can result in inter-individual variation and disease. Finally, the last section will focus on the inheritance of these genetic variations and how this can account for the inheritance of quantitative traits.

2.2.1 Deoxyribonucleic acid: structure and function.

Although Mendel’s work in the 19th century led to the formulation of the laws of heredity, the molecular vector of this heredity was not known and for long it was assumed that the “genes” were in fact proteins (Voet & Voet, 2004). It was not until the mid-20th century

that a series of experiments would demonstrate, first, that DNA is the carrier of genetic information (Avery, MacLeod, & McCarty, 1944) and, second, that it is structured as a double helix (Watson & Crick, 1953). Though the nucleic acids themselves had already been identified, the elucidation of the structure of DNA marked the beginning of modern biology because it provided the starting point from which we could understand how genetic information is encoded and inherited. In short, it revealed to us the “replicator”, the central molecule of life.

The double helix structure of DNA is formed by two complementary molecules of deoxyribonucleic acid (DNA), which are long sequences of deoxyribonucleotides, better known as nucleic acids (Figure 2.9). The four nucleic acids that form DNA are: adenine (A), tymine (T), guanine (G) and cytosine (C). DNA itself is a single stranded molecule and its helical structure arises from a phenomenon known as “complementary base pairing”. Adenine always pairs exclusively with thymine and guanine with cytosine, such that any single stranded molecule of DNA is mirrored in its complementary strand and the two strands form the double helix. Within either of these strands, genetic information is encoded by the specific sequence of the nucleotides that form DNA (Voet & Voet, 2004).

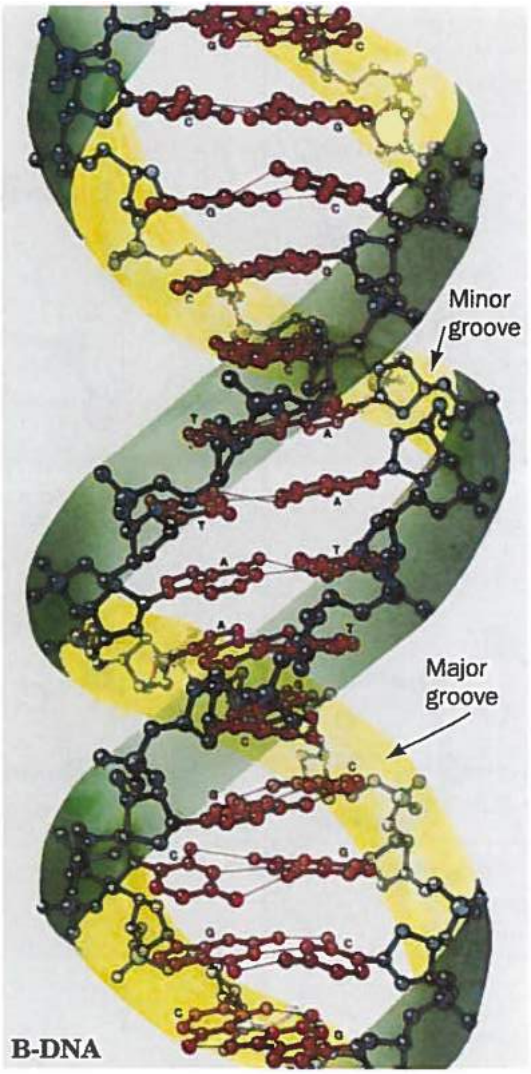


Figure 2.9: The structure of deoxyribonucleic acid.

Representation of the double helix structure of DNA. Note the nucleotides annotated near the middle of the helix and the complementary of the two strands, dictated by the pairing of the bases.

From: Voet & Voet (2004).

The processes through which this information is preserved and used in any living organism is summarized in the central dogma of molecular biology: “DNA directs its own replication and its transcription to yield RNA which, in turn, directs its translation to form proteins” (Crick, 1970). The transcription of DNA into RNA is a precisely controlled process that is initiated when the RNA polymerase enzyme binds to a sequence of DNA known as the “promoter”. Promoter sequences are complex and highly variable across different genes, mainly because they contain numerous sites, “bar codes” of sorts, that can be recognized by proteins known as transcription factors that can stimulate or inhibit the binding of RNA polymerase (Voet & Voet, 2004). Once the RNA polymerase begins its work, however, it will read the sequence of the DNA and create an exact copy of this sequence until it reaches a termination sequence (Figure 2.10). The termination sequence is typically much simpler and common examples found in eukaryotes are sequence of 4 to 10 consecutive adenines or palindromic sequences of guanine and cytosine which will fold on themselves to form a “hairpin” structure, thereby terminating the transcription. It is through this process that the information contained in the genome is “expressed” and in cases where the transcribed sequence encodes for a protein, the product is known as a messenger RNA (mRNA) (Voet & Voet, 2004).

Within mRNAs, the information is encoded in sequences of three nucleotides known as codons. This information is decoded through the action of ribosomes, complex cytosolic organelles that are part RNA part protein. On the ribosome, each codon will successively be recognized by a transfer RNA (tRNA) containing the complementary trinucleotide sequence known as an anticodon. Each tRNA carries an amino acid residue, such that the successive recognition of each codon by its corresponding tRNA results in

the assembly of the amino acids into resulting protein by the ribosome (Figure 2.11). The encoding of each amino acid by the codons is formally known as the genetic code (see Figure 2.12) and “its universality among all forms of life is compelling evidence that life on earth arose from a common ancestor” (Voet & Voet, 2004).

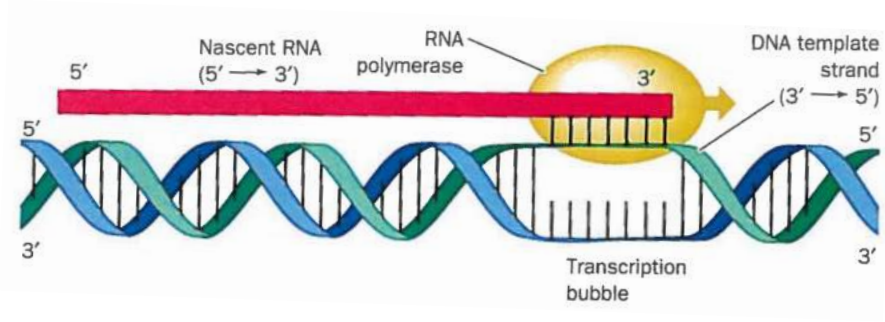


Figure 2.10: The transcription of DNA into mRNA.

Schematic representation of the process of transcription of the DNA into mRNA. Note how the two strands of DNA are temporarily separated in order to be read by the RNA polymerase.

From: Voet & Voet (2004).

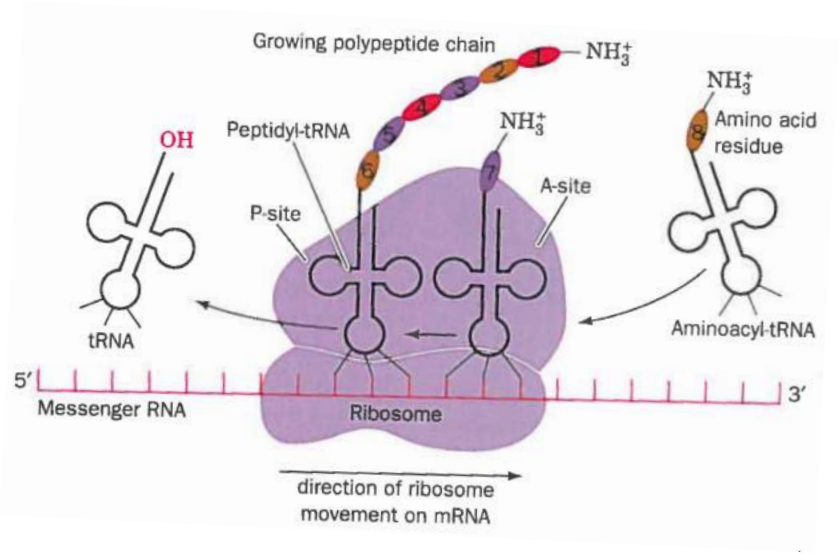


Figure 2.11: The translation of mRNA into a peptide.

Schematic representing the translation the mRNA into an amino-acid sequence to form a peptide. Note the “reading” of the mRNA in sequences of three nucleotides the tRNA. From: Voet & Voet (2004).

Protein translation is probably the best example of how the genome encodes information and how it is functionally expressed, but it is not the only one. RNA molecules can also be functional without the need of being translated into proteins. This is obviously the case for tRNAs, but also for other lesser known molecules such as microRNAs (Ambros, 2004; Bartel, 2004; Bentwich et al., 2005) and small interfering RNAs (Hamilton & Baulcombe, 1999; Piatek & Werner, 2014). Other DNA sequences, such as those found in promoters, are functional in of themselves by forming recognizable elements through which proteins exert their functions. The functionality of these sequences is not limited to gene expression as they can also “encode” important physical structures of the genome,

such as centromeres (Pluta, Mackay, Ainsztein, Goldberg, & Earnshaw, 1995) and telomeres (Blackburn & Gall, 1978).

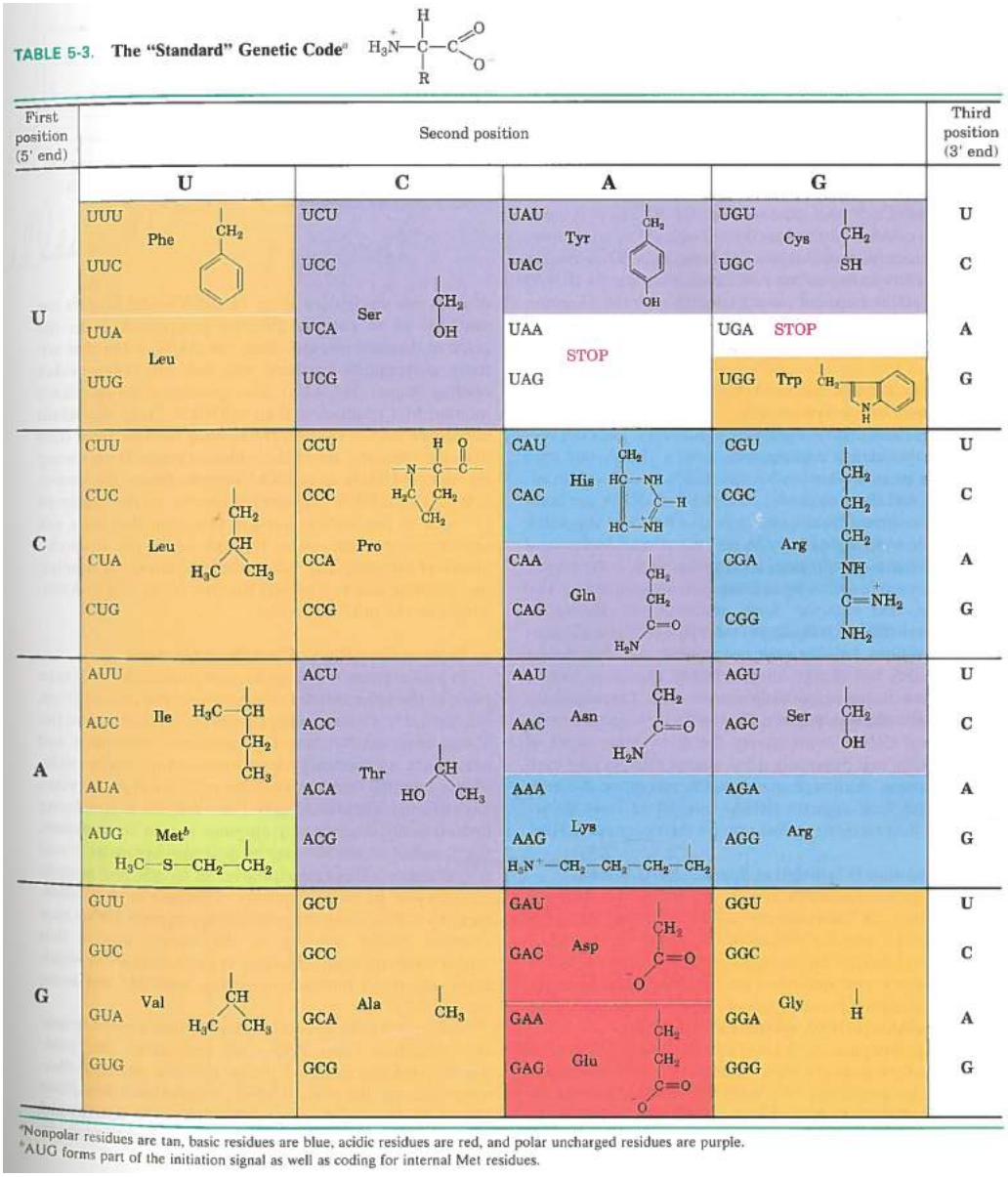


TABLE 5-3. The "Standard" Genetic Code[a]

First position (5′ end)	Second position U	Second position C	Second position A	Second position G	Third position (3′ end)
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA STOP	UGA STOP	A
	UUG Leu	UCG Ser	UAG STOP	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met[b]	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

[a]Nonpolar residues are tan, basic residues are blue, acidic residues are red, and polar uncharged residues are purple.
[b]AUG forms part of the initiation signal as well as coding for internal Met residues.

Figure 2.12: The genetic code.

This figure details the genetic code, where codons (read clockwise around the edge) dictate which amino-acid is to be added or whether to stop the translation.

From: Voet & Voet (2004).

Taken together, all these mechanisms provide an overview of how the sequences that form the genome express their functions. For any given organism, this information, contained in its entirety in the nucleus of every single cell, represents everything that is required for the development and functioning of an individual. This is a fact that was most convincingly demonstrated by the cloning of the sheep Dolly (Campbell, McWhir, Ritchie, & Wilmut, 1996). This historical experiment, as well as naturally occurring clones (i.e. monozygotic twins), highlights another important fact. If this was all there is to know about the human genome, then we would all be as similar as clones.

2.2.2 Genetic variation.

From a more philosophical standpoint, what we define as “the human genome” is very concretely a well formalized form of inductive reasoning (International Human Genome Sequencing Consortium, 2004). This is to say that “the human genome” cannot itself be observed in reality; there only exists specific observations of it, extant copies, and each of them is unique. The reason for this unicity is the presence of variations in its sequence. These can take many forms, but at their core they simply represent alterations in the linear sequence of nucleotides that is the genome.

The simplest and most prevalent of these are Single Nucleotide Polymorphisms (SNPs). As the name indicates, these are mutations where a single base in the nucleotide sequence has been altered. As of February 2017 (build 150 of the dbSNP database, www.ncbi.nlm.nih.gov/projects/SNP/), a total of 325,658,303 reference SNPs had been catalogued in the human genome. These mutations can be of three different types: (1) substitutions where a base is replaced with another, (2) deletions where a base is

removed, and (3) insertions where a base is added (see Figure 2.13). Though they are the most common, SNPs are not the only class of mutations and the same types of sequence alterations can affect more than base. One increment higher are microsatellites, repetitive sequences of DNA where two or three bases are repeated a variable number of time (Vieira, Santini, Diniz, & Munhoz, 2016). Another increment higher are Copy Number Variants (CNVs) where sequences ranging from 1000 bases to 5 Megabases can be repeated (Eichler, 2008; McCarroll & Altshuler, 2007). Other types of mutations can be large insertions (or deletions) where a complete segment of DNA is inserted somewhere in the genome. A good example of this are Alu insertions, sometimes referred to as a "jumping gene", where an entire well-defined sequence is inserted in the genome. These transposable elements can be found in excess of 500,000 copies throughout the genome and are, interestingly, specific to primates (Stoneking et al., 1997). Rarer types of sequence alteration are inversions, where a given segment is reversed end to end on the same chromosome. Very large alterations can also occur, such as polysomy, chromosomal heteromorphism and fragile sites, but these are less relevant to topics discussed herein.

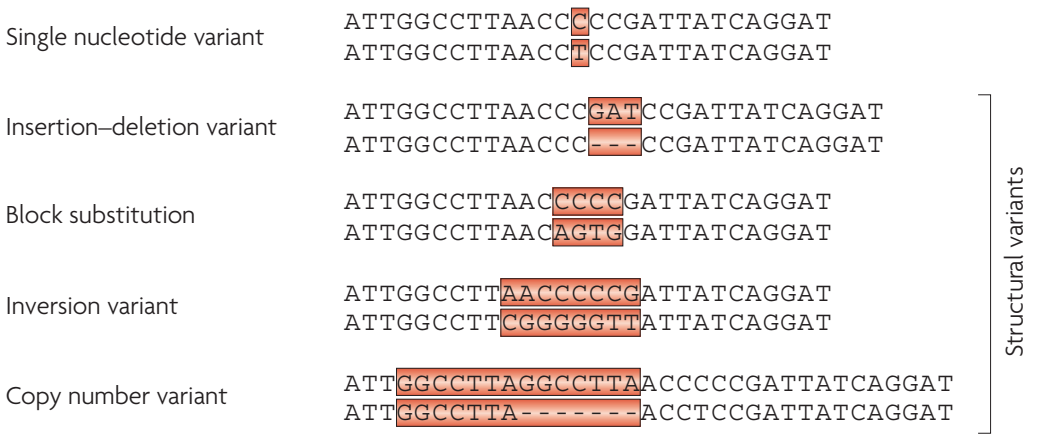


Figure 2.13: Classes of sequence variation in the human genome.

Main types of sequence variation found in the human genome. Note that structural variants can affect much larger sequences than what is shown.

From: (Frazer, Murray, Schork, & Topol, 2009).

It is currently estimated that the genome of any individual differs from the reference sequence at 4 to 5 million sites. Of these more than 99.9% are SNPs, around 1000 are large deletions, around 1098 are insertions of specific elements such as Alu sequences, around 160 are CNVs and around 10 are inversions (The 1000 Genomes Project Consortium, 2015). Needless to say, all of these do not cause diseases. The impact of any given mutation on the phenotype of the individual will depend on the surrounding sequence in which it is found. Large scale mutations, such as CNVs and Alu insertions, can involve the sequence of entire genes and are therefore more likely to have a functional impact. A good example of this the salivary amylase gene, where copy numbers of the gene correlate positively with the level of expression of the gene (Perry et al., 2007). Yet, all types of mutation can also occur in non-coding parts of the genome and be functionally silent. In addition, the genomic size of the mutation (in base pairs) is not indicative of the size of its effect. The mutation of a single base can be sufficient to completely disrupt the expression of a protein and cause extreme phenotypes, or mendelian disorders. A good example of this are frameshift mutations, where the deletion of a base disrupts the reading of the codons in the coding sequence of a gene. These have notably been implicated in congenital leptin deficiency causing extreme and early

onset obesity (Funcke et al., 2014). In other cases, substitutions in specific codons can result in a change in the amino acid sequence of a protein affecting its function (Al-Haggar et al., 2012). Many other mechanisms including mutations in promoter sequences, splice site mutations or mutations of CpG sites could also be discussed, which can affect the level of expression of a gene or the functionality of the resulting protein(s).

Together, these examples provide is an overview of the types of mutation that can be found in the human genome and how they can have an impact on the phenotype of an individual. In other words, how genetic variation can lead to inter-individual variation in the population. Yet, it should be noted that many of the examples given correspond to rare diseases which are usually all-or-none phenotypes that are not necessarily expressed in every generation of carriers. On the other hand, a lot of the inter-individual variation found in the population (i.e. variation in height, hair color, body shape, etc.) seems to be common, to follow a continuous distribution and to be found in every single generation. This apparent paradox brings us to the field of quantitative genetics.

2.2.3 Quantitative genetics.

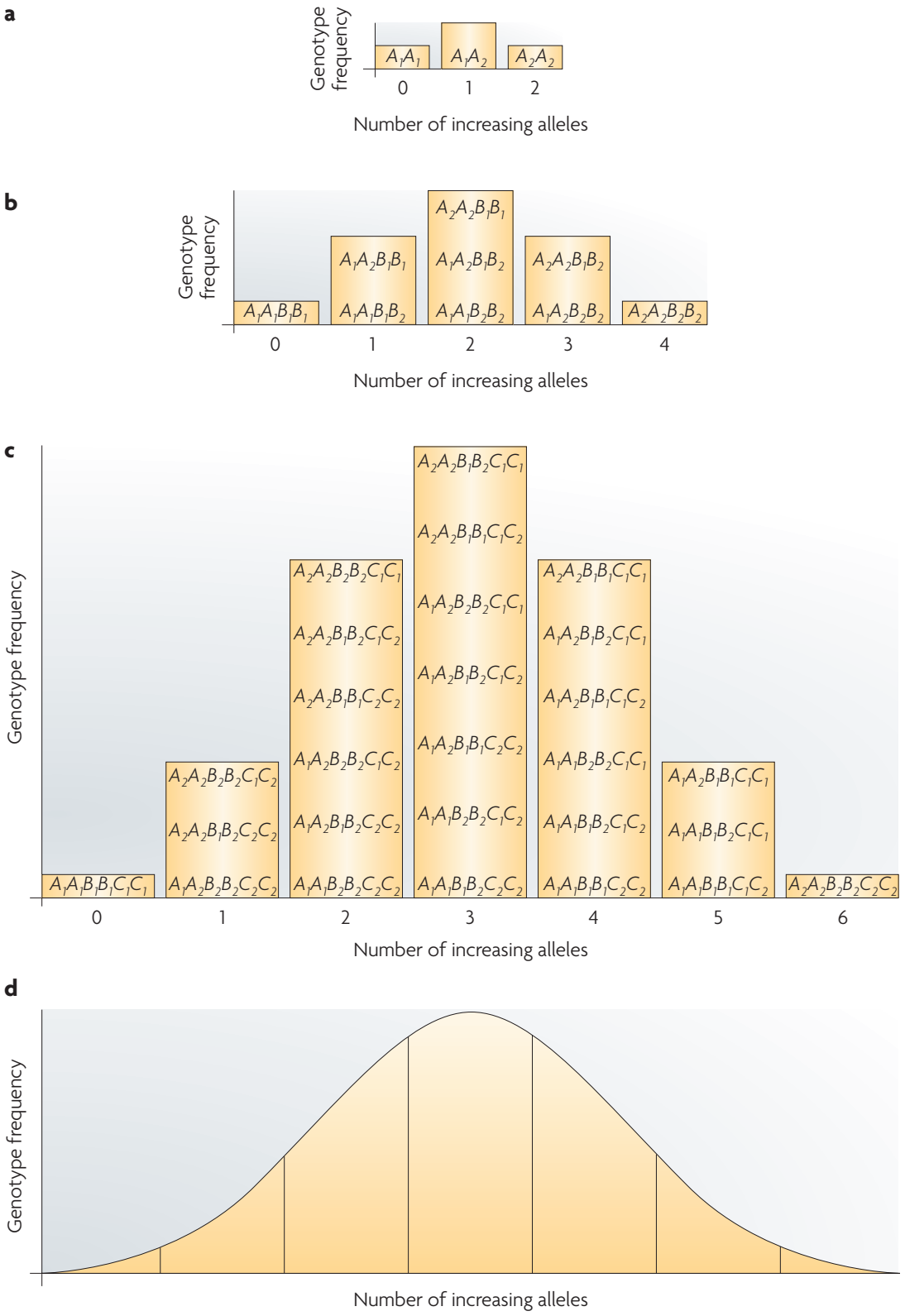
When a mutation occurs in the genome, regardless of its type, two different copies of the DNA are created: an ancestral copy and a mutated copy. These are referred to as alleles and annotated as A1 and A2. By convention, the deleterious allele is referred to as A2. Since human beings are diploid organisms, any individual will carry two alleles. The specific combination of alleles carried by an individual is called the genotype, which can be homozygous (A1A1, A2A2) or heterozygous (A1A2). In some cases, where a mutation has a large effect on the phenotype, it is possible to infer the genotype of an individual

based on its phenotype and ancestry. This was the case in Mendel's experiments, which allowed him to establish the rules of inheritance. However, although familial resemblance hints at a certain degree of inheritance, most quantitative traits do not follow a simple Mendelian pattern. This issue was at the core of the historic debate between Mendelians and Biometricians (Robert Plomin, Haworth, & Davis, 2009). The debate was settled by Sir Ronald A. Fisher in his paper on "The correlation between relatives on the supposition of Mendelian inheritance" (Fisher, 1918). In essence, the argument was that the summed influences of a large number of Mendelian factors, each accounting for a small portion of the variance, would result in the continuous normal distribution of the phenotype (Figure 2.14). This section covers the theory behind the inheritance of quantitative traits and how it can be quantified in practice.

Figure 2.14: From discrete genetic factors to continuous variation.

(Next page) Schematic representation of how, by the addition of a great number of loci, a continuous normal distribution can be achieved. While the Y-axis here is the genotype frequency, which translates to the frequency of phenotypic values when a given trait is considered.

From: Plomin et al. (2009).


a
Genotype frequency
A_1A_1
A_1A_2
A_2A_2
0
1
2
Number of increasing alleles
b
Genotype frequency
$A_1A_1B_1B_1$
$A_1A_2B_1B_1$
$A_1A_1B_1B_2$
$A_2A_2B_1B_1$
$A_1A_2B_1B_2$
$A_1A_1B_2B_2$
$A_2A_2B_1B_2$
$A_1A_2B_2B_2$
$A_2A_2B_2B_2$
0
1
2
3
4
Number of increasing alleles
c
Genotype frequency
$A_1A_1B_1B_1C_1C_1$
$A_2A_2B_1B_1C_1C_1$
$A_1A_2B_1B_1C_1C_1$
$A_1A_1B_2B_1C_1C_1$
$A_1A_1B_1B_2C_1C_1$
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$A_2A_2B_1B_1C_1C_2$
$A_1A_2B_2B_1C_1C_1$
$A_1A_2B_1B_2C_1C_1$
$A_1A_2B_1B_1C_2C_1$
$A_1A_2B_1B_1C_1C_2$
$A_1A_1B_2B_2C_1C_1$
$A_1A_1B_2B_1C_2C_1$
$A_1A_1B_2B_1C_1C_2$
$A_1A_1B_1B_2C_2C_1$
$A_1A_1B_1B_2C_1C_2$
$A_1A_1B_1B_1C_2C_2$
$A_2A_2B_2B_2C_1C_1$
$A_2A_2B_2B_1C_2C_1$
$A_2A_2B_2B_1C_1C_2$
$A_2A_2B_1B_2C_2C_1$
$A_2A_2B_1B_2C_1C_2$
$A_2A_2B_1B_1C_2C_2$
$A_1A_2B_2B_2C_1C_1$
$A_1A_2B_2B_1C_2C_1$
$A_1A_2B_2B_1C_1C_2$
$A_1A_2B_1B_2C_2C_1$
$A_1A_2B_1B_2C_1C_2$
$A_1A_2B_1B_1C_2C_2$
$A_1A_1B_2B_2C_2C_1$
$A_1A_1B_2B_2C_1C_2$
$A_1A_1B_2B_1C_2C_2$
$A_1A_1B_1B_2C_2C_2$
$A_2A_2B_2B_2C_2C_1$
$A_2A_2B_2B_2C_1C_2$
$A_2A_2B_2B_1C_2C_2$
$A_2A_2B_1B_2C_2C_2$
$A_1A_2B_2B_2C_2C_1$
$A_1A_2B_2B_2C_1C_2$
$A_1A_2B_2B_1C_2C_2$
$A_1A_2B_1B_2C_2C_2$
$A_1A_1B_2B_2C_2C_2$
$A_2A_2B_2B_2C_2C_2$
0
1
2
3
4
5
6
Number of increasing alleles
d
Genotype frequency
Number of increasing alleles

For any specific phenotype (i.e. height, cortical thickness, etc.), the specific measure of that phenotype for an individual is called the phenotypic value (P). The phenotypic value can be divided into components attributable to different causes: the genotypic value (G) and the environmental deviation (E). A good way to understand the genotypic value is to imagine a group of clones each bearing the same genotype. Under normal conditions, their mean environmental deviation will be 0 and their mean phenotypic value will equal the genotypic value (Falconer & Mackay, 1996). Then, if we consider a single mutated locus with two alleles, we can set the origin at the mid-point between the two homozygotes and express the genotypic values as $A1A1 = a$ and $A2A2 = -a$. Here, the genotypic value of the heterozygote (d) depends on the degree of dominance of the alleles (see Figure 2.15).

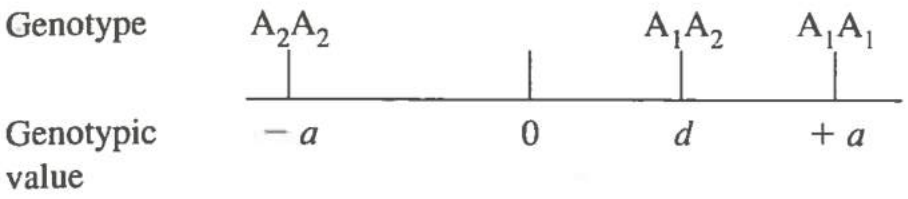

Figure 2.15: Definition of the genotypic values.

Theoretical definition of the genotypic values. Note that here both a and d are defined relative to the midpoint between the genotypic values of the two homozygotes, which corresponds to the genotypic value of the heterozygote in the absence of dominance.

From: Falconer & Mackay (1996).

Since the phenotypic values equal the genotypic values, it is now possible to express the mean (M) phenotypic value of the population based on the frequencies of the alleles. If we note the frequency of A1 as p and the frequency of A2 as q, then the frequencies of the genotypes are $A1A1 = p^2,\ A1A2 = 2pq$ and $A2A2 = q^2$. The mean phenotypic value of the population is given by the sum of the genotypic values multiplied by their frequency:

$$M = p^2a + 2pqd - q^2a$$

Which simplifies to:

$$M = a(p - q) + 2dpq$$

Note that based on the definitions above, M represents a deviation from the midpoint between the two homozygotes. If the origin is not corrected and the raw genotypic values are used, then this gives the population mean (Falconer & Mackay, 1996). This might seem somewhat convoluted because in reality the values of a and d are not known and M can be estimated directly from the data. The usefulness of this theoretical definition is that it allows us to define the average effect (α) of an allele. This is critical because alleles rather than genotypes are inherited, so that defining the effects of the alleles is required for us to understand how quantitative variation can be inherited. By definition, the average effect of an allele corresponds to the deviation from the population mean of the genotypes it produces (Falconer & Mackay, 1996). If gametes carrying the A1 allele unite at random in the population, they will produce p homozygotes and q heterozygotes. Since the genotypic value of A1 homozygotes is a and that of heterozygotes is d, their mean will be $pa + qd$ and their deviation from the mean will be:

$$\alpha_1 = pa + qd - (a(p - q) + 2dpq)$$

which reduces to:

$$\alpha_1 = q\big(a + d(q - p)\big)$$

In the same way, the mean value of the genotypes produced by A2 will be $pd - qa$ and its deviation from the mean will be:

$$\alpha_2 = -p\big(a + d(q - p)\big)$$

From there, the average effect that comes from inheriting one allele versus the other (α) corresponds to the difference between the average effects of the two alleles:

$$\alpha = \ q\big(a + d(q - p)\big) + p\big(a + d(q - p)\big)$$

Since $p + q = 1$, this reduces to:

$$\alpha = a + d(q - p)$$

The average effect (α) is critical because it represents the amount of deviation from the population mean that is inherited with each allele from parent to offspring. Then, the sum of the average effects (α) of all the alleles that an individual carry over all loci of its genome is the definition of its breeding value. The average breeding value of the two parents is the average breeding value of their offspring and, consequently, their average phenotypic value (Falconer & Mackay, 1996). When a large number of alleles are involved, α will be relatively small compared to the total deviation from the mean in the population and the breeding values will assume a continuous normal distribution in the population, which forms the main mechanism for the inheritance of quantitative traits (Fisher, 1918).

Based on this theoretical formulation, the breeding value is defined as a property of an individual. As such, it contains both the additive (a) and dominance (d) deviations of the polymorphisms it carries. However, in practice, breeding values are estimated based on the resemblance among relatives. Since dominance reflects an interaction

between the alleles at one locus and only one allele is passed from parent to offspring, this leads to a disparity between the theoretical and practical definitions. The same principle applies to interactions between alleles at different loci (i.e. epistatic interactions). What this means is that dominance and interaction deviations will contribute differently to the resemblance among relatives (Falconer & Mackay, 1996). Therefore, it is more practical to express the genotypic value of an individual (G) as the sum of its additive effects (i.e. the breeding value: A), dominance deviations (D) and interactions deviations (I):

$$G = A + D + I$$

Since these values are expressed as deviations from the mean, the variances in the population correspond to the mean of their squares, and the total variation of the population can be decomposed in the same way as the phenotypic value of an individual:

$$V_P = V_A + V_D + V_I + V_E$$

One important concept here is that additive genetic variance (V_A) corresponds to the variance of the breeding values in the population (Falconer & Mackay, 1996). Since offsprings inherit half their breeding value (i.e. one chromosome) from each parent, it can be shown that the genetic covariance of parents and offsprings equals half the additive genetic variance of the parental population. For two offsprings of the same parents (full siblings), each will inherit half the breeding value of each parent, such that their covariance will also be:

$$var\left(\frac{1}{2}(A_F + A_M)\right) = \frac{1}{4}(V_A + V_A) = \frac{1}{2}V_A$$

However, since full siblings share both parents, there is also a 25% chance that they will inherit the same genotype from their parents. Thus, the expected covariance between full siblings is:

$$cov_{FS} = \frac{1}{2}V_A + \frac{1}{4}V_D$$

For half-siblings, since they only share half the breeding value of the parent they have in common, their genetic covariance is the variance of half the breeding value:

$$cov_{HS} = var\left(\frac{1}{2}A\right) = \frac{1}{4}V_A$$

Then, for any given pair of relatives y_1 and y_2, the expression of the expected phenotypic covariance can be generalized to:

$$cov(y_1, y_2) = 2\phi V_A + \delta_\tau V_D$$

where ϕ is the expected kinship coefficient and δ_τ is the expected probability of sharing two alleles identical by descent (Almasy & Blangero, 1998). A summary of coefficients for first, second and third-degree relationships can be found in Table 2.1.

Table 2.1: Coefficients of the additive and dominance variance components.

Relationship		*Coefficient* r (of V_A)	u (of V_D)
MZ twins		1	1
First-degree	Offspring: parent	$\frac{1}{2}$	0
	Full sib	$\frac{1}{2}$	$\frac{1}{4}$
Second-degree	Half sib		
	Offspring: grandparent	$\frac{1}{4}$	0
	Uncle (aunt): nephew (niece)		
	Double first cousin	$\frac{1}{4}$	$\frac{1}{16}$
Third-degree	Offspring: great-grandparent	$\frac{1}{8}$	0
	Single first cousin		

From: Falconer & Mackay (1996).

These examples demonstrate that additive and dominance variance contribute differently to the resemblance among relatives. Therefore, when data including multiple degrees of relatedness beyond full sibs is available, it is possible to obtain an unbiased partitioning of V_P into V_A versus $V_D + V_I + V_E$ (Falconer & Mackay, 1996).

Though this can be achieved in many different ways, the general method that will be used here relies on the restricted maximum likelihood estimation of parameters based on mixed linear models. The mixed linear model for the estimation of additive genetic variance is:

$$\Omega_{ij} = 2\Phi_{ij}\sigma_a^2 + \delta_{ij}\sigma_e^2$$

where Ω_{ij} is the phenotypic covariance of subject i and j, Φ_{ij} is their kinship coefficient, σ_a^2 is the observational additive genetic variance component, δ_{ij} is an identity matrix, and σ_e^2 is the residual variance component (Almasy & Blangero, 1998). Then, the parameters can be estimated by maximising the ln-likelihood function:

$$\ln L(\mu, \sigma_a^2, \sigma_e^2, \beta | y, X) = -\frac{t}{2}\ln(2\pi) - \frac{1}{2} ln|\Omega| - \frac{1}{2}\Delta'\Omega^{-1}\Delta$$

where μ is the phenotypic mean, β is the matrix of regression coefficients for the covariates, y is the vector of observed phenotypic values, X is the matrix of covariates, and $\Delta = \mathrm{y} - \mu - \mathrm{X}\beta$ (Almasy & Blangero, 1998). The null hypothesis can then be tested by comparing the likelihood of the model where the parameters (here σ_a^2) are estimated to the restricted model where they are constrained to 0. The test statistic from which we can assess significance corresponds to twice the difference between the ln likelihoods of the two models and is distributed as a 50:50 mixture of a chi-squared variable with one degree of freedom and a point mass at zero (Blangero, Williams, & Almasy, 2000; Self & Liang, 1987).

This shows how the amount of additive genetic variance present in a trait can be estimated. Once it is estimated, several parameters can be computed. The first and most common is the heritability (h^2), which is the ratio of additive genetic variance to the full phenotypic variance of the trait (Falconer & Mackay, 1996). The second is the genetic correlation (ρ_g), which quantifies the degree of overlap between the vectors of average effects (α) that influence two traits (Almasy et al., 1997). Lastly, it is also possible to test whether the amount of additive genetic variance found in a trait changes (γ_g), or if the vector of average effects contributing to a trait (λ_g) changes depending on environmental conditions (Blangero, 1993). All of these parameters provide valuable information regarding quantitative genetic influences on one or more traits. These will be described in more detail in the following chapters, as they are applied to the study of cortical thickness, surface area, gray matter volume and functional connectivity.

Chapter 3: Heritable changes in regional cortical thickness with age.

Preface:

At the onset of this first study, the heritability of cortical thickness had already been widely studied. As such, it was a good starting point to try replicate these findings in order to validate the preprocessing and quality control of the data which had just been carried out and provide a strong foundation on which subsequent studies could build upon.

The novel aspects of this study are separated on two fronts. First is the use of a novel clustering method based on the works of Dr. Bellec (Bellec, Rosa-Neto, Lyttelton, Benali, & Evans, 2010). The rationale behind this approach was, first, to reduce the problem of multiple comparisons and increase our ability to detect the effects of interest. Secondly, the purpose was also to reduce the computational burden of this analysis, given that at the time the analysis software was not designed to natively handle the large number of tests require to derive a full surface map (i.e. >80 000 tests). While scripts were developed in house to perform such analyses in the following chapters, it is worth noting that significant developments have since been made on the SOLAR-Eclipse version of the software (http://solar-eclipse-genetics.org/) which now allows such analyses to be performed natively.

More importantly, the second novel aspect of this study was to test for the presence of age-related interactions with the heritability of cortical thickness. Such interactions can be present in two non-exclusive forms. First, there can be an age-related change in the

amount of additive variance found in the trait, second there can be a change in the set of genetic loci that account for the additive genetic variance over age (i.e. incomplete pleiotropy over age). While a previous study had found age-related changes in additive variance during development (Lenroot et al., 2009), the test of incomplete pleiotropy over age had never been performed. In addition, the previous study was performed in pediatric twins (age: 5-18) while ours was performed over adulthood and early ageing (age: 18-77), thus providing some degree of complementarity. These results were published in the journal Brain Imaging and Behavior, 2014;8(2):208-216.

Heritable changes in regional cortical thickness with age

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Abstract

It is now well established that regional indices of brain structure such as cortical thickness, surface area or grey matter volume exhibit spatially variable patterns of heritability. However, a recent study found these patterns to change with age during development, a result supported by gene expression studies. Changes in heritability have not been investigated in adulthood so far and could have important implications in the study of heritability and genetic correlations in the brain as well as in the discovery of specific genes explaining them. Herein, we tested for genotype by age (G×A) interactions, an extension of genotype by environment interactions, through adulthood and healthy ageing in 902 subjects from the Genetics of Brain Structure (GOBS) study. A “jackknife” based method for the analysis of stable cortical thickness clusters (JASC) and scale selection is also introduced. Although additive genetic variance remained constant throughout adulthood, we found evidence for incomplete pleiotropy across age in the cortical thickness of paralimbic and parieto-temporal areas. This suggests that different genetic factors account for cortical thickness heritability at different ages in these regions.

Introduction

Regional indices of brain structure such as cortical thickness, surface area or grey matter volume exhibit spatially variable patterns of heritability. For instance, the highest estimates of heritability for these measures are commonly found in prefrontal and temporal areas (Hulshoff Pol et al., 2006; Joshi et al., 2011; Kremen et al., 2010; Lenroot et al., 2009; Rimol et al., 2010; Thompson et al., 2001; I. C. Wright, Sham, Murray, Weinberger, & Bullmore, 2002) Moreover, genetic correlation studies have shown that common genetic factors appear to influence distributed brain regions with mostly bilateral patterns. This organization is explained largely by the similarity of genetic influences in spatially adjacent regions and in homologous regions of the left and right hemispheres (C.-H. Chen et al., 2012, 2013; Rimol et al., 2010; J Eric Schmitt et al., 2010).

Heritability, however, is an estimate that can change with age. In one study of pediatric development, Lenroot et al. (2009) found primary sensorimotor areas to exhibit decreasing genetic effect with age. Conversely, genetic variance increased in the dorsal prefrontal cortex and temporal lobes up to 18 years old, where regional patterns of heritability resembled those observed in adults. These results suggest higher initial heritability in regions developing earlier in childhood and increasing genetic effects in late-developing regions associated with higher cognitive functions. Such genotype by age (G×A) interactions have not been investigated in adulthood so far and could have important implications in the study of heritability and genetic correlations in the brain as well as in the discovery of specific genes explaining them. Additionally, global measures of brain structure such as mean cortical thickness, intracranial volume or total gray matter volume are also highly heritable (Panizzon et al., 2009; Pennington et al., 2000;

Pfefferbaum, Sullivan, Swan, & Carmelli, 2000). These global effects can mask spatial variation in heritability at the regional level (J Eric Schmitt et al., 2010; U Yoon, Perusse, & Evans, 2012), which in turn can mask variation in heritability at the vertex or voxel level (Eyler et al., 2012). Thus, appropriate scale and global covariate selection is very important for the study of genetic effects in the brain.

In this study, we tested for G×A interactions in regional cortical thickness by estimating age-related changes in additive genetic variance and regional decreases in genetic correlation with increasing age difference (Blangero, 1993). To reduce the computational load of these advanced variance component analyses, we used the validated approach of cortical thickness clustering based on correlated variations. In addition to efficient data reduction, this method has also been shown to exhibit features that have functional significance in healthy and diseased conditions (Bassett et al., 2008; Chen, He, Rosa-Neto, Germann, & Evans, 2008; Kelly et al., 2012). The stability of the clusters was assessed prior to the genetic analyses with a novel “jackknife” method for the analysis of stable cortical thickness clusters (JASC) and a silhouette analysis was also introduced to select the appropriate scale for data reduction.

Material & Methods

Subjects

The sample included 902 subjects from randomly selected families enrolled in the Genetics of Brain Structure and Function Study (GOBS) before December 31st 2012 (see Supplementary Table 1 for a summary of the pedigree structure). The GOBS study is a collaborative effort between Texas Biomedical Research Institute, University of Texas Health Science Center at San Antonio (UTHSCSA), Yale University School of Medicine and McGill University. Subjects were recruited if they were part of a large family of Mexican-American ancestry from the San Antonio, TX, area (see Olvera et al. 2011 for recruitment details). Exclusion criteria were MRI contraindications, history of neurological illness, stroke or another major neurological event. Mean age was 43±15 (mean±SD) with a range of 18 to 77 and 546 of the subjects were women. All participants provided written informed consent and the study was approved by the institutional review boards at the UTHSCSA, Texas Biomedical Research Institute, Yale University and McGill University.

Image acquisition and analysis

All MRI images were acquired at the UTHSCSA Research Imaging Center on a Siemens 3T Trio scanner (Siemens, Erlangen, Germany). High-resolution (isotropic 800 μm) 3D Turbo-flash T1-weighted images were acquired with the following parameters: TE/TR/TI = 3.04/2100/785ms, flip angle = 13°. Seven images were acquired consecutively using this protocol for each subject and the images were then co-registered and averaged to increase signal-to-noise ratio and reduce motion artifacts (Kochunov et al., 2006). Native averaged T1-weighted MRI scans were corrected for non-uniformity artifacts with the N3

algorithm (Sled, Zijdenbos, & Evans, 1998). The corrected volumes were then masked (Smith, 2002) and registered into stereotaxic space (Collins, Neelin, Peters, & Evans, 1994). The registered, corrected images were segmented into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and background using an advanced neural net classifier (Tohka, Zijdenbos, & Evans, 2004). The WM and GM surfaces were extracted using the Constrained Laplacian-based Automated Segmentation with Proximities algorithm (Kim et al., 2005; MacDonald, Kabani, Avis, & Evans, 2000) and were resampled to a stereotaxic surface template to provide vertex based measures and lobar segmentation (Lyttelton, Boucher, Robbins, & Evans, 2007). Cortical thickness was measured in native space using the linked distance between the two surfaces across 81 924 vertices (Im et al., 2008). The processing pipeline was executed on the Canadian Brain Imaging Network (CBRAIN) platform, a network of five imaging centers and eight High Performance Computers for collaborative sharing and distributed processing of large MRI databases (Frisoni et al., 2011).

Cortical surface parcellation and clustering

The automatic anatomical labeling (AAL) atlas was used to parcellate the surface into 78 cortical regions (N Tzourio-Mazoyer et al., 2002). Cortical thickness was averaged over all vertices in each region of interest for each subject (He, Chen, & Evans, 2007) and the effect of mean cortical thickness was regressed to allow for regional analysis (Eyler et al., 2012). The residuals were clustered using a customized version of the Bootstrap Analysis of Stable Clusters (BASC) pipeline (Bellec et al., 2010). Briefly, a jackknife procedure was used to generate B subsamples where Pearson's correlation coefficients were computed

for each possible pair of the 78 regions of interest. This yielded a correlation matrix C_{ij} (where i,j = 1, 2 ... 78) that was then clustered using a Hierarchical Agglomerative Clustering (HAC) algorithm based on Ward's criterion with K clusters (Batagelj, 1988). The resulting B adjacency matrices were averaged to generate a group stability matrix where each cell represented the proportion of time that regions i and j were considered as connected over the subsamples:

$$(1) \qquad S_{ij} = Pr\left(\phi_{ij}(y) = 1 | Y \xrightarrow{f} y\right)$$

This group stability matrix was itself entered into one last consensus HAC to build a final set of K group clusters (Fred & Jain, 2005), that captured the most stable associations of the cluster replications over B jackknife subsamples. A modified version of the silhouette criterion was then computed using the consensus clusters and the group stability matrix (Bellec et al., 2010; Rousseeuw, 1987). This criterion represents the difference of average within-cluster stability minus the maximal average between-cluster stability. In order to select the first stable scale of regional organization, we selected the lowest scale where an increase in the number of clusters stopped resulting in a substantial increase in the silhouette criterion.

Quantitative Genetic Analyses

The additive polygenic variance (σ_a^2) of a normally distributed trait can be estimated from familial data by modelling the covariance of two individuals as a function of kinship. This method assumes that the pedigree is drawn from a non-inbred population in Hardy-

Weinberg equilibrium with random mating. The covariance between individuals i and j is expressed as:

$$(2) \qquad \Omega_{ij} = 2\Phi_{ij}\sigma_a^2 + \delta_{ij}\sigma_e^2$$

where Ω_{ij} is the phenotypic covariance of subject i and j, Φ_{ij} is their kinship coefficient and δ_{ij} is an identity matrix. Here σ_e^2 is a residual term containing all effects not accounted for by the additive component. Heritability (h^2) is obtained by expressing σ_a^2 as a proportion of the phenotypic variance (Falconer & Mackay, 1996). For all networks we used age, age^2, sex, the product of age and sex and the product of age^2 and sex as covariates.

$$(3) \qquad h^2 = \frac{\sigma_a^2}{\sigma_p^2}$$

Blangero et al. defined genotype by environment interaction as a significant additive component of variance in response to the environment (Blangero, 1993, p. 199; David C Glahn et al., 2013). This additive genetic variance in response ($\sigma_{G\Delta}^2$) is a function of the additive genetic variance of the trait expressed in the two environments and the additive genetic correlation between the trait's expression in the two environments:

$$(4) \qquad \sigma_{G\Delta}^2 = (\sigma_{G1} - \sigma_{G2})^2 + 2\sigma_{G1}\sigma_{G2}\left(1 - \rho_g\right)$$

The null hypothesis of no polygenic interaction, $\sigma^2_{G\Delta} = 0$, requires the additive variances to be equal $(\sigma^2_{G1} = \sigma^2_{G2})$ and full pleiotropy $\left(\rho_g = 1\right)$ between the two environments. Pleiotropy generally refers to a given gene influencing two or more traits. In the context of G×A interactions, the requirement of full pleiotropy means that the same set of genes must account for the observed additive variance of the trait across age. For a continuous environment (z), the first requirement can be tested by modelling the polygenic variance as an exponential function of the environment:

$$\sigma_{Gz} = \exp\left(\kappa_g + \gamma_{Gz}\right) \quad (5)$$

where γ_{Gz} determines the rate of change in σ_{Gz}. The second requirement can be tested by modelling the genetic correlation as a function of the difference between environmental indices:

$$\rho_g = \exp\left(-\lambda_g |z_i - z_j\right) \quad (6)$$

where λ_g determines the rate of exponential decay in the genetic correlation as environmental difference increases. Using these variance functions, the phenotypic covariance between two non-inbred individuals i and j is given by:

$$\Omega_{ij} = 2\Phi_{ij}\rho_g\sqrt{\exp\left(\alpha_g + \gamma_g(z_i - \overline{z})\right)} \times \sqrt{\exp\left(\alpha_g + \gamma_g\left(z_j - \overline{z}\right)\right)} + \mathrm{I}_{ij}\sqrt{\exp\left(\alpha_e + \gamma_e(z_i - \overline{z})\right)} \times \sqrt{\exp\left(\alpha_e + \gamma_e\left(z_j - \overline{z}\right)\right)} \quad (7)$$

where γ_g and λ_g are the parameters of interest in the polygenic genotype by environment interaction test (Blangero, 1993). These parameters are estimated using Maximum Likelihood variance-decomposition methods and significance is tested by comparing the log-likelihood for the two restricted models (with γ_g or λ_g constrained to 0) with the log-likelihood for the model where they were estimated. A significant test for σ_{Gz} or ρ_g after Bonferroni correction for the number of clusters is considered as evidence for a polygenic variance component in response to age. For the current analyses, an inverse normal transformation was applied to all traits of interest to ensure normality of the data and sex was used as a covariate for the interaction analysis. All quantitative genetic analyses were carried out using the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package (Almasy & Blangero, 1998).

Results

Clustering and regional age effects

The Silhouette Criterion peaked early (see Figure 1A) and scale 9 was chosen as the lowest scale at high stability to parcellate the cortical surface. The stability matrix, consensus clustering and surface representation of the clusters for this scale are shown in Figure 1B, C and D, respectively. Details on the attribution of each AAL region to each cluster can be found in Supplementary Table 2. Of interest for the G×A results, cluster 2 included the cingulate gyrus, the medial orbital part of the superior frontal gyrus and the insula (all bilaterally). The stability of correlations within this cluster (S_{intra}), based on Equation 1, was very high with values of 0.99 to 1. Conversely, the stability of correlations with regions outside this cluster (S_{inter}) was very low, ranging from 0 to 0.003. Cluster 5 included the parahippocampal, fusiform and inferior occipital gyri (S_{intra}= 0.66 to 0.91, S_{inter} = 0 to 0.29) and cluster 8 consisted of the superior and inferior parietal gyri, the supramarginal, angular and middle temporal gyri as well as the right superior temporal gyrus (S_{intra} = 0.47 to 0.81, S_{inter} = 0 to 0.37). Also of note, language-related areas formed a lateralized cluster (#7) involving the bilateral inferior frontal gyri (opercular and triangular parts), rolandic operculum and Heschl's gyrus, along with the left superior temporal gyrus (S_{intra} = 0.59 to 0.80, S_{inter} = 0 to 0.46).

Genetic and age-related variance components

Estimates of additive genetic heritability were significant for all clusters after Bonferroni correction ($p < 1\times10^{-5}$) and ranged from 0.36 to 0.6. Detailed results can be found in Table 1. The highest values ($h^2 > 0.5$) were found in cluster 4 (inferior temporal gyrus and

temporal pole), cluster 7 (language-related areas), cluster 1 (frontal areas) and cluster 2 (cingulate gyrus, insula and medial orbital part of the superior frontal gyrus). Significant age-related variance was found in four of the nine clusters, see Table 1, corresponding to parieto-temporal cortices, primary sensorimotor areas and language areas. The absence of age effects in five clusters is likely due to the removal of mean cortical thickness from the data and the four significant clusters thus represent regional effects of age, beyond those observed in the mean. Although not all regions showed fixed effects of age on phenotypic variance, it remains possible for anti-correlated effects on the additive and environmental variance components to be present. Also, different sets of genetic factors might explain an otherwise stable additive variance component. Hence, all networks were included in the G×A analysis.

Genetic interaction with age

Complete results for the G×A interaction test are shown in Table 2. For the test of additive genetic variance in response to age (σ_{Gz}), we found marginal significance in cluster 3 (sensorimotor cortices), but this did not survive correction for multiple comparisons. Estimates of γ_g over all brain regions were thus not statistically different from 0 and we consider additive genetic variance to be stable over our age range. For the test of incomplete pleiotropy across age (ρ_g) significant effects were found in cluster 2 (cingulate gyrus, insula and medial orbital part of the superior frontal gyrus), cluster 5 (fusiform, parahippocampal and inferior occipital gyri) and cluster 8 (parieto-temporal areas). These effects survived the Bonferroni corrected threshold (0.006) for nine tests at α = 0.05 and are shown in Figure 2.

Discussion

Here we report the first evidence for incomplete pleiotropy across age in regional cortical thickness, showing that different sets of genetic factors contribute to heritability over healthy ageing. The strongest effects were observed in a network of paralimbic regions including the cingulate gyrus, the medial orbital part of the superior frontal gyrus and the insula (cluster 2). Significant effects were also found in a cluster of temporal paralimbic cortices (cluster 5) and in parieto-temporal areas (cluster 8). Human gene expression studies have shown that healthy ageing is accompanied by a reduction of gene expression levels and a diversification in gene expression patterns throughout the brain, a finding consistent with the notion of incomplete pleiotropy (Lu et al., 2004; Somel, Khaitovich, Bahn, Pääbo, & Lachmann, 2006). The heterogeneity of the set of expressed genes peaks around the ages of 40 to 70 years old, also consistent with the later end of our age range (Lu et al., 2004). This finding has important implications for the genetic analysis of cortical thickness, especially regarding methods based on pleiotropy such as genetic correlations.

We also found estimates of additive genetic variance for regional cortical thickness to be constant over our age range. Such age-related changes have previously been investigated in a developmental study by Lenroot (2009). Although changes were found during childhood, they reported that by the age of 18 years old heritability patterns were similar to those reported in adults. Together with our results, this suggests that heritability reaches steadier values during early adulthood. This is also supported by gene-expression studies showing more variance in expression levels before the age of 15 (Sterner et al., 2012) while the set of expressed genes and expression levels then seems

to remain homogeneous until the age of 40 (Lu et al., 2004). Although heritability cannot be directly equated to the number of genes expressed and their expression levels, our findings agree in that they reach a steady state during adulthood. Similarly, the decline in expression levels from the ages of 40 to 70 might be offset by the diversification of expressed genes, yielding a similar total amount of genetic contributions. It is also interesting to note that expression patterns become more homogeneous again at ages above 70, where they correlate negatively with those observed during development (Lu et al., 2004; Somel et al., 2006). Therefore, heritability estimates might change again past this point.

In agreement with previous studies, cortical thickness was significantly heritable in all clusters. The highest values were observed in temporal cortices (cluster 4), language areas (cluster 7) and prefrontal areas (cluster 3). This pattern is consistent with previous studies of brain structure where high heritability estimates were commonly found in prefrontal areas (Joshi et al., 2011; Kremen et al., 2010) as well as the anterior, superior and inferior temporal cortices (Hulshoff Pol et al., 2006; Lenroot et al., 2009; Thompson et al., 2001; I. C. Wright et al., 2002). Our finding of high heritability in a lateralized language-related cluster is also in agreement with (Thompson et al., 2001) who observed high heritability in language areas with significant lateralization in Wernicke's area. High heritability estimates have also been reported for the posterior cingulate gyrus and insula (Hulshoff Pol et al., 2006; Joshi et al., 2011; I. C. Wright et al., 2002). Other regions have shown more variable estimates, notably in parietal cortices, visual areas and the pre-post central gyri (Hulshoff Pol et al., 2006; Joshi et al., 2011; Kremen et al., 2010). These discrepancies could be due to differences in the structural traits used, such as gray matter

density, cortical thickness or surface area, since they are known to be affected by different sets of genes (Winkler et al., 2010). The most replicable findings of high heritability in prefrontal, temporal and language-related cortices could be attributed to the role of these regions in higher cognitive functions and their recent evolution in humans (Carroll, 2003; S. E. Fisher & Marcus, 2006).

Finally, we report that regional cortical thickness based on an anatomical atlas can be clustered into highly stable networks. The high levels of stability observed for many clusters in the presents study are likely attributable to the large sample size and quality of the anatomical images. The clusters we identified were mostly bilateral, reflecting strong homotopic correlations, with the exception of the language network (\#7), which was lateralized to include the left superior temporal gyrus (Figure 1). The presence of a distinct language module in human cortical thickness data was previously reported by (Z. J. Chen et al., 2008). Although their network was not lateralized for the same regions we found, this discrepancy may be due to the optimization of network modularity rather than correlation stability as the criterion for network definition and to the use of different scales. Our finding is also in agreement with functional data showing left lateralization in language areas, notably in the superior and middle temporal gyri (Parker et al., 2005) and studies of left-right asymmetry showing higher heritability in language areas of the left hemisphere (Uicheul Yoon, Fahim, Perusse, & Evans, 2010). It is interesting to note that our coarse parcellation of the cortical surface yielded patterns of heritability similar to previous studies at the voxel-level (Hulshoff Pol et al., 2006; Lenroot et al., 2009; Thompson et al., 2001; I. C. Wright et al., 2002), suggesting that clustering and silhouette analysis are an effective way to minimize redundant tests while retaining meaningful regional

organization. Finally, it is important to note that our analysis was restricted to cortical thickness and that results might differ for other indices of brain structure or function. Future work should extend these analyses to other traits such as surface area and resting-state connectivity. The inclusion of measured genotypes for linkage analysis would also be of interest to uncover specific genetic loci interacting with age in the human brain.

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Tables and Figures

Table 3.1 Cluster level age effects and heritability

Cluster	$p_{value}(Age)$	h^2	SE	$p_{value}(h^2)$
1	0.14	0.55	0.10	9.9×10^{-11}
2	< 0.001	0.52	0.09	3.3×10^{-10}
3	0.14	0.40	0.09	2.0×10^{-7}
4	< 0.001	0.60	0.09	3.1×10^{-14}
5	0.78	0.47	0.08	9.9×10^{-10}
6	0.03	0.36	0.09	3.8×10^{-6}
7	< 0.001	0.57	0.09	1.4×10^{-13}
8	< 0.001	0.46	0.09	3.7×10^{-8}
9	0.74	0.42	0.09	1.0×10^{-7}

Table 3.2 Results for the test of G×A interaction

	Test for σ_{Gz}			Test for ρ_G		
Cluster	γ_G	χ^2	p_{value}	λ_g	χ^2	p_{value}
1	−0.007	0.04	0.83	0.006	0.28	0.30
2	0.007	0.74	0.39	0.057	16.31	2.7×10^{-5}
3	0.042	3.88	0.05	0.010	0.74	0.20
4	−0.001	0.00	0.95	0.019	4.34	0.02
5	−0.003	0.09	0.77	0.050	8.74	0.002
6	0.023	2.16	0.14	0.020	1.28	0.13
7	0.014	2.28	0.13	0.010	2.96	0.43
8	−0.008	0.48	0.49	0.039	8.30	0.002
9	−0.006	0.25	0.62	0.000	0.00	0.50

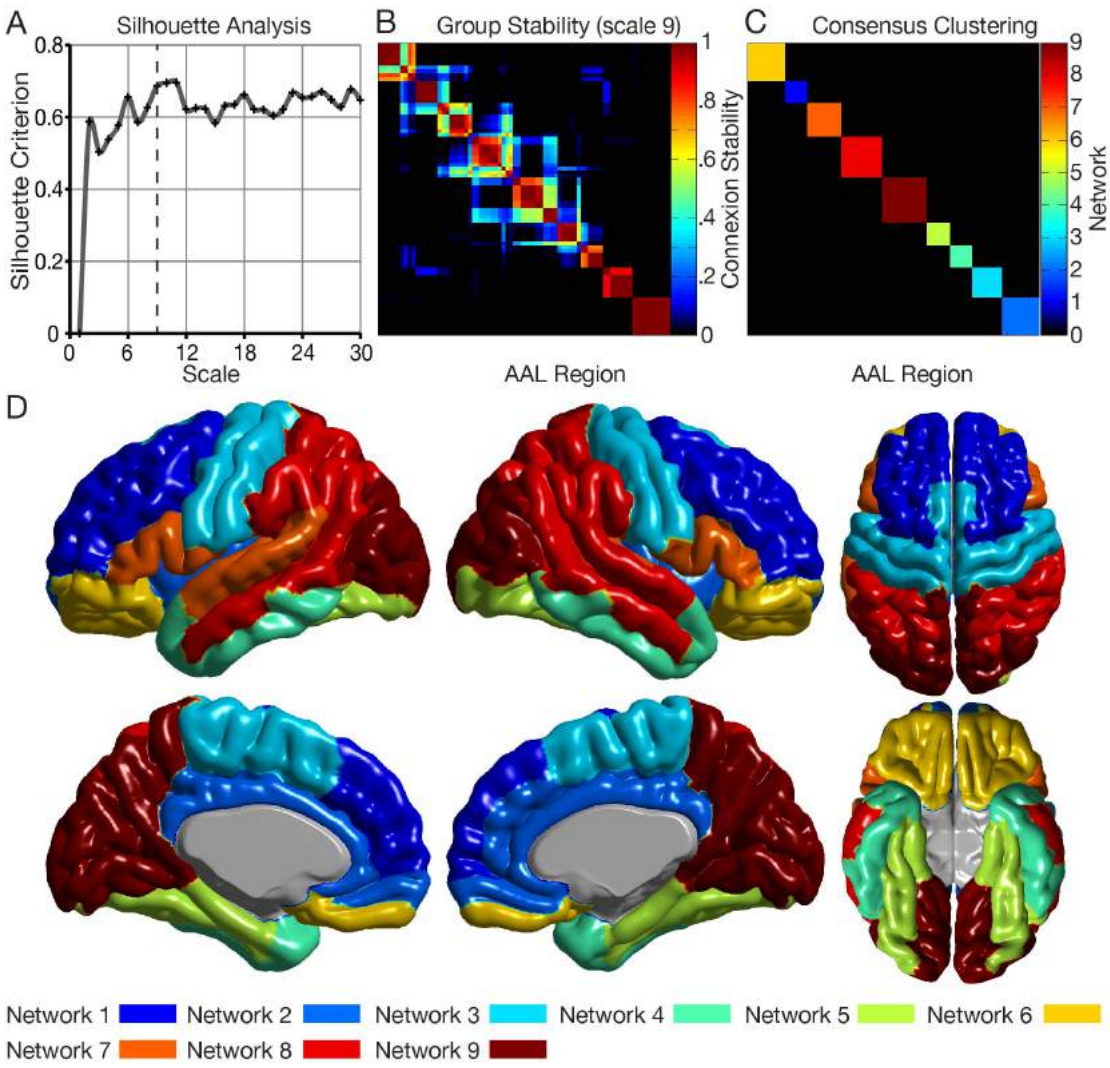

Figure 3.1: Clustering of Cortical Thickness Regions.

(A) Changes in the silhouette criterion with increasing number of clusters, the vertical dashed line marks the scale shown in panels B, C and D. (B) Group matrix showing the stability of individual correlations between each cortical region over the jackknife subsamples. The matrix was reordered based on the consensus clustering to facilitate comparison with panel C. (C) Consensus clustering of the cortical regions based on the group stability matrix (D) Surface representation of the consensus clusters. Color scales are shared between panels C and D.

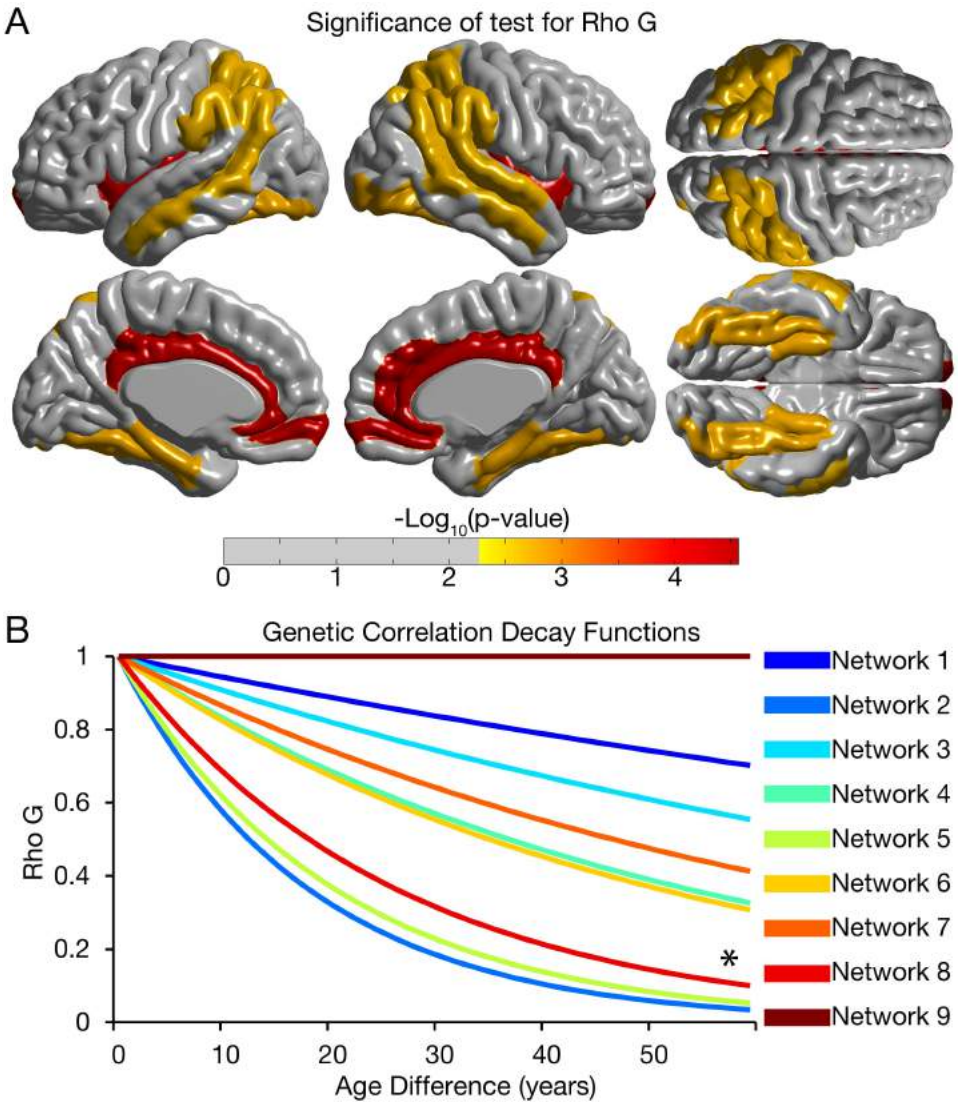

Figure 3.2: Test of incomplete pleiotropy over age.

(A) Surface representation of clusters 2, 5 and 8 where significant estimates of λ_g were found. The gray area of the color scale marks the Bonferroni corrected threshold for significance (p = 0.006). (B) Genetic correlation decay functions for all clusters based on Equation 6 and estimates of λ_g. The asterisk is set above the three functions where the effects were significant. The color coding of networks in 2B corresponds to the one used in Figure 1.

Chapter 4: Additive genetic variance in the resting-state functional connectome.

Preface:

While many studies had already estimated the heritability of cortical thickness, much less work had been done on the heritability of resting-state functional connectivity. Most published findings had focused on connections within specific networks and many different operational definitions of the phenotype had been used, complicating the comparison of results across studies. Initially, this study therefore set out to provide a complete mapping of the heritability of resting-state functional connectivity using a well-established definition of the phenotype. As with the previous study, this also included the investingation of GxA interactions.

The results of this first analysis created the opportunity to test whether these genetic influences were share across functional connections and to use this information to extract clusters of functional connections under shared genetic influence. This approach had previously been applied successfully to cortical thickness and surface area, but not yet to resting-state functional connectivity. The second aim of this manuscript was therefore to provide a complete mapping of shared genetic influences among functional connections.

Finally, resting-state functional connectivity also offered another unique opportunity. Based on two specific assumptions, it was possible to reconstruct an approximate phylogeny of this trait based published findings in comparative anatomy.

Specifically, this relied on the assumption that (1) the finding of homologous brain areas across species indicates homologous patterns of functional connectivity and (2) that this set of areas and its corresponding pattern of connectivity was also present in the last common ancestor of the species in which they are found. Based on this, it was possible to rank areas and connections based on their degree of conservation and to assess the relationship between this evolutionary ranking and the distribution of additive genetic variance in the connectome. Together, the results provide the most detailed mapping of genetic influences on resting-state functional connectivity so far and make a compelling argument regarding its interpretation.

Additive genetic variance in the resting-state functional connectome

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Summary

The human brain is a remarkably complex cellular network which's functional organization can now be probed non-invasively using resting-state functional magnetic resonance (rs-fMRI). Here we propose a complete mapping of both heritability and genetic correlations in the functional connectome. Our results provide evidence that genetic influences on functional connectivity are much more widespread than previously thought, which has far reaching implications for their interpretation. In addition, given the importance of additive genetic variance for the response to selection, we assess the relationship between this parameter and the evolutionary history of the brain's functional systems. Our results not only suggest that functional connectivity could be a valuable endophenotype for the study of common disorders, but might also inform us about the evolution of the brain's functional organization.

Introduction

The brain is an intricate cellular network, organized in modules and submodules, that has evolved over hundreds of millions of years (Striedter, 2005). This process requires that inter-individual variability caused by genetic variations be present in the population so that selection can operate. When it comes to quantitative traits, additive genetic variation is the main source of this inter-individual variability (R. A. Fisher, 1918). Consequently, the contribution of additive genetic variance to the total variance of a trait, defined as its heritability, reflects not only the degree of familial resemblance for a trait but how well it can respond to selection in a population (Falconer & Mackay, 1996; Houle, 1992). Though heritability can be estimated for any trait, resting-state functional connectivity offers unique opportunities for the study of the human brain. Notably, it allows us to probe its network architecture non-invasively and identify its functional modules and submodules based on the coherence of their activity over time (Yeo et al., 2011). In addition to this, variables describing cognition, behavior, and common disorders are themselves heritable quantitative traits (Robert Plomin et al., 2009; Turkheimer, 2000). Tracking these genetic influences through the functional connectome could therefore offer us an unprecedented window into their neurobiology.

Mapping the heritability of functional connectivity is then a required first step and a complex one for several reasons. For example, while the connectome is generally defined through a set of brain areas and the connections or interactions found between them (Craddock et al., 2013), most studies have so far focused on specific subnetworks (Fu et al., 2015; D C Glahn et al., 2010; Korgaonkar, Ram, Williams, Gatt, & Grieve, 2014; Sudre et al., 2017; Yang et al., 2016). Thereby, vast expanses of between-network

connectivity have been left unexplored. This underscores the importance of mapping heritability across the entire connectome. Another difficulty is that multiple operational definitions of functional connectivity are currently in use, which complicates comparisons across studies (Khalili-Mahani et al., 2017). This is particularly relevant because heritability is specific to the trait for which it is estimated and nearly all studies on functional connectivity so far have used different traits (Fornito et al., 2011; Fu et al., 2015; Ge, Holmes, Buckner, Smoller, & Sabuncu, 2017; D C Glahn et al., 2010; Korgaonkar et al., 2014; Sinclair et al., 2015; Sudre et al., 2017; Yang et al., 2016). Herein we will use the definition initially proposed by (Karl J. Friston, 1994) of functional connectivity as "the temporal correlation between spatially remote neurophysiological events". Beyond the definition of the trait and the space in which it is mapped, several factors can also interfere with the estimation of heritability. Most relevant to functional connectivity is head motion, which is known to influence both long and short distance functional correlations (K. J. Friston, Williams, Howard, Frackowiak, & Turner, 1996; Jiang et al., 1995; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Satterthwaite et al., 2012; Van Dijk, Sabuncu, & Buckner, 2012). The fact that head motion is heritable makes it an important confound to be addressed for the proper estimation of the heritability of functional connectivity (Couvy-Duchesne et al., 2014; Engelhardt et al., 2017). It is also well known that heritability is prone to change depending on environmental conditions, which includes ageing (Blangero, 1993). Such gene-environment interactions should therefore be considered for the proper estimation and interpretation of heritability.

In the first section of this manuscript we present a mapping of the heritability of functional connectivity at the connection level across the whole connectome taking into

account the aforementioned considerations. Concurrently, we assess the presence of age-related changes in either additive genetic variance or in the set of genetic loci that influence functional connectivity over adulthood and early ageing. Since genetic factors can influence more than one trait at once, the second section focuses on shared genetic influences among functional connections. We provide a full map of genetic correlations among heritable functional connections and perform a genetic clustering to extract groups of connections under shared genetic influence. Finally, it is important to remember that heritability is a population parameter that can easily be misinterpreted (Visscher et al., 2008). In the third section, we look at variations in heritability and additive genetic variance across the connectome and argue that these are better interpreted in an evolutionary context. We then present an analysis relating the evolutionary history of brain's functional systems to the amount of additive genetic variance found in their functional connections.

Results

Mapping heritability across the functional connectome.

Our mapping of the heritability of functional connectivity can be found in Figure 1. The data-driven parcellation with which we defined the functional connectome is shown in Supplementary Figure 1. The 30-cluster resolution was chosen because it provides the first degree of decomposition of RSNs into meaningful functional regions and affords a good trade-off between spatial resolution and multiple testing. Overall, out of 435 potential connections, 166 were significantly heritable and estimates ranged from 0.18 to 0.59 (See Figure 1c). As can be seen in Figure 1b, heritable functional connections were found throughout the connectome. The spatial distribution of heritability estimates was also not correlated with that of average functional connectivity ($p>0.05$) (see Figure 1d). Since RSNs are defined to exhibit high degrees of functional connectivity, this suggests that higher estimates of heritability are not found preferentially within RSNs. In fact, the negative quadratic association significant ($p < 0.05$), suggesting that higher estimates of heritability tend to be found for connections with more moderate degrees of coherence in the population.

Genetic influences on a trait can also change depending on their environmental context. This can be modeled as a change in amount of additive genetic variance found across environmental conditions, or a change in the set of genetic loci that account for additive variance across environments (See Equation 3 and Blangero, 1993). Such interactions have already been found for a number of traits including gene expression, cardiovascular risk factors, brain structure, and cognition, but have not yet been estimated for functional connectivity (Chouinard-Decorte et al., 2014; David C Glahn et al., 2013;

Havill & Mahaney, 2003; Kent et al., 2012; Kraft, Bauman, Yuan, Horvath, & Framingham Heart Study, 2003). Using the same methodology, we found no evidence of GxA interactions in functional connectivity. This suggests that the heritability estimates we present here are stable and reflect the influence of the same genetic loci over our age range. Detailed statistics for the heritability and G×A analyses as well as FDR-corrected p-values can be found in Supplementary Table 1.

Shared genetic influences in the functional connectome.

As mentioned in the previous section, heritability is not characterized only by its magnitude, but also by the specific set of genetic loci that account for it. Since genetic factors can influence more than one trait at once, a phenomenon known as pleiotropy, it is possible for two traits to covary in their additive genetic variance components. This is commonly referred to as "genetic correlation" or ρ_g (Almasy et al., 1997; Falconer & Mackay, 1996). Regarding functional connectivity, genetic correlations have indeed been found between the first principal eigenvectors of connectivity of different regions involved in the DMN (D C Glahn et al., 2010). While this does suggest that shared genetic factors influence functional connections within that network, the rest of the functional connectome remains to be explored. Our next aim was therefore to provide a complete map of shared genetic influences across the functional connectome.

The resulting genetic correlation matrix of all heritable functional connections can be found in Figure 2d. All of the 166 heritable functional connections exhibited at least 1 significant genetic correlation, with a maximum of 98 and an average of 37 per connection. In total 2974 genetic correlations, 14 of which were negative, were detected.

Estimates of ρ_g ranged from 0.48 to 1 on the positive end and from -0.78 to -1 on the negative end (Figure 2a). The fact that we detected numerous genetic correlations and that parameter estimates were generally high indicates that it is possible to identify groups of functional connections under shared genetic influences. This “genetic clustering” approach has so far been applied successfully only to measures of brain structure (C.-H. Chen et al., 2012, 2013; J E Schmitt et al., 2008). As a proof of concept, we present the ordered genetic correlation matrix showing the 40-cluster solution along with the full dendrogram of the genetic clustering of functional connections (Figure 2c and d). These results, along with the large number of significant genetic correlations found for each connection, are indicative that shared genetic influences extend beyond the confines of RSNs to include numerous between-network connections.

Variations in additive genetic variance across the functional connectome.

Aside from shared genetic influences, it might also be interesting to look at the magnitude of genetic influences across functional connections. However, variations in heritability are difficult to interpret as they can arise through its numerator or denominator. It is therefore more meaningful to look at variations in the variance components themselves. In this regard, it is important to remember that the “environmental” component is always the residual term of the variance partitioning. As such, it contains non-additive genetic effects, environmental effects, and measurement error, which again confuses the interpretation. The additive genetic variance, because it is directly estimated from the kinship data, is therefore the one component that lends itself to interpretation. A simple model to explain the standing levels of genetic variance in a trait is to view them as the result of a balance

between the processes of mutation and selection (Lande, 1975; Turelli, 1984). In short, most forms of selection deplete genetic variance as long as they are maintained, while mutagenesis continually replenishes it. This underscores the fact that the sustained responses to selection that lead to evolutionary change depend on an input of mutational variability, which makes mutational variance “an attractive candidate for high heritabilities across diverse traits and organisms” (Barton & Keightley, 2002). Based on this, we could hypothesize that high heritability would be found for traits that have evolved recently in the human lineage, while lower heritability would be found for traits that have been conserved over extended periods of time.

In order to test this hypothesis, we established the degree of conservation or evolutionary recency of each brain area in our parcellation based on the comparative neuroanatomy literature (see Table 1). We opted to establish the degree of conservation of each area rather than connection because the published literature is comparatively scarce for connectivity. This allowed us to reorder and visualize the matrix of additive genetic variance according to the degree of conservation (Figure 3a). Visual inspection of this reordered matrix already suggests that higher estimates of additive variance tend to be found with areas that have evolved more recently. To test this formally, each functional connection was assigned the rank of the most recent area it involved and we used the Spearman rank-order correlation to assess the relationship between the degree of conservation and the amount of additive genetic variance found in each connection. We found a weak but significant positive association between the two ($r2 = 0.0844$, $p<0.001$, see Figure 3b). It is important to note, however, that the relationship was visibly more heteroscedastic than linear. Nevertheless, additive genetic variance tended to be

ubiquitously low for connections involving phylogenetically old areas of the brain while progressively higher estimates could be found with increasingly more recent areas.

Discussion

Herein we presented three experiments aimed at mapping and interpreting the heritability of functional connectivity. First, we demonstrate that functional connectivity can generally be considered as a heritable trait and, more importantly, that heritability is found throughout the functional connectome. In addition, we show that genetic influences are widely and strongly shared amongst functional connections. These findings have serious implications in the context where the most common interpretation of the heritability of functional connectivity has so far been that it represents a “genetic control” over RSNs. In light of the fact that heritability is found outside RSNs and that the same genetic factors can influence connections both within and between networks, it might be more accurate to say that the “genetic control” is exerted over the functional connectome itself. In parallel, this interpretation might seem at odds with recent evidence that brain regions involved in the same RSNs also share similar patterns of gene expression (Richiardi et al., 2015; Wang et al., 2015). However, the fact that gene expression is itself a heritable quantitative trait shows that it is fundamentally distinct from the concept of genetic variance and that these two lines of evidence should not simply be equated (Cheung et al., 2003; Schadt et al., 2003; F. A. Wright et al., 2014).

This obviously raises the question of what heritability actually means and what it does not. By far, one of the most pervasive misinterpretation of heritability is to see it as a measure of the genetic determination of a trait (Visscher et al., 2008). On the contrary,

considerable shifts in the population means of even highly heritable traits can be observed in response to changes in environmental conditions. Two historical observations of this phenomenon were made, in humans, with height (Cole, 2000; Komlos & Lauderdale, 2007) and intelligence (Flynn, 1987). For the same reason, it would be erroneous to see low heritability, or rather high “environmental” variance, as an indication that a trait is more susceptible to environmental influences over the course of individual development. Simply put, heritability is a population parameter, specific to a realized phenotypic distribution, in a given environmental context. Thus, when looking at a mapping of heritability such as the one presented here, the first thing we should see is the fact that human populations are incredibly diverse and harbor millions of allelic variants of the sequences that form the human genome (The 1000 Genomes Project Consortium, 2015). Then, what the numerical value of heritability tells us is the relative importance of this genetic diversity for the phenotypic diversity observed for a trait in a specific population.

In this spite of this very specific meaning, the relevance of heritability and quantitative genetics in humans is obvious in the context where common disorders often represent the extremes of normally distributed quantitative traits (Robert Plomin et al., 2009). The usefulness of intermediate measures, such as functional connectivity, is that they can not only provide valuable insight into the underlying biology of these traits, but also empower us to detect specific variants associated with increased liability to disease. However, it is also important to remember that the theoretical foundations of heritability came from the need to explain how the inheritance of discrete genetic factors could lead to familial resemblance on quantitative scales (R. A. Fisher, 1918). This is why at their core heritability and additive genetic variance are measures of great evolutionary

relevance (Houle, 1992). It is then not entirely surprising that we found an association between the evolutionary history of the brain's functional systems and the amount of additive genetic variance found in their functional connections. In fact, such a relationship was also reported for gene expression, such that genes with recent evolutionary acceleration in the human and primate lineages also tended to have more heritable expression levels (F. A. Wright et al., 2014). In addition, it had already been shown that the spatial distribution of phenotypic variance in functional connectivity across the cortical surface was similar to the distribution of differences in cortical surface area between humans and macaques. This already suggested that evolution might be related to functional variability but, as the authors noted, "the spatial distribution of the heritability of functional connection strength across the entire brain is yet to be unveiled" (Mueller et al., 2013). Our results show that the relationship between evolutionary history and functional variability is likely mediated, at least in part, through additive genetic variance.

Here again, we must consider the potential misinterpretations that come with this finding. The fact that we assigned a certain "degree of conservation" to each brain area does not mean that these stopped evolving that much time ago. On the contrary, there is evidence for human-specific characteristics even in some of the oldest and most conserved areas of the brain (Letinic & Rakic, 2001). Our assumption is that functional connectivity, specifically, has been maintained across the range of species in which homologous functional systems can be observed. So far, this seems to be supported by the literature available in macaques and marmoset monkeys (Belcher et al., 2013; Margulies et al., 2009; Shen et al., 2012). A consequent limitation of this assumption is

that the rough phylogeny we outlined is unlikely to be applicable to the study of other traits such as those quantifying brain structure.

The results presented here have wide-ranging implications for the genetic analysis of functional brain systems. For the first time, we present complete maps of both heritability and genetic correlations across the functional connectome. This leads us to reinterpret the classical view of a genetic control over RSNs, which fails to acknowledge that heritability and genetic correlations are also found for connections that lie between RSNs. The presence of strong and widespread pleiotropy also shows that genetic influences are exerted jointly over groups functional connections. Further studies aimed at better characterizing these could increase our understanding of how the genetic predisposition to certain diseases is mediated and empower us to discover disease associated variants. Finally, the demonstration of a relationship between the evolutionary history of the brain's functional systems and the amount of additive genetic variance found in their connections is a reminder of the evolutionary relevance of these measures. This core perspective should not be lost as we apply these methods to an increasing number of traits. The quantitative genetic analysis of the human brain offers us a unique opportunity to not only better understand the genetic underpinnings of common disorders, cognition and behavior, but to better understand the evolution of this intricate cellular network.

Methods

Subjects & Data Acquisition

The analyses were performed using 653 subjects from extended pedigrees of Mexican-American ancestry who participated in the GOBS study (Curran et al., 2013; Olvera et al., 2011). Subjects were excluded if they had MRI contraindications, a history of neurological illness, stroke or another major neurological event. Age ranged from 18 to 85 (42.6±14.7) and the sample included 253 men and 400 women. All participants provided written informed consent and the study was approved by the institutional review boards at participating institutions. The MRI data was acquired on a Siemens 3T Trio Scanner with an eight-channel head coil at the Research Imaging Institute of the University of Texas Health Sciences Center at San Antonio. Seven high-resolution T1-weighted images were acquired consecutively for each subject with a 3D Turbo-FLASH sequence with an adiabatic inversion contrast pulse and the following parameters: TE/TR/TI=3.04/2100/785ms, flip angle=13°. The Resting-state functional data was acquired using a gradient-echo echo planar imaging sequence sensitive to the BOLD effect with the following parameters: TE/TR=30/3000ms, flip angle=90°, voxel size=1.72mm isotropic. Forty-three slices were acquired in the axial plane parallel to the anterior and posterior commissures. Resting-state data was acquired over 7.5 minutes and the subjects were instructed to lie in dimmed light with their eyes open and try not to fall asleep.

Image processing and functional clustering

For each subject, the seven structural images were corrected for inhomogeneity, co-registered and averaged (Kochunov et al., 2006). The resulting average T1 images were processed using the CIVET 1.1.12 pipeline on the CBRAIN computing platform (Frisoni et al., 2011). The non-linear deformations of each structural T1 image to the MNI ICBM 152 template (Fonov et al., 2011) were then used for functional image preprocessing. Preprocessing of the functional data was carried out using the Neuro Imaging Analysis Kit version 0.7.2.2 (NIAK, http://niak.simexplab.org). For each dataset, the first three volumes were removed to allow the magnetisation to reach equilibrium. Corrections for inter-slice difference in acquisition time and rigid-body motion parameters were then applied for each time frame. The median volume of each functional dataset was co-registered to its corresponding T1 structural image and the functional-to-T1 and T1-to-template deformations were then combined to resample each dataset in MNI space. In order to minimize motion-related artifacts, volumes with a frame displacement greater than 0.5 mm were removed from each dataset (Power et al., 2012). Datasets with less than 90 remaining volumes, a maximal displacement greater than 2mm or maximal rotation greater than 2° were excluded from the analyses. The time-series were also corrected for slow time drifts, average signals in the white matter and lateral ventricles, as well as the first principal components (accounting for 95% energy) of the six rigid-body motion parameters and their squares (Giove, Gili, Iacovella, Macaluso, & Maraviglia, 2009; Lund, Madsen, Sidaros, Luo, & Nichols, 2006). Each dataset was then smoothed using a 6mm isotropic Gaussian blurring kernel.

To define functionally relevant areas from which to define our functional connectome, we used the Bootstrap Analysis of Stable Clusters pipeline (Bellec et al.,

2006). The general philosophy behind BASC is to replicate the clustering process a large number of times to define areas that exhibit stable functional relationships over time and are spatially stable across subjects. In short, a spatially constrained k-means clustering was first applied to the datasets concatenated across subjects and stopped when regions reached a threshold of 1000mm^3, yielding a fine-grained parcellation of 1067 regions. This allowed the reduction of each individual dataset to a $T \times R$ array where T is the number of time samples and R is the number of regions. A Hierarchical Agglomerative Clustering (HAC) algorithm was then applied to each reduced dataset and replicated 1000 times using a circular block bootstrap to yield an $R \times R$ individual stability matrix. This matrix represents the frequency with which a pair of regions fell in the same cluster for a given subject. The individual stability matrices were then averaged and a second HAC algorithm was applied to the resulting matrix. This process was again bootstrapped across subjects to yield a group stability matrix ($R \times R$). A final hierarchical clustering was then performed on the group stability matrix to derive a consensus parcellation of brain. The number of clusters (k) used to generate the individual stability matrices, group stability matrices and consensus clustering was the same.

In order to select the number of clusters (k) with which to parcellate the brain we inspected the resulting clusters at several resolutions, keeping in mind that our goal was to map heritability at the connection level across the functional connectome. Coarse levels of parcellation (5-10 clusters) identified large ensembles corresponding to well-known RSNs (see Supplementary Figure 2). At the next level of resolution, where these were decomposed into an average of two to three subclusters ($k = 30$), the parcellation contained easily recognizable functional neuroanatomical areas. We therefore decided to

use the 30 cluster parcellation for the current analyses because it provided the first level of decomposition of the RSNs into their constituent areas, allowing a mapping of the connectome at the connection level.

Cluster labeling

Each of the 30 clusters in the parcellation was visually inspected and attributed a short anatomical description and abbreviation (See Table 1). The only exception to this was cluster 20, which was labeled functionally as Supplementary Motor Areas (SMA) because its anatomical correspondences were too complex to describe succinctly. In all cases the clusters were in close agreement with known areas of functional neuroanatomy and decomposition patterns replicated those reported in previous clustering studies (Kelly et al., 2012; Yeo et al., 2011). One noteworthy exception was cluster 15, which clearly captured a residual motion artifact and was labeled as Superficial Prefrontal cluster (SUPF). Since we used average time courses for each cluster, we would expect that of cluster 15 to be closely related to those of the underlying clusters 17 and 19, only with a higher proportion of noise. Since the results obtained with cluster 15 did fit this pattern, we decided to include them in the current report in the interest of completeness.

Phylogenetic annotation

Based on the labeling of the clusters we then searched the comparative neuroanatomy literature to identify the range of species across which homologs of a given area could be found. We then assigned the degree of conservation based on the most distant species for which homologs were found. This resulted in seven categories

depending on whether an area could be considered as conserved across all (1) vertebrates, (2) jawed vertebrates, (3) tetrapods, (4) eutherians, (5) primates, (6) simians, or (7) human specific. Although there is extent literature on the anatomy of the cat and dog brain, we refrained from including Carnivores as a category because the rapid cladogenesis that characterises the mammalian tree makes it difficult to establish an unambiguous ranking (Sims, Jun, Wu, & Kim, 2009). All details regarding the assigned categories and pertinent references can be found in Table 1.

Quantitative genetic analyses

All quantitative genetic analyses were carried out using mixed linear models implemented in the SOLAR software (Almasy & Blangero, 1998). An inverse normal transformation was applied to all traits prior to analysis and the effects of frame displacement (FD), age, age^2, sex, age×sex and age^2×sex interactions were covaried out. The three mixed linear models used in our analyses were as follows:

Equation 1: $$\Omega_{ij} = 2\Phi_{ij}\sigma_a^2 + \delta_{ij}\sigma_e^2$$

Equation 2: $$\Omega_{ij} = \left(2\Phi_{ij}(\sigma_{a1}\sigma_{a2})\times(d\rho_g + s) + \mathrm{I}_{ij}(\sigma_{e1}\sigma_{e2})\times(d\rho_e + s)\right)\times(\sigma_{p1}\sigma_{p2})$$

Equation 3: $$\Omega_{ij} = 2\Phi_{ij}\exp\left(-\lambda_g|z_i - z_j\right)\sqrt{\exp\left(\alpha_g + \gamma_g(z_i - \overline{z})\right)}\times$$

$$\sqrt{\exp\left(\alpha_g + \gamma_g(z_j - \overline{z})\right)} + \mathrm{I}_{ij}\sqrt{\exp(\alpha_e + \gamma_e(z_i - \overline{z}))}\times\sqrt{\exp\left(\alpha_e + \gamma_e(z_j - \overline{z})\right)}$$

In all equations Ω_{ij} is the phenotypic covariance matrix and Φ_{ij} is the kinship matrix. In equation 1 δ_{ij} is an identity matrix, σ_a^2 is the additive genetic variance component and σ_e^2 is the residual variance component. Narrow-sense heritability is then defined as the ratio of the additive genetic variance to the phenotypic variance. In equation 2 indices 1 and 2 refer to the two traits for which the genetic correlation is estimated, ρ_g is the genetic correlation and ρ_e is the residual correlation. Equation 3 is used to assess G×A interactions so that γ_g is an estimate of the rate of change in additive variance across environments and λ_g an estimate of the decay of pleiotropy across environments. All analyses were corrected for multiple comparisons using the FDR method (Benjamini & Hochberg, 2000).

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Tables and Figures

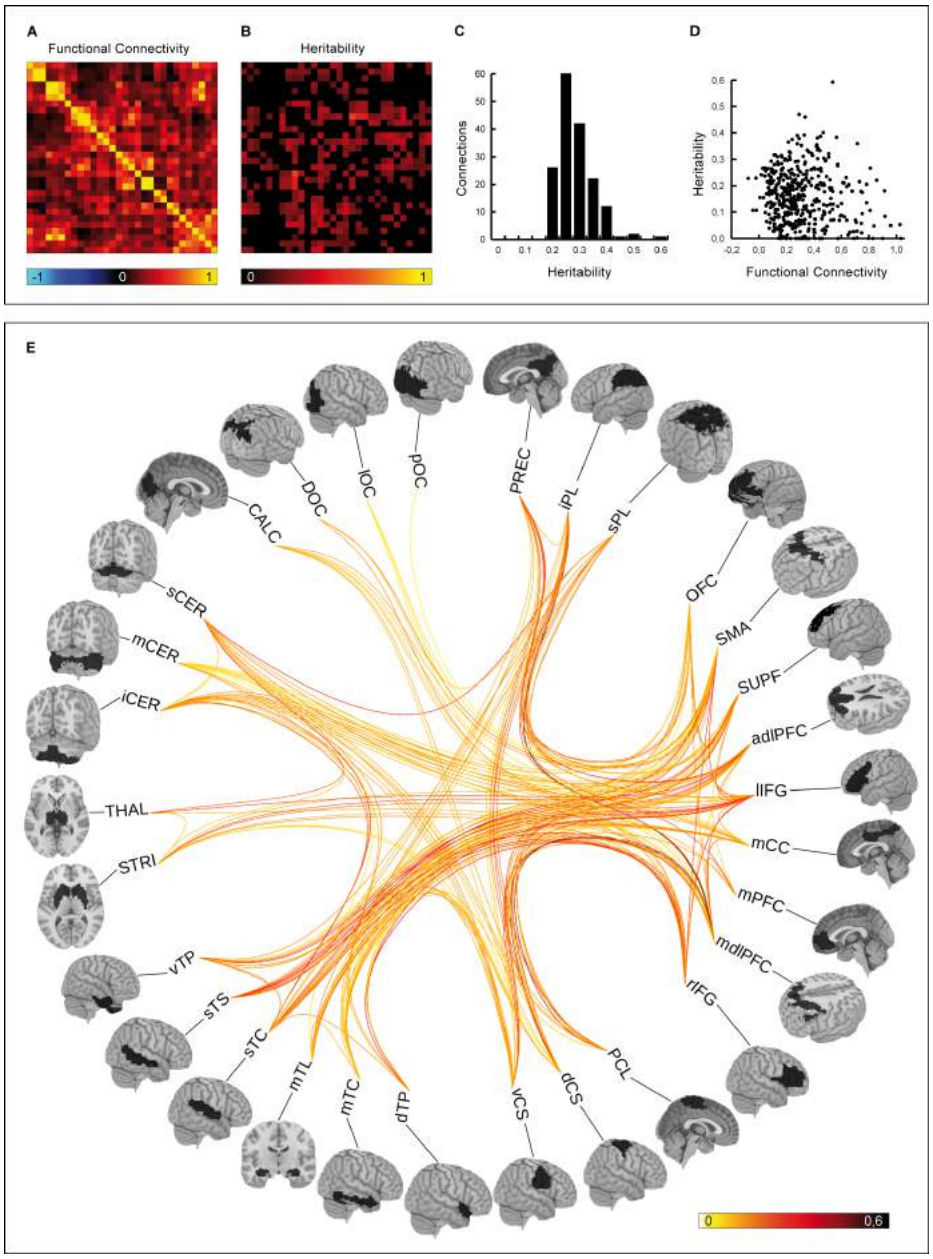


Figure 4.1: Heritability in the functional connectome

(A) Average values of functional connectivity. (B) Heritability of functional connectivity. (C) Histogram showing the distribution of significant heritability estimates. (D) Distribution of heritability estimates in relation to average functional connectivity. (E) Circular graph of the heritability matrix showing individual areas of the parcellation.

Table 4.1: Anatomical labeling and annotation of the clusters.

Cluster	Anatomical Description	Abbreviation	Network	Conservation	References
1	ventral Central Sulcus	vCS	Sensorimotor	Mammals	(Kaas, 2008)
2	ventral Temporal Pole	vTP	Temporal	Primates	(Insausti, 2013)
3	dorsal Central Sulcus	dCS	Sensorimotor	Mammals	(Kaas, 2008)
4	Thalamus	THAL	Basal Ganglia	Vertebrates	(Striedter, 2005)
5	Medial Prefrontal Cortex	mPFC	Default Mode	Primates	(Wallis, 2012)
6	superior Temporal Cortex and Caudal Insula	sTC	Temporal	Primates	(Karnath, 2001)
7	dorsal Occipital Cortex	DOC	Visual	Primates	(Kaas, 2012)
8	Precuneus and Posterior Cingulate Cortex	PREC	Default Mode	Primates	(Margulies et al., 2009)
9	Superior Cerebellum	sCER	Cerebellar	Gnathostomes	(Striedter, 2005)
10	Superior Parietal Lobule	sPL	Fronto-Parietal	Primates	(Karnath, 2001)
11	Superior Temporal Sulcus	sTS	Default Mode	Primates	(Ghazanfar et al., 2008)
12	Paracentral Lobule	PCL	Sensorimotor	Mammals	(Kaas, 2008)
13	Calcarine Cortex	CALC	Visual	Mammals	(Kaas, 2008)
14	Right Inferior Frontal Gyrus	rIFG	Ventral Prefrontal	Simians	(Petrides and Pandya, 2002)
15	Superficial Dorsal Prefrontal cluster	SUPF	Dorsal Prefrontal	Primates	(Petrides and Pandya, 1999)
16	Medial temporal lobe and hippocampus	mTL	Temporal	Tetrapods	(Striedter, 2005)
17	middle dorsolateral Prefrontal Frontal Cortex	mdlPFC	Dorsal Prefrontal	Primates	(Petrides, 2005)
18	middle Cingulate Cortex and marginal sulcus	mCC	Fronto-Parietal	Mammals	(Vogt and Paxinos, 2014)
19	anterior dlPFC and dorsal anterior cingulate cortex	adlPFC	Dorsal Prefrontal	Primates	(Petrides, 2005)
20	posterior Superior and Middle Frontal Gyri	SMA	Dorsal Prefrontal	Primates	(Petrides, 2005)
21	lateral Occipital Cortex	lOC	Visual	Primates	(Kaas, 2012; Kolster et al., 2009)
22	inferior Cerebellum	iCER	Cerebellar	Gnathostomes	(Striedter, 2005)
23	middle Temporal Cortex	mTC	Temporal	Primates	
24	middle Cerebellum	mCER	Cerebellar	Gnathostomes	(Striedter, 2005)
25	posterior Occipital Cortex	pOC	Visual	Mammals	(Kaas, 2008)
26	Striatum	STRI	Basal Ganglia	Vertebrates	(Grillner et al., 2013)
27	Dorsal temporal pole and ventral Insula	dTP	Temporal	Primates	(Insausti, 2013)
28	Inferior Parietal Lobule	iPL	Default Mode	Humans	(Karnath, 2001; Van Essen, 2007)
29	Left Inferior Frontal Gyrus and Right Inferior Frontal Gyrus pars orbitalis	lIFG	Ventral Prefrontal	Simians	(Petrides and Pandya, 2002)
30	Orbitofrontal Cortex and Frontal Pole	OFC	Ventral Prefrontal	Mammals	(Wallis, 2012)

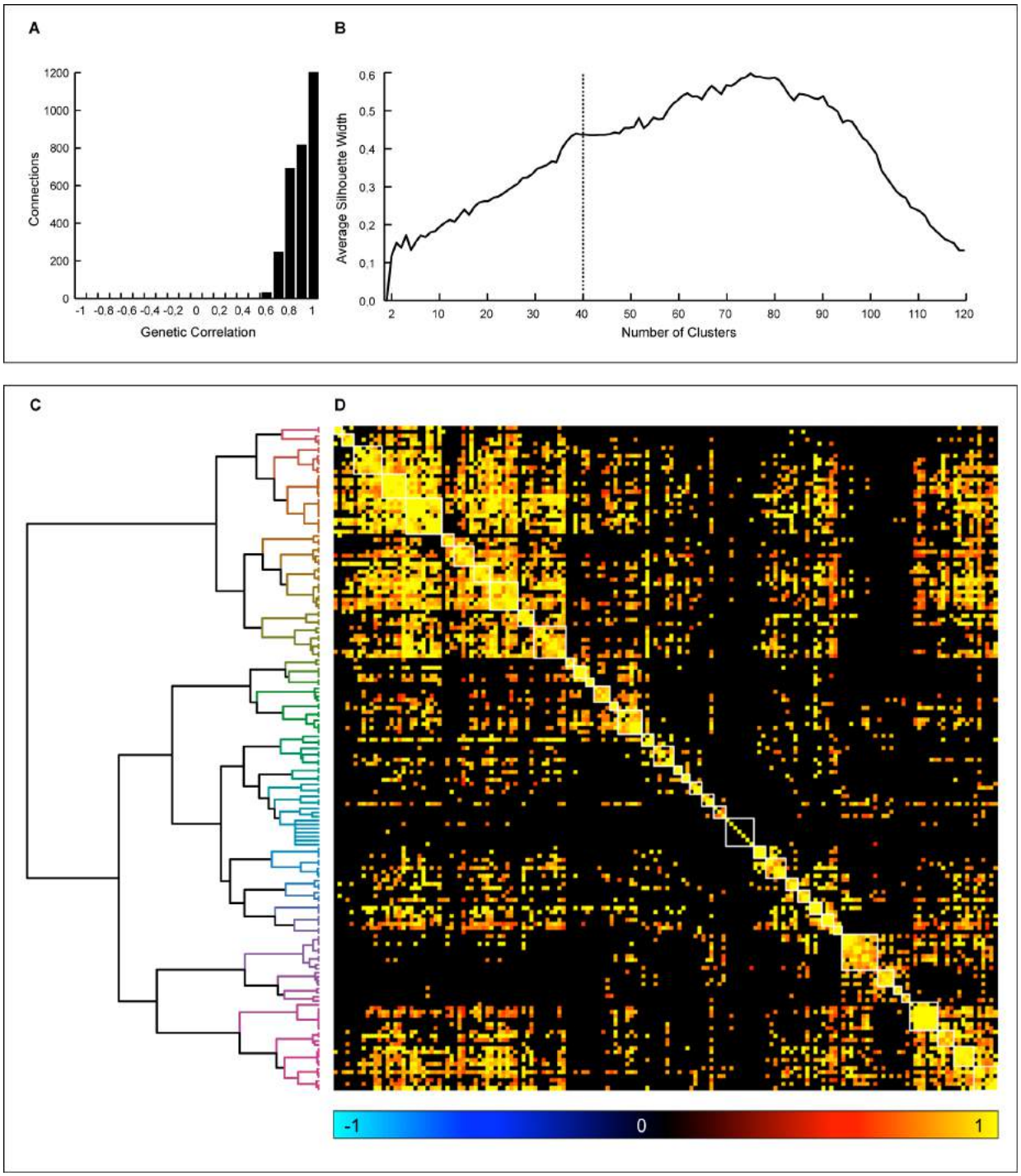


Figure 4.2: Genetic correlations in the functional connectome.

(A) Histogram of the distribution of significant genetic correlations. (B) Graph of average silhouette width across clustering solutions. (C) Dendrogram of the hierarchical agglomerative clustering. (D) Matrix of absolute genetic correlation values.

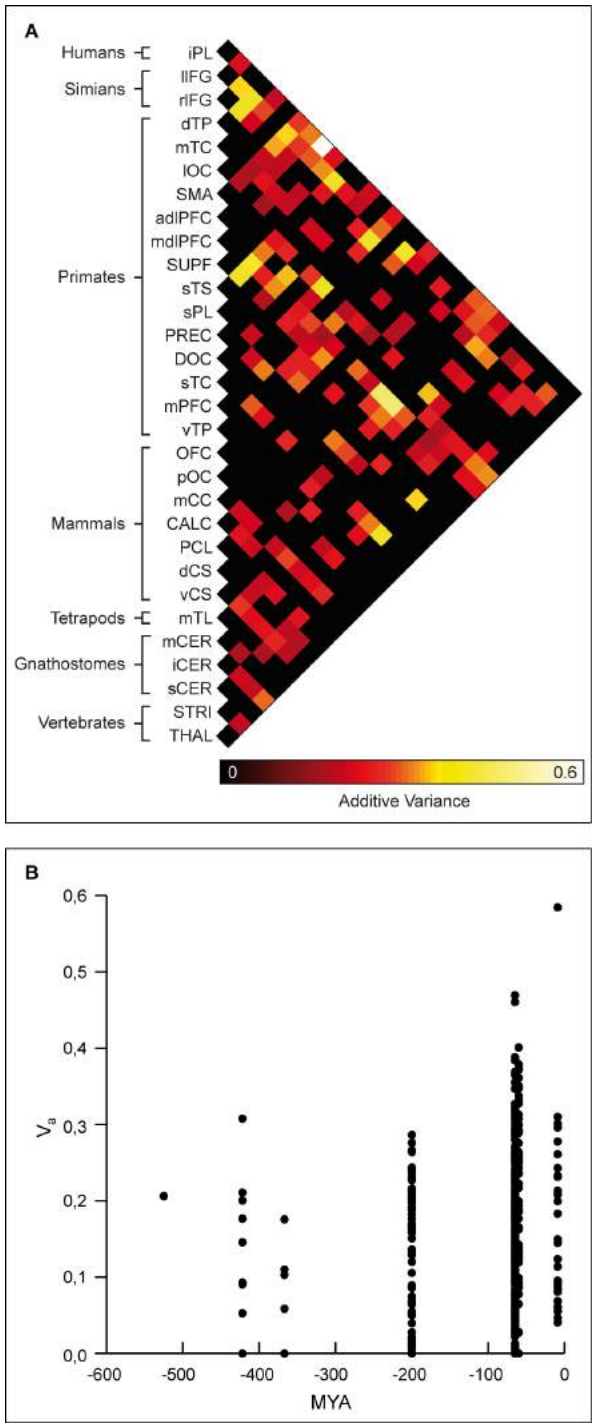
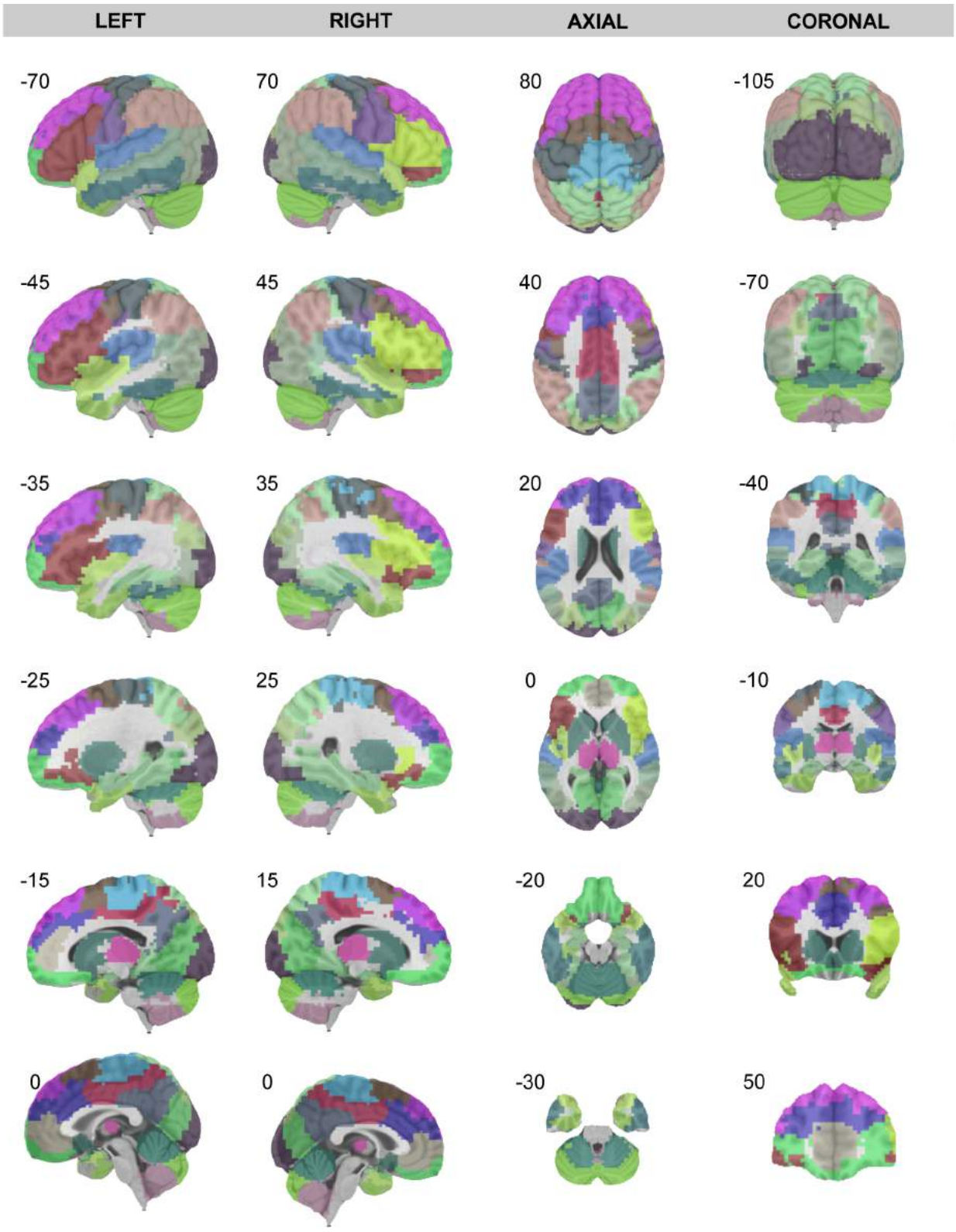


Figure 4.3: Evolutionary association with additive genetic variance.

(A) Matrix of additive genetic variance with brain areas reordered according to their phylogenetic ranking. (B) Distribution of additive genetic variance estimates for each connection according to their assigned phylogenetic ranks.



Supplementary Figure 4.4: 30-cluster parcellation of the GOBS dataset.

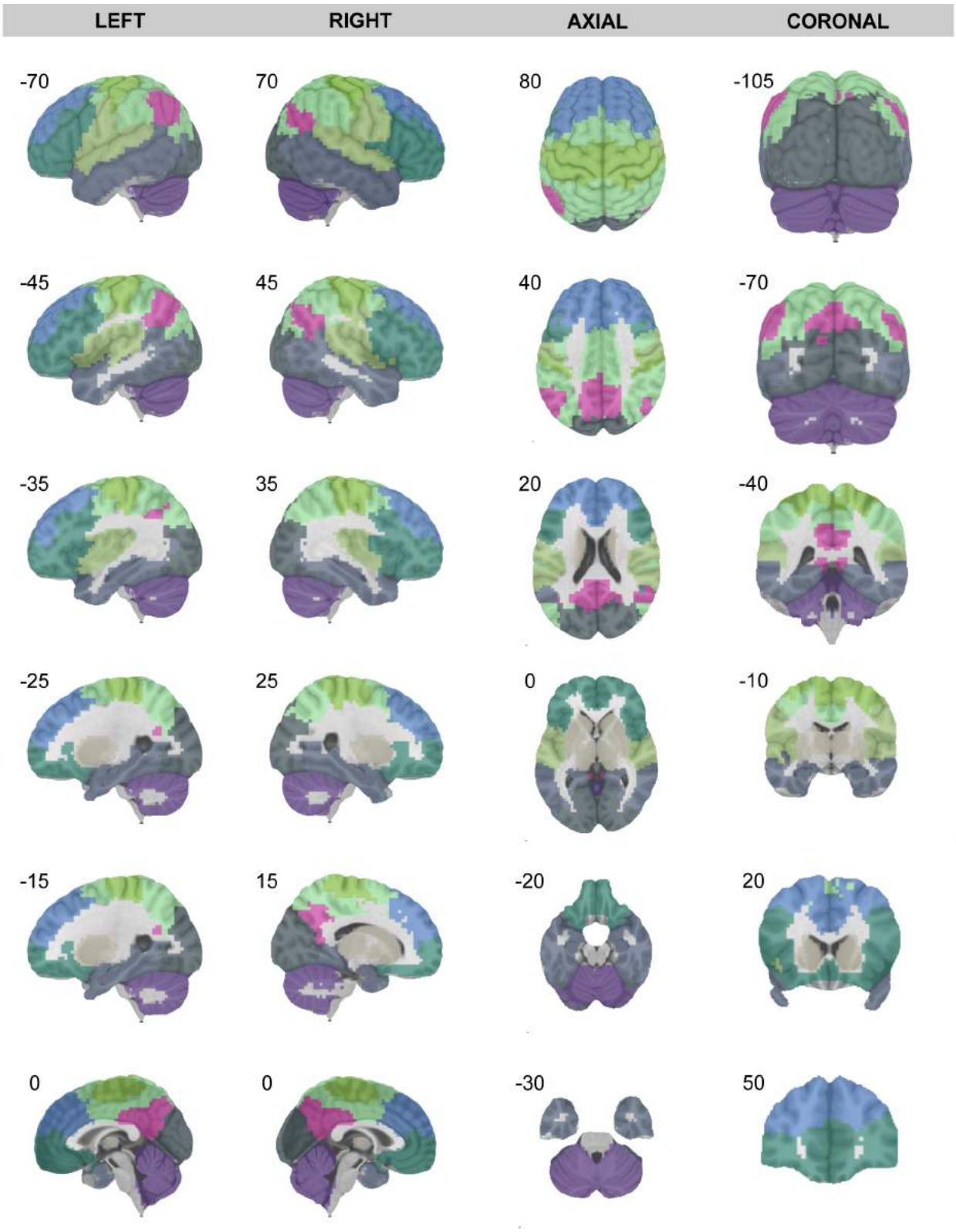


Figure 4.5: 10-cluster parcellation of the GOBS dataset.

Chapter 5: Shared genetic influences on brain structure and intelligence.

Preface:

The previous two chapters, were focused on providing detailed accounts and interpretations of genetic influences on brain structure and function. The third part of the equation was now to demonstrate how this could be used to provide information on other traits which are known to be under genetic influence and to involve the brain. The general idea was that by locating which areas of the brain and more importantly which measurable properties of these areas were under the influence of the same genetic factors as these other traits, some insight would be gained intro their underlying biology.

Obviously, this is an approach that could be applied to many different phenotypes relevant to both health and disease. Here the choice to use data from that WASI-II test for this analysis was motivated by a number of factors. First, intelligence and cognitive function in general tend to display fairly high estimates of heritability, making them good targets for the identification of shared genetic influences with the brain. Second, most investigations of the genetic correlations between intelligence and brain structure had so far focused on gray matter volume. Since cortical gray matter volume, surface area and thickness are not influenced by the exact same sets of genes, mapping genetic correlations between intelligence and these various metrics could offer some better insight into the nature of the association. I was also already in collaboration with Dr. Sherif Karama, Canadian expert in the field of intelligence research, which greatly facilitated this

work and contributed to its quality. Finally, intelligence holds a special place in the evolution of the human being and felt like a natural candidate in the broader context of this thesis. Though this topic is too complex to be dealt with in a single chapter, these analyses lay a strong foundation upon which future work could be built.

Finally, it is also important to consider this chapter as a proof of concept for an analytical framework that could be applied in many different contexts. As an example, these analyses could also be performed using body mass index, which could provide some valuable insight into the neurobiology of obesity. In fact, most common disorders in modern society are thought to lie at the extremes of quantitative traits, making this a potentially very valuable approach for the study of a great number of diseases.

Shared genetic influences on brain structure and intelligence

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Abstract

Intelligence is a highly heritable trait in humans that correlates with the structural properties of numerous brain areas. It has been shown that this relationship can largely be explained by shared genetic influences on brain structure and cognition. However, most studies have so far focused only on gray matter volume and it has also been suggested that association patterns might differ among specific cognitive measures. Here, using a large extended familial pedigree, we test the hypothesis that patterns of genetic correlations observed between cognitive measures and cortical traits vary depending on which measures are used. We provide high resolution mappings of the genetic correlations of IQ, vocabulary and matrix reasoning with local cortical thickness, surface area and gray matter volume. While the areas involved tended to be similar, the lack of significant associations with some highlights the importance of trait selection in the investigation of the relationships between genes, brain and intelligence.

Introduction

The first law of behavior genetics is that “all human behavioral traits are heritable” (Turkheimer, 2000). Accordingly, most measures of cognitive function do exhibit some degree of heritability (Robert Plomin, Fulker, Corley, & DeFries, 1997). In fact, there is mounting evidence that most measures of learning ability and cognitive function are under the influence of shared genetic factors (Robert Plomin & Kovas, 2005). This underscores the fact that general cognitive ability, or intelligence, is well established as a highly heritable trait in humans (Deary, Johnson, & Houlihan, 2009). In turn, this raises the question of how such genetic influences on cognition and behavior can be mediated. Arguably, if mutations are to influence intelligence, they must do so through the expression of their effects in specific cells and tissues.

An obvious candidate to bridge the gap between genes and cognitive function is the brain. Indeed, it is already well established that intelligence and total brain volume are correlated (Andreasen et al., 1993; McDaniel, 2005). Numerous studies have refined our understanding of this relationship by establishing the regional patterns of association between intelligence and brain structure (Colom et al., 2009; Haier, Jung, Yeo, Head, & Alkire, 2004; Karama et al., 2011; Narr et al., 2007). Overall, intelligence tends to be associated with a great number of areas distributed across the frontal, parietal, temporal, and occipital lobes (Jung & Haier, 2007). In addition, as is the case with behavior, most brain-related traits tend to show some degree of heritability. This is notably the case for global measures such as brain volume, total gray matter volume and average measures of cortical thickness and surface area (Panizzon et al., 2009; Pennington et al., 2000; Pfefferbaum et al., 2000). This also holds true for regional measures of cortical thickness,

surface area and volume (Eyler et al., 2012; Panizzon et al., 2009; J Eric Schmitt et al., 2010; Winkler et al., 2010; U Yoon et al., 2012). Taken together, these observations lead to the hypothesis that intelligence and brain structure might be under the influence of the same genetic factors (Toga & Thompson, 2005). Formally, this phenomenon where genetic factors simultaneously influence more than one trait is referred to as pleiotropy and can be tested using bivariate quantitative genetic models, better known as genetic correlations (Almasy et al., 1997; Falconer & Mackay, 1996).

Initial support for hypothesis came from the observation that IQ and working memory are both genetically correlated with total gray and white matter volumes (Posthuma et al., 2002). Although the genetic correlation between intelligence and gray matter volume was fairly low ($\rho_g = 0.29$), which indicates that the majority of their respective genetic influences are not shared, this was enough to account for more than 95% of their observed phenotypic correlation (Posthuma et al., 2002). Yet, it remained unclear if this relationship would be shared equally by all areas of the brain. In line with what had been observed for phenotypic correlations, subsequent studies identified distributed patterns of genetic correlations between intelligence and gray matter volume in a number of frontal, parietal, temporal and occipital areas (Bohlken et al., 2016; Hulshoff Pol et al., 2006). An important point suggested by the most recent of these analyses, though not yet demonstrated, is that patterns of regional genetic correlations might differ among subtests of cognitive function (Bohlken et al., 2016). In the same vein, it has recently been shown that cortical thickness and surface area exhibit different trajectories of association with intelligence over age (Schnack et al., 2015), such that the

patterns of regional genetic correlations for a given cognitive component might differ depending on which measure of brain structure is used.

Specifically, we hypothesized that patterns of genetic correlations observed between cognitive and cortical traits might vary depending on which measures are used. To test this, we estimated genetic correlations between three cognitive measures derived from the WASI-II test (Vocabulary, Matrix Reasoning and Subscale IQ) and three measures of cortical gray matter (Thickness, Area and Volume). In addition, in order to improve on the anatomical precision of these associations, we provide high-resolution mappings of genetic correlations across 81924 points covering the whole cortical surface.

Material and Methods

Subjects

The final analysis sample included 661 subjects from extended pedigrees of Mexican American ancestry who participated in the GOBS study (Curran et al., 2013; Olvera et al., 2011). Notable advantages of the extended pedigree design in the context of this study include increased power to detect heritability and lesser confounding effects of shared environmental influences due to the inclusion of multiple households within pedigrees (Blangero, Williams, & Almasy, 2003). Subjects were excluded if they had MRI contraindications, a history of neurological illness, stroke or another major neurological event. The sample included 247 men and 414 women with ages ranging from 18 to 77. Cognitive measurements included the vocabulary, matrix reasoning and subscale IQ scores of the WASI-II test (see Wechsler Abbreviated Scale of Intelligence^{TM}). Descriptive statistics for the variables used in the current analyses can be found Table 1. All

participants provided written informed consent and the study was approved by the institutional review boards at participating institutions.

Image acquisition and analysis

The MRI data was acquired on a Siemens 3T Trio Scanner with an eight-channel head coil at the Research Imaging Institute of the University of Texas Health Sciences Center at San Antonio. Seven high-resolution (isotropic 800μm) T1-weighted images were acquired consecutively for each subject with a 3D Turbo-FLASH sequence with an adiabatic inversion contrast pulse and the following parameters: TE/TR/TI=3.04/2100/785ms, flip angle=13°. For each subject, each structural image was inspected manually for artifacts and the remaining images were then co-registered and averaged to increase signal-to-noise ratio and reduce motion artifacts (Kochunov et al., 2006). The resulting average images were then processed using the CIVET pipeline1 (v.2.0) to extract measure of local cortical thickness, surface area and gray matter volume sampled at 81 924 vertices across the cortical mantle. The processing pipeline was executed on the Canadian Brain Imaging Network (CBRAIN) platform, a network of five imaging centres and eight High Performance Computers for collaborative sharing and distributed processing of large MRI databases (Frisoni et al., 2011).

Quantitative Genetic Analyses

All quantitative genetic analyses were carried out using the SOLAR software (Almasy & Blangero, 1998). In order to ensure the normality of the data, an inverse normal

1 http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET

transformation was applied to all traits prior to analysis. The effects of age and sex were regressed as covariates of no interest. For the estimation of heritability, we used the standard parameterization of the mixed linear model:

$$\text{Equation 1: } \Omega_{ij} = 2\Phi_{ij}\sigma_a^2 + \delta_{ij}\sigma_e^2$$

where Ω_{ij} is the phenotypic covariance matrix, Φ_{ij} is the kinship matrix, δ_{ij} is an identity matrix, σ_a^2 is the additive genetic variance component and σ_e^2 is the residual variance component. Narrow-sense heritability is then defined as the ratio of the additive genetic variance to the phenotypic variance. For the estimation of genetic correlations, we used the bivariate mixed linear model:

$$\text{Equation 2: } \Omega_{ij} = \left(2\Phi_{ij}(\sigma_{a1}\sigma_{a2})\times\left(d\rho_g + s\right) + \mathrm{I}_{ij}(\sigma_{e1}\sigma_{e2})\times(d\rho_e + s)\right)\times\left(\sigma_{p1}\sigma_{p2}\right)$$

where indices 1 and 2 refer to the two traits for which the genetic correlation is estimated, ρ_g is the genetic correlation and ρ_e is the residual correlation. All analyses were corrected for multiple comparisons using the FDR method (Benjamini & Hochberg, 2000).

Results

Heritability of cortical structure and intelligence

Descriptive statistics and estimates of heritability for the cognitive measures can be found in Table 1. Surface maps displaying heritability estimates for cortical thickness, surface area and gray matter volume can be found in Figure 1. Significant heritability estimates were found for more than 98% of vertices for all three measures, which is indicative of the high power to detect heritability afforded by the current pedigree. For cortical thickness the estimates ranged from 0.13 to 0.78 with the strongest effects found predominantly in the ventral pre- and post-central gyri, superior temporal gyri, insula and posterior cingulate cortex. For surface area, the estimates ranged from 0.13 to 0.99 with the strongest effects found in the calcarine cortex, posterior cingulate, caudal insula and planum temporale. For gray matter volume, the estimates ranged from 0.13 to 0.92 with the strongest effects found in the same areas as for surface area.

Correlations between cortical structure and intelligence

Surface maps displaying significant phenotypic correlations between structural brain measures and the cognitive measures can be found in Figure 2. Correlations with gray matter volume were widespread, estimates of ρ_p ranged from 0.07 to 0.25 and followed very similar patterns across the cortex for IQ, Vocabulary and Matrix reasoning. In all cases the strongest associations were found with the superior temporal gyri, planum temporale, insula, right caudal middle frontal gyrus and isthmus of the cingulate cortex. Correlations with surface area were again widespread, with estimates of ρ_p ranging from 0.05 to 0.23, but patterns differed slightly across cognitive measures. For IQ, the strongest

associations were found with the superior temporal gyri and were visibly stronger in the left hemisphere. For matrix reasoning, the strongest associations involved the dorsal aspect of anterior half of the temporal lobe, the left anterior half of the cingulate gyrus and the insula. For vocabulary, associations were similar to those observed for IQ with the strongest correlations found in the superior temporal gyri. In contrast, correlations with cortical thickness were much more focal and involved the posterior cingulate and precuneus for both IQ and matrix reasoning. Parameter estimates for ρ_p ranged from 0.12 to 0.20 and no significant correlations were found between cortical thickness and vocabulary.

Pleiotropic influences on cortical structure and intelligence

Surface maps displaying significant genetic correlations between measures of cortical structure and cognitive measures can be found in Figure 3. Overall, patterns of genetic correlations were much more focal and significant findings involved primarily the correlations of IQ and matrix reasoning with gray matter volume and surface area. For gray matter volume, the patterns were similar for both IQ and matrix reasoning with estimates of ρ_g ranging from 0.28 to 0.75. The strongest effects were found in the left dorsomedial prefrontal cortex and weaker but significant evidence of pleiotropy was also found with the left and right insula, right dorsal cingulate cortex as well as the parahippocampal and fusiform gyri. For surface area, estimates of ρ_g ranged from 0.55 to 0.72 and were found focally in the left dorsomedial prefrontal cortex for matrix reasoning only. We found no evidence of pleiotropy between surface area and IQ, nor in any correlation involving either vocabulary or cortical thickness.

Discussion

Herein we have reported on the mapping of genetic correlations between traits describing cortical structure and intelligence. These analyses rest first on the replication of findings concerning the heritability of these variables. The heritability estimates we observed for cortical metrics were in agreement with previous surface-based studies both in terms of the range of parameter estimates and their spatial distribution (Eyler et al., 2012; Winkler et al., 2010). Our estimates of heritability for cognitive measures were also in close agreement with those typically observed in adulthood (Bouchard, 2013; Deary et al., 2009). In fact, the higher heritability observed for the vocabulary versus the matrix reasoning subscale of the WASI-II is in agreement with the findings of Kan et al. showing that measures related to crystallized intelligences tend to exhibit both greater cultural influences and greater heritability (Kan, Wicherts, Dolan, & van der Maas, 2013).

This deserves to be discussed briefly because it leads to an apparent paradox: crystallized intelligence is heavily influenced by cultural factors over the lifespan, whereas life-history traits generally tend to exhibit lower heritability (Price & Schluter, 1991). One hypothesis reconciling these two observations is that gene-environment correlations inflate heritability estimates for measures of crystallized intelligence. Plomin et al. discussed this issue in some detail and defined three possible types of gene-environment correlations: passive, reactive and active (Plomin, DeFries, & Loehlin, 1977). In short, the replicability of heritability estimates in adoption studies leaves only the possibility of reactive correlations, where the environment reacts differently based upon genotype, and active correlations, where individuals bearing certain genotypes seek different environments depending on their propensity. The examples provided are that a teacher

might recognise a student's abilities and furnish an enriched environment (reactive) or a gifted child might seek more stimulating environments that foster its cognitive development (active). Such positive correlations could indeed lead to an overestimation of the additive genetic variance component. However, it is also important to remember that correlations might be negative: teachers might recognise students in difficulty and provide them with enriched environments and gifted individuals might seek a more standard or even unfavorable environment because of normative pressure. In this case, variance components would instead be under-estimated. In both cases, gene-environment correlations can distort estimates of each component, such that they will have less effect on their relative sizes. Also, the variance due to positive gene-environment correlations cannot outweigh the individual genetic and environmental variances (Plomin et al., 1977). Therefore, the potential presence of gene-environment correlations should not obscure the fact that a substantial amount of genetic variance is present in most measures of intelligence (Deary et al., 2009).

Moving on to the relationship between intelligence and cortical structure, broad patterns of correlation were observed for gray matter volume and surface area, but not cortical thickness. These patterns were generally consistent with those previously reported in that they involved numerous areas of the frontal, parietal, temporal and occipital lobes (Colom et al., 2009; Haier et al., 2004; Jung & Haier, 2007; Karama et al., 2011; Narr et al., 2007). Yet, the more restricted patterns we observed for cortical thickness might seem at odds with previous reports (Karama et al., 2011; Menary et al., 2013). This could reflect two important properties of the interplay between genetic factors, brain structure and intelligence. First, it has been shown that the trajectory of changes

cortical thickness is more closely related to intelligence than cortical thickness per se (Shaw et al., 2006). Second, it is now well established that genetic influences on intelligence change over age (Bouchard, 2013). Thus, it is possible that patterns of phenotypic and genetic correlations between intelligence and brain structure might change over age.

Regarding genetic correlations, the one area in which strongest parameter estimates were found for all trait pairs was the right medial prefrontal cortex. This is in line with previous a previous report of genetic correlation between IQ and gray matter density in the right medial prefrontal cortex (Hulshoff Pol et al., 2006). The specificity of these results for IQ and Matrix Reasoning versus Vocabulary might reflect the importance of the medial prefrontal cortex for fluid intelligence (Gong et al., 2005) and the importance of the inhibitory control it exerts in order to provide accurate responses when faced with perceptual mismatch (Prado & Noveck, 2007). Our results also provide convergent evidence for genetic correlations between gray matter volume and both IQ and Matrix Reasoning in the parahippocampal and fusiform gyri (Bohlken et al., 2016; Hulshoff Pol et al., 2006). In addition to these, we also found significant genetic correlations with gray matter volume bilaterally in the insula. This might reflect the involvement of the insula, particularly its anterior division, in higher order in cognitive control and attentional processes (Menon & Uddin, 2010). It is also worth mentioning that we did not replicate genetic correlations for many previously reported areas including the superior temporal gyrus, precuneus, and occipital cortex. However, we did observe significant phenotypic correlations with all of these. These discrepancies in the patterns of genetic correlations

might be related to differences in the cognitive assessments, image processing techniques or statistical power.

From a broader perspective, it is also important to define exactly what the observed estimates of heritability and genetic correlation reflect and what they do not. The generally high parameter estimates (h^2>0.5), observed notably for intelligence, indicate that genetic variants rather than differences in environmental conditions account for most of the inter-individual variation observed in the population. This should be interpreted with care, specifically regarding the fact that heritability does not deal with the genetic determination of these traits, nor with their sensitivity to environmental factors. A classic demonstration of these two points is the Flynn effect, which shows that the population means of highly heritable traits can nevertheless exhibit strong responses to changes in environmental conditions (Flynn, 1987). In turn, this also shows that low heritability is not indicative of greater environmental sensitivity. Though it is arguably true that the conserved neural substrate of intelligence is genetically encoded and that educational environment affects intelligence scores, what heritability truly deals with is how variations in these variables results in inter-individual variation in intelligence across the population. In light of this, it might then be misleading to say that intelligence and brain structure share some of their genetic determinants based on the observed genetic correlations. Rather, what we see is that some of the genetic variants influencing intelligence also influence brain structure, and vice versa.

In summary, our results support not only the hypothesis that the neural substrate of intelligence involves several distributed areas of the brain (Jung & Haier, 2007), but also that genetic influences on intelligence are mediated through such distributed areas.

The fact that results varied widely depending on which measures of cognitive function and brain structure were used supports our initial hypothesis and suggests that studying different combinations of traits might better inform us on the genetic relationships between intelligence and the brain. The brain regions identified here provide valuable targets for future studies, notably for the investigation of the structural and functional impact, both at the macro and microscale, of new genetic variants found to influence human intelligence (Sniekers et al., 2017; Zabaneh et al., 2017).

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Tables and Figures

Table 5.1: Descriptive statistics and heritability of cognitive assessments.

Trait	Mean	SD	h^2	SE	P-value
Age	40	13	-	-	-
Vocabulary	38	11	0.75	0.08	1×10^{-22}
Matrix Reasoning	48	10	0.58	0.10	2×10^{-11}
IQ	89	14	0.76	0.08	4×10^{-21}

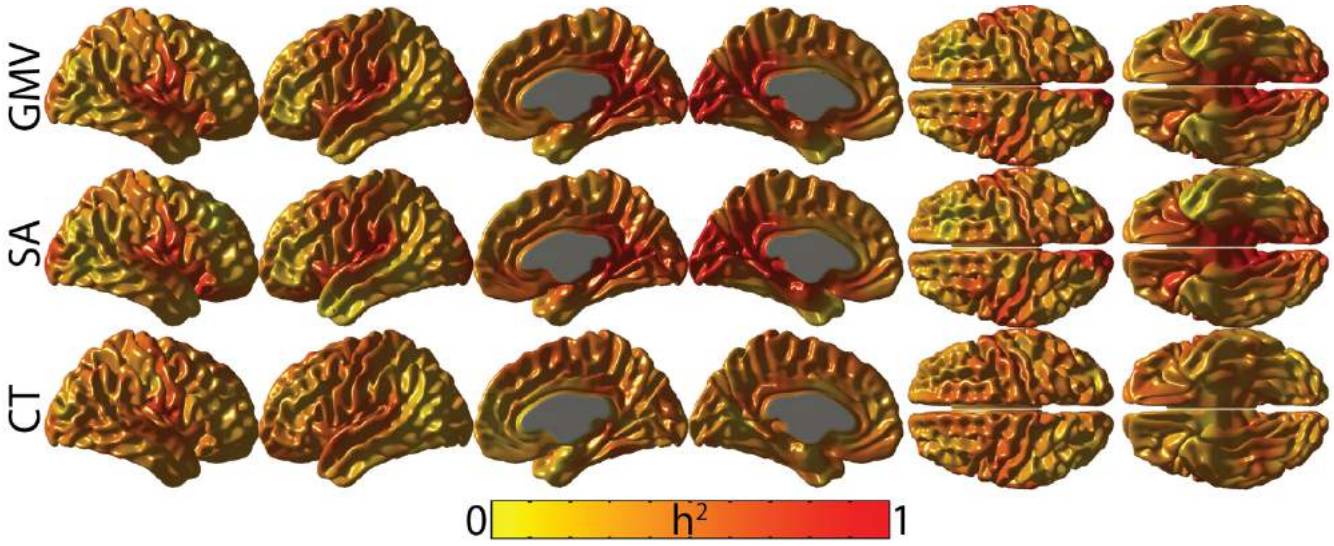

Figure 5.1: Heritability of cortical morphology.

Surface maps representing the relative contribution of additive genetic variance to the population variance of three measures of cortical morphology. Results are shown in the first row for Gray Matter Volume (GMV), in the second row for Surface Area (SA) and in the third row for Cortical Thickness (CT).

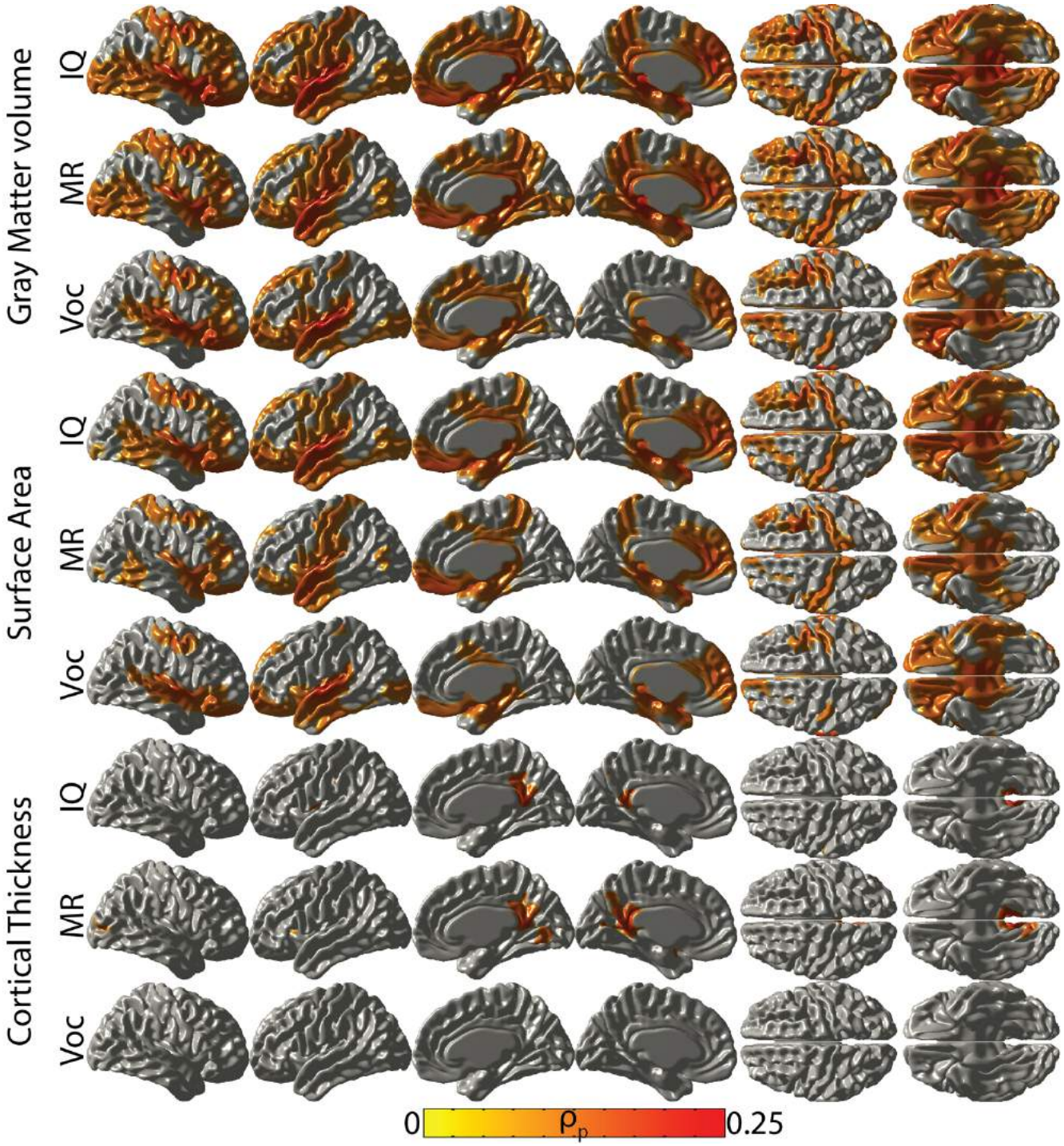

Figure 5.2: Phenotypic correlations between cortical structure and intelligence.

Surface maps displaying significant correlations between measures of brain structure and intelligence. For each cortical trait, the rows correspond to Subscale IQ (IQ), Matrix Reasoning (MR) and Vocabulary (Voc).

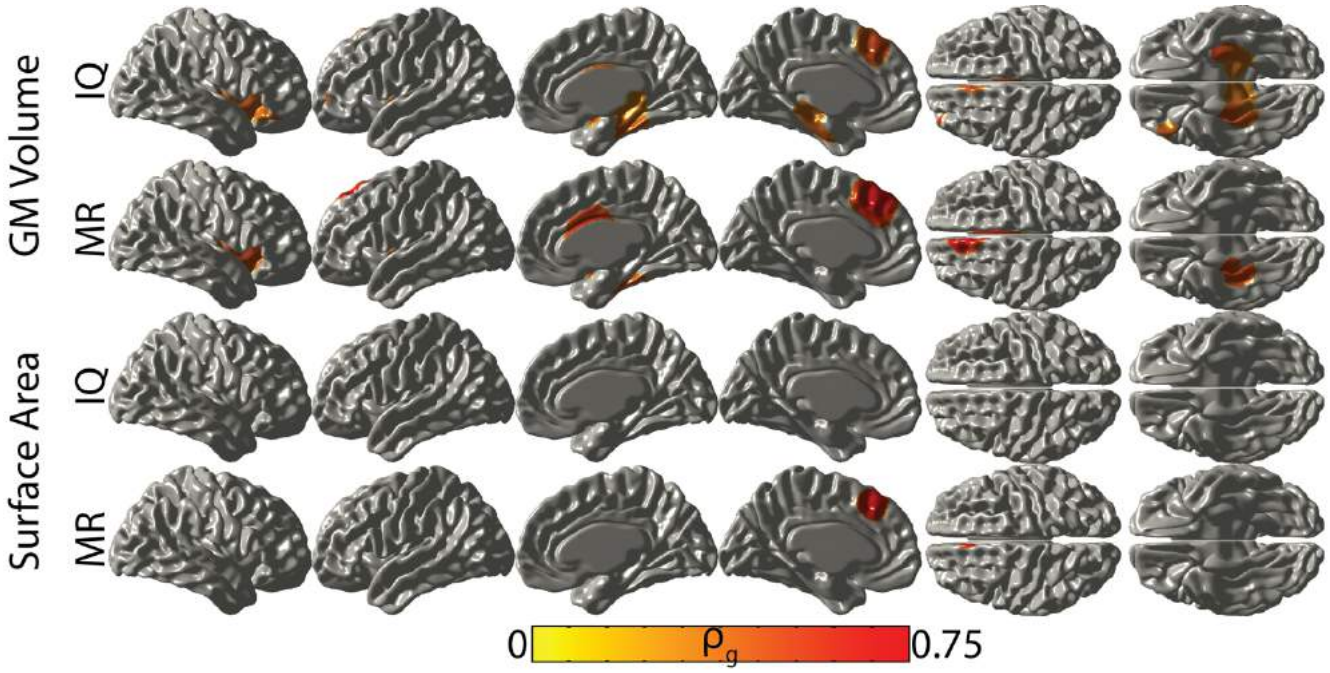

Figure 5.3: Pleiotropic influences on brain structure and intelligence.

Surface maps showing significant estimates of ρ_g between measures of intelligence and brain structure. For each cortical trait, the rows correspond to Subscale IQ (IQ) and Matrix Reasoning (MR).

Chapter 6: Conclusions.

This thesis described three studies aimed at better understanding the quantitative genetics of brain structure, function, and how this can be used to inform other quantitative traits related to normal cognition and disease. The specific goals that were achieved were to: (1) replicate previous findings on the heritability of cortical thickness, (2) to establish whether these genetic influences change over adulthood and early ageing, (3) to provide a complete mapping the heritability of functional connectivity and test for GxA interactions with this trait, (4) to map shared genetic influences across the functional connectome, (5) to demonstrate a link between the amount of genetic variance found in functional connectivity and the evolution of the brain's functional systems, (6) to map genetic influences on additional measures of cortical structure and cognitive function and (7) to show how the use of different quantitative traits can inform us about shared genetic influences between brain structure and cognition.

The most significant scientific contribution of study presented in Chapter 3 was that it was the first to test statistically for changes in the amount of additive genetic variance and changes in the sets of genetic loci that influence cortical thickness. The study also introduced a novel method, based the works of Dr. Bellec, for the "jackknife"-based analysis of stable clusters in cortical thickness. This method proved to be an effective way to minimized the problem of multiple testing while retaining meaningful regional organization. The results demonstrated that while heritability estimates remained constant, different sets of genetic factors were contributing to heritability over early ageing. This effect was significant in cluster 2 which covered the cingulate gyrus, the medial orbital part of the superior frontal gyrus and the insula, cluster 5 which included

the parahippocampal and fusiform gyri, and cluster 8 which covered the lateral parietal cortex and the superior temporal cortex.

The study presented in Chapter 4 presented three different significant contributions to scientific knowledge. First, it provides a complete mapping of heritability and GxA interactions of the connection level in the resting-state functional connectome. Second, it provides a complete mapping of shared genetic influences among functional connections. Finally, it demonstrates a relationship between the distribution of additive genetic variance in the functional connectome and the evolutionary history of the brain's functional systems. The complete mapping of heritability, the testing of GxA interactions and in the mapping of genetic correlations are important firsts and the study of genetic influences on functional connectivity. In addition, the demonstration of a relationship with evolution also helps to provide a clear context for the correct interpretation of these results.

The study presented in Chapter 5 looked at shared genetic influences between different measures of intelligence and brain structure. The results are consistent with previous findings on gray matter volume and extend these to show that surface area might also be a valuable endophenotype for the study of genetic influences on intelligence. The discrepancies observed in the patterns of genetic correlations for the vocabulary and matrix reasoning subscales also suggests that different brain-related traits might differ in their ability to detect shared genetic influences with different cognitive variables.

Taken together these results have important implications. First, as might have been expected (Polderman et al., 2015; Turkheimer, 2000), all traits studied exhibited significant heritability. This indicates that genetic variation has an important impact on many different aspects of the human brain. Second, it is also clear that these genetic

influences are often shared between different brain areas and functional connections. These two facts indicate that the mapping of genetic influences on various phenotypes might reveal new properties of the organization of the human brain. The demonstration of shared genetic influences between brain structure and intelligence also shows that quantitative genetic analysis offers a unique opportunity to better understand the underlying neurobiology of many different traits related to cognition and neurological disorders (Glahn et al., 2012). In the context where brain-related traits can be used as endophenotypes for the identification of specific genetic factors influencing cognitive function and diseases, the demonstration of GxA interactions is also important (Blangero, 1993). Specifically, it indicates that association studies might detect different genetic factors at different ages or in different environmental conditions. This concept is critical for the interpretation of results from genome wide association studies and the design of therapeutic approaches for common disorders.

In the context where significant heritability paves the way for the identification of the underlying genetic factors, it is also important to remember the potential pitfalls of this approach. Very large sample sizes are typically required, at least in part because of the small effect sizes of the mutations and the very large number of tests being performed (McCarthy et al., 2008). In imaging-genetics, this is compounded by the greater number of traits that have to be tested due to the spatial nature of the data, the potential for a greater proportion of noise, which is often magnified in multi-site studies, and the greater cost and time-requirement associated with the acquisition of the data. The works presented in Chapter 4 demonstrate that leveraging the genetic correlations present in the data could be an effective way to increase statistical power in gene identification

studies by reducing dimensionality through genetic clustering, and incidentally also reducing the proportion of noise.

Meanwhile, the difficulties associated with the process of gene identification should not deter us from using other complementary analysis methods. For example, it is possible to use results from well powered GWAS of various traits and diseases to generate polygenic risk scores that can then be used in regression analyses with brain-related traits (Euesden, Lewis, & O'Reilly, 2015). This is analogous to a genetic correlation analysis, as in chapter 5, where the specific genetic factors contributing to the correlation are now known. To take the example of Alzheimer's Disease or obesity, the identification of brain regions where gray-matter volume or cortical thickness is associated with polygenic risk score for the disease could provide valuable targets for further molecular analyses. Specifically, knowledge of target regions could dramatically reduce the search space, while knowledge of the trait of interest could help guide the choice of method (i.e. histochemical tract tracing, cytoarchitectonic analysis, functional recordings, proteomic analysis, etc).

Finally, the results presented herein also highlight the relevance of additive genetic variance when it comes to the evolution of quantitative traits. The joint analysis of genetic variation and brain-related traits could offer valuable insight not only into cognition, behavior and neurological disorders, but also into the evolution of the human being.

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