

# Global-To-Local Segmentation and Genotypic Analysis Of Brain Shape Asymmetry

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# Preface

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*The Author*  
1 January 2010

# Contents

<b>Preface</b>	i
<b>List of Figures</b>	iii
<b>List of Tables</b>	iii
<b>List of Abbreviations</b>	v
<b>Abstract</b>	vii
<b>1 Introduction</b>	1
1.1 Biomedical and anatomic principles . . . . .	1
1.2 Genetics of multivariate quantitative traits . . . . .	12
1.3 Related studies . . . . .	19
1.4 Phenotypic trait analysis . . . . .	21
1.5 Breaking the complexity into parts . . . . .	22
1.6 Searching for the origin . . . . .	22
1.7 Data description . . . . .	22
1.8 Novelties based on related literature . . . . .	22
<b>2 Materials and Methods</b>	25
2.1 General . . . . .	25
2.2 Phenotype . . . . .	25
2.3 Magnetic resonance imaging (MRI) Shapes Normalization . . . . .	25
2.4 Symmetry Statistical analysis . . . . .	26
2.5 Genome . . . . .	26
<b>3 Data Preprocessing</b>	27
<b>4 Asymmetry Phenotypic Analysis</b>	29
<b>5 Asymmetry Genetic Analysis</b>	31
5.1 Post-Processing . . . . .	31
5.2 Meta-Analysis . . . . .	31
<b>6 Discussion</b>	33
<b>Bibliography</b>	35

# List of Figures

1.1	Bilateria clade [48]	2
1.2	Human cerebrum brain asymmetry	4
1.3	A classical model of radial glial cells division processes [81]	6
1.4	Magnetic resonance imaging (MRI) screening of gray and white matter	7
1.5	A crude cerebrum partitioning	8
1.6	Brodmann map of functional partitions.	8
1.7	Desikan-Killiany atlas on midthickness surface	10
1.8	Yakovlevian Torque [62]	12
1.9	Examples of GWAS Manhattan plots [55]	15

# List of Tables

# Abbreviations

**3D** three-dimensional

**AD** Alzheimer's disease

**ADHD** attention-deficit / hyperactivity-disorder

**AI** asymmetry index

**ANOVA** analysis of variance

**ASD** autism spectrum disorder

**CCA** canonical correlation analysis

**CNS** central neural network

**D-V** dorsal-ventral

**DA** directional asymmetry

**DK** Desikan-Killiany

**DNA** deoxyribonucleic acid

**DOF** degree of freedom

**FA** fluctuating asymmetry

**FDR** false discovery rate

**GLM** generalized linear model

**GO** gene ontology

**GPA** generalized Procrustes analysis

**GRM** genetic relationship matrix

**GSEA** gene set enrichment analysis

**GWAS** genome wide association studies

## LIST OF TABLES

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**HSC** hierarchical spectral clustering

**L-R** left-right

**LD** linkage disequilibrium

**LDSC** LD score regression

**MAF** minor allele frequency

**ML** machine learning

**MRI** magnetic resonance imaging

**mvGWAS** multivariate genome-wide association study

**NPC** neuroepithelial cell

**R-C** rostral-caudal

**RGC** radial glial cell

**RNA** ribonucleic acid

**RSS** residual sum of squares

**SNP** single nucleotide polymorphism

**TF** transcription factor

# Abstract

Overall purpose of this thesis is to complement the existing bibliography on the detection and examination of the genetic associations of brain shape asymmetry. Asymmetry components are computed based on the brain magnetic resonance imaging (MRI) dataset provided by UK Biobank database. A data-driven approach is followed, where the brain surface is partitioned in an unsupervised manner, through hierarchical spectral clustering (HSC), a technique that allows for a coarse-to-fine segmentation. Aggregated asymmetry measurements are retrieved from the segments, whose genetic correlation is examined through a multivariate genome-wide association study (mvGWAS) statistical analysis. Recognized significant single nucleotide polymorphisms (SNPs) are then analyzed individually or in groups, through comparison with existing results and databases. The genetic overlap with neurodevelopmental disorders and traits, that have been reported to exhibit phenotypic associations with brain structure asymmetry, such as autism, Alzheimer's disease or intelligence, are examined. Functional annotations of variants associated with the genes where significant SNPs were detected are constructed, offering an insight into the functional reasoning behind the brain shape asymmetry existence.



# Chapter 1

## Introduction

### 1.1 Biomedical and anatomic principles

#### 1.1.1 Bilateria lineage

Cerebral bilateral symmetry is a universal quality of organisms belonging to the Bilateria lineage [20, 21], the phylum incorporating all species with a single plane of symmetry, in contrast with their sister group, Cnidaria (Figure 1.1). Bilateral symmetry is a byproduct of the activity of two separate developmental processes, that produce two axes of polarity [37], and therefore a symmetry plane; the formation of a primary body axis, that corresponds to the long anatomical dimension of the animal, called rostral-caudal (R-C) (i.e. head-to-tail), primarily dictated by highly conserved controlled activation of HOX genes during cell differentiation; the shaping of a secondary body axis, orthogonal to R-C, named dorsal-ventral (D-V) (i.e. back-to-front), attributed to a variety of genes, such as the chromatin organizer CTCF, the left-right determination factor Nodal and central HOX genes [46]. The remaining axis, left-right (L-R), is the one along which the symmetry pattern is manifested. On account of the high biodiversity that bilateria group includes, only the subgroup of vertebrates is examined in the following literature study. In addition, any reference to symmetry or asymmetry from now on corresponds to the L-R direction, unless explicitly mentioned.

This study makes an effort to statistically identify the genetic origins of a complex structural phenotype. Hence, examining, based on existing research, the main brain developmental stages is essential to discern the processes that induce bilateral symmetry. An important vertebrates (and bilateria) common characteristic is the germ line **triploblasticity**: the embryo begins as a flat disk, through a process called **gastrulation**, with three distinct cell layers; **endoderm**, **mesoderm**, and **ectoderm** [33]. Of significance in the neural system formation is the ectoderm, which is initially equivalent to one of the flat disk sides. Under the context of this study, although a fact not directly connected to the brain cortex, it is necessary to mention that the perfect bilateral symmetry pattern appears to break even before gastrulation. In Xenopus (frog species) embryos, during fertilization and the initial 4-cell cleavage of the fertilized egg , the **cytoskeleton microtubules** appear to

## 1. INTRODUCTION

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asymmetrically localize the ion channels proteins, whose RNA has been passed on by the mother, with a preference for the right side of the complex [6]. Chicks embryos also exhibit a similar pattern. The occurrence of asymmetry at this extremely early time point underlines the significant role it has on the embryo development, species fitness, and, concomitantly, the conservation potential of this trait drivers [5]. Another cellular component that is considered to enhance asymmetry, during gastrulation, is the motile cilia, hair-like organelles on the cell surface with the ability to beat [44]. Their movement is by construction asymmetric, causing a leftward flow of extraembryonic fluid and, subsequently, asymmetric distribution of exogenously introduced proteins [78]. Both studied phenomena point to early initiation of asymmetric genes expression.

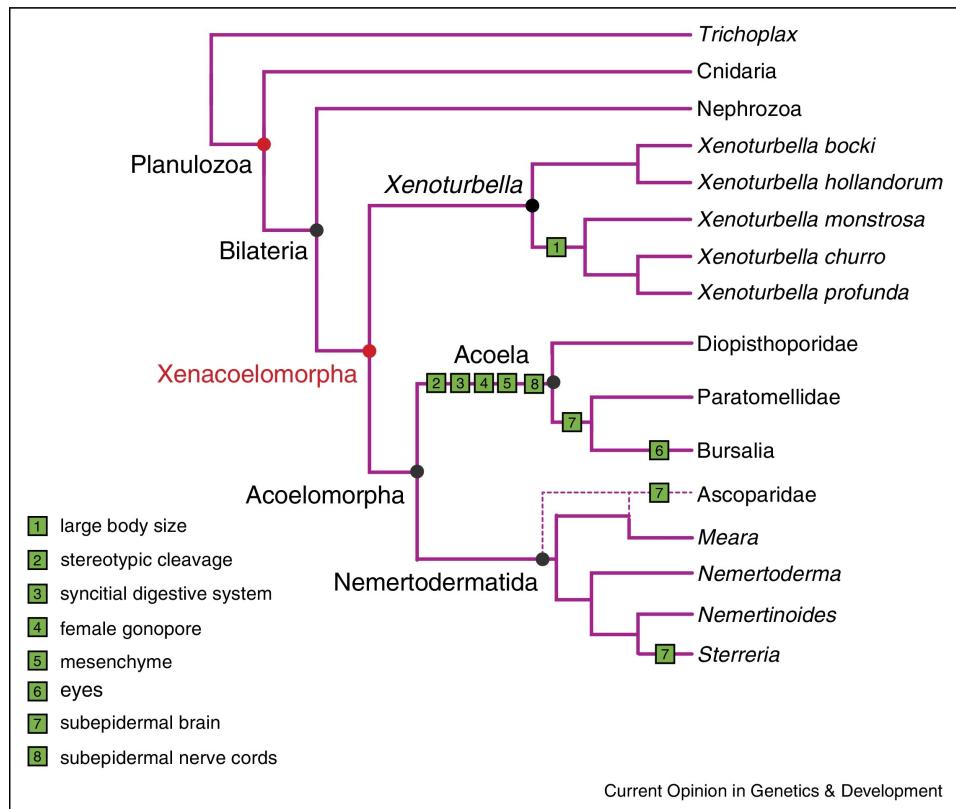


FIGURE 1.1: Species phylogenetic tree subset, displaying bilateria clade, its sister clade, Cnidaria, and the direct children[48]. Of great importance on the evolutionary studies of bilateral symmetry is the Xenacoelomorpha clade.

### 1.1.2 Symmetry during CNS formation

Shortly after gastrulation, the disk folds, in a way that the central region of the ectoderm, called neural plate, forms a tube-like shape, the **neural tube**, which acts as the neural system precursor, under a process called **neurulation**. All bilateria have a central neural network (CNS), which entirely develops from the neural tube

## 1.1. Biomedical and anatomic principles

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walls [33]. The next pivotal step in the brain development, **differentiation**, leads to the creation of three distinct compartments along R-C axis, at the neural tube rostral end, the **prosencephalon** (forebrain), which develops into the brain cerebrum, the **mesencephalon** (midbrain), and the **rhombencephalon** (hindbrain), that is later attached to the spinal cord in vertebrates. For the subsequent mechanisms and terminology to be compatible with human cerebrum related literature, the focus is shifted on mammals phylum and, spatially, on the prosencephalon. The differentiation proceeds, with two pairs of lumps extruding symmetrically from the prosencephalon, the **telencephalic** vesicles, the predecessors of cerebral region, and the optic vesicles, the precursors of optic nerves and retinas, while the central remaining, linking structure is called **diencephalon** [34]. The formed symmetry plane is called **midsagittal**. The telencephalic vesicles continue to grow, expanding also caudally and in parallel with the diencephalon, gradually assuming the form of the two hemispheres, while a new pair of vesicles appears on the rostral part of the diencephalon, giving rise to the **olfactory bulbs**. The neural tube shape also reacts to the changes, forming four distinct **ventricles** along the neural tube, with two of them, named **lateral ventricles**, being mirrored inside each of the telencephalic vesicles. The earliest stage where asymmetry is noted in an anatomic level inside the human brain is during the end of the first trimester of gestation [2]. Specifically, the choroid plexus, a specialized cell network that lies inside the ventricles, attached to the diencephalon, and produces most of the **cerebrospinal fluid** in the CNS, develops asymmetrically in each lateral ventricle. The cerebrospinal fluid is of great value for the developing brain, as the main source of nourishment, waste removal and protection [96]. Such an asymmetry manifestation in a macroscopic level, therefore, may be the progenitor of other forms of asymmetry at a later developmental stage [89], even at the brain surface. Cerebral bilateral symmetry therefore begins breaking down during fetal development, producing an asymmetric brain (Figure 1.2), and giving rise to partial functional disassociation, called **brain lateralization**. Lateralization becomes visible when examining organisms' behavior, with the most studied trait in humans being handedness and language [89, 21]. To better understand why and how the inner functions are related with the external brain cortex development, the underlying cellular processes of **neurogenesis** and **neuron migration**, active throughout differentiation, need to be identified, before introducing the reader to the anatomy of the fully grown brain. For this purpose, a further focus on primates phylum is needed, given the differences exhibited when comparing different mammals, such as rodents[70].

## 1. INTRODUCTION

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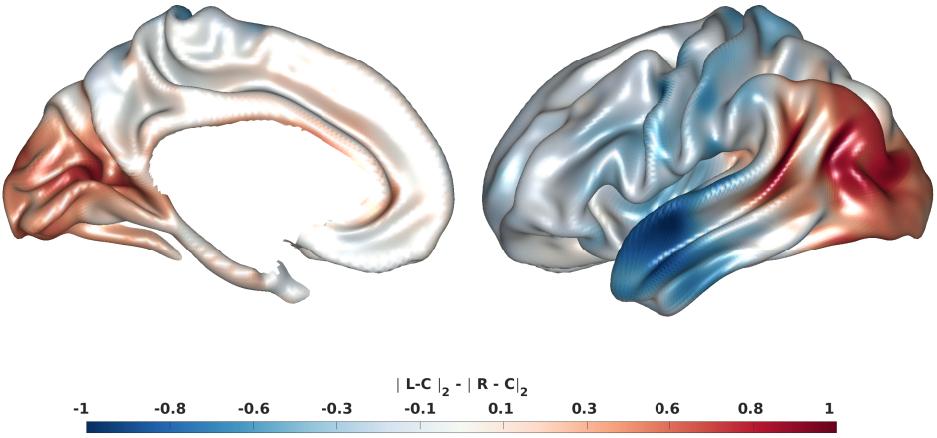


FIGURE 1.2: Illustration of human cerebrum brain asymmetry. Normalized differences of the distances of each hemisphere rescaled, rotated and averaged surface landmarks from the center of mass. See section 1.4 for more details on the preprocessing.

### 1.1.3 Neurogenesis, Neuronal Migration and Plasticity

The cells initially comprising the neural tube walls are named neuroepithelial cells (NPCs), and exhibit similar properties with stem cells, that is limited multipotency (i.e. they can differentiate into multiple cell types) and limited self-renewing (i.e. they can divide symmetrically into new NPCs a finite number of times), while also properties of epithelial cells, that is polarity (i.e. asymmetric cellular organization, with distinct basal and apical surfaces) and attachment (i.e. junctions tightly connect adjacent cells) [42]. This cells array is contained between the basal and apical laminae, lipid membranes lateral to each other, with the apical lamina facing the neural tube lumen [1], and the cells being radially distributed. During anatomical differentiation, around the 7th gestational week in humans [77], self-renewing is activated, leading to cells proliferation and CNS bilateral expansion, while attachment is hindered, gradually exchanging the NPCs with radial glial cells (RGCs), the fate-restricted progenitors of neurons, marking the initiation of **neurogenesis**[42]. A RGC acts as the main building block of the brain, from which a single neuron or a neural progenitor, that later divides symmetrically in neurons, is generated. RGCs' pivotal role does not end here. As it can be seen in Figure 1.3, RGCs are stretched during development, with processes connected to the surface of neural tube successor ventricles and to the outer cortical region surface, forming thread-like scaffolds. Newly formed neurons, generated from the RGCs main, oval body, which remains close to the ventricles, use this structure as a guide to move towards the outer region of the cortex, under a process named **neuronal migration**[81]. This type of movement actually implies that the newly formed neurons head towards the brain surface, building the brain

## 1.1. Biomedical and anatomic principles

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in an inside first, outside last fashion [70]. At later stages of human gestation, around week 19, studies have shown that a morphological transition is observed, where the majority of RGCs stops being attached to the **pial surface**, the outer surface of the brain, limiting the migration ability of neurons [77] and affecting the way new layers are formed. Human neurogenesis extends to the third gestation trimester, being suppressed in case of premature birth [67]. Postnatal neurogenesis is therefore presumed to be quite limited for primates [31], despite the fact that the postnatal brain dramatically increases in size , with that attributed to a rapid increase in neurons connections and glial cells (i.e. cells that provide physical and metabolic support to neurons) number [30]. The environmental factors that may affect brain lateralization are mainly detected before or during birth, with epigenetics and birth complications appearing to be mostly correlated with handedness [89, 13]. However, the human brain exhibits high **plasticity**, namely the ability of intrinsic or extrinsic factors to change the neurons connectivity, setting aside the genetic predisposition, a property that has been proven to particularly affect the the brain surface asymmetry in studies with monozygotic twins [110, 24]. In general, though, the more complex the phenomenon and the closer it is to humans, the higher the uncertainty and the greater the ethical restrictions. Only recently, non-invasive imaging and transcriptomic techniques have given further details regarding the brain development sequence, with genetic studies indirectly identifying the landscape of the underlying genes that affect different brain regions formation and symmetry [13]. Moving on the literature study path and getting closer to the studied phenotype, the fully grown human brain cerebrum is subsequently anatomically described.

## 1. INTRODUCTION

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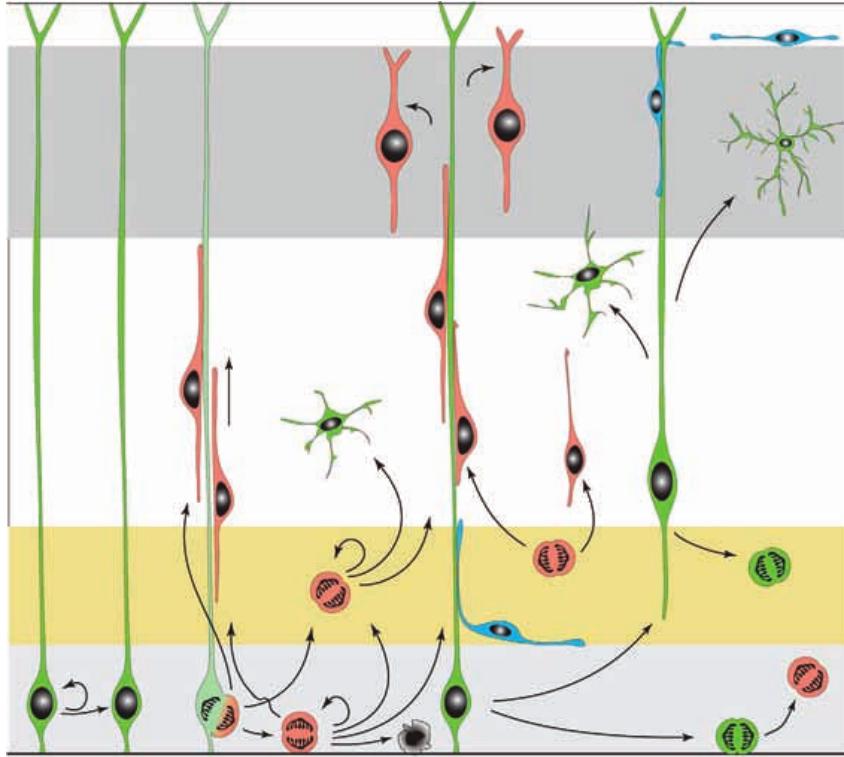


FIGURE 1.3: Illustration of a classical model of radial glial cells complex nonlinear division processes and neuronal migration [81]. From left to right: NPCs (green) originally divide symmetrically; During differentiation, NPCs become RGCs, which divide asymmetrically, generating neurons or neural progenitor cells (orange). Neural progenitor cells eventually divide symmetrically into neurons. The majority of neurons in humans is produced by neuronal progenitors. A part of the generated neurons migrate radially towards the cortical plate, by attaching on the RGCs projections; Eventually, after brain maturation, most RGCs in humans undergo apoptosis (i.e. cell death) or generate neurons-supporting cells, such as astrocytes.

### 1.1.4 The adult human cerebrum anatomic and functional properties

Human cerebrum is the center of sensations and thinking. The following excerpt provides a summarized anatomic [32] and functional [36] perspective. As aforementioned, cerebrum is entirely produced from the telencephalon during fetal development, with the telencephalic vesicles ending up becoming the two hemispheres, that remain connected through what is known as the **Corpus callosum**. The side view of each hemisphere is named **lateral**, and the view of the inner side is called **medial**. The human cerebrum outer covering surface is called **cerebral cortex**, the region on which the current study focuses. The human cerebrum appears distinctly different from other organisms, mainly due to the **sulci** (i.e. grooves) and **gyri** (i.e. bumps), with them being the result of the tremendous expansion of the cerebral cortex surface

## 1.1. Biomedical and anatomic principles

area during fetal development, folding and wrinkling in order to fit the skull. The precise pattern of gyri and sulci varies significantly across populations, rendering the brain surface unique per individual. Under a biopsy dissection or a magnetic resonance imaging (MRI) scan, the cerebrum appears to consist of two distinctly colored types of matter, implying changes in composition and consistency; the gray matter, at the outer part of the cerebrum, which contains the cell bodies, dendrites and the axon terminals, where all synapses are, and the white matter, at the inner part, made up of myelinated (i.e. biologically insulated) axons, which connect different parts of gray matter to each other (Figure 1.4). Protective layers on top of the gray matter, called **meninges**, ensure that the brain does not come in contact with the outer bone, with the one attached on and marking the outer borders of the gray matter named **pial surface**. In this study, the midthickness surface is examined, a term referring to the surface halfway between the pial and white matter surface.

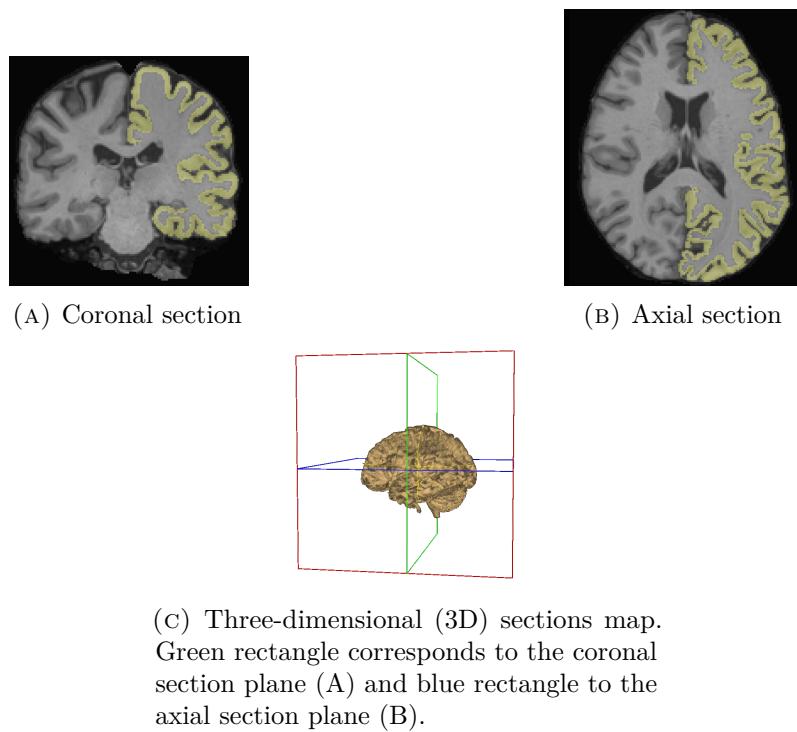


FIGURE 1.4: Gray and white matter as seen from different sections, in an MRI screening, as retrieved from Freesurfer freeview routine. The gray matter is annotated with yellow color in the right hemisphere. Non brain regions have been removed.

## 1. INTRODUCTION

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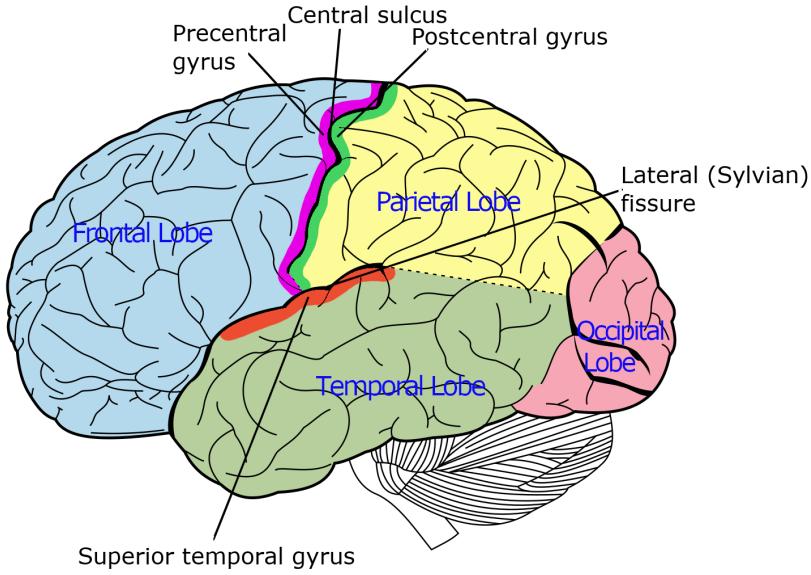


FIGURE 1.5: Cerebrum lobes (blue font) and main gyri, sulci and fissures approximate positions (black font).

Efforts of partitioning the brain have been numerous throughout the years of medicine, with diverse resolution and purpose. Crudely, the cerebrum hemisphere is divided into lobes, that are named, by convention, after the bones of the skull that lie over them (Figure 1.5). A more detailed approach is based on the identification of the functional processes that take place in each part of the cortex, with Korbinian Brodmann being the first person constructing a 52-partitions experimentally based approximation of the hemisphere [9] (Figure 1.6). The main regions identified are:

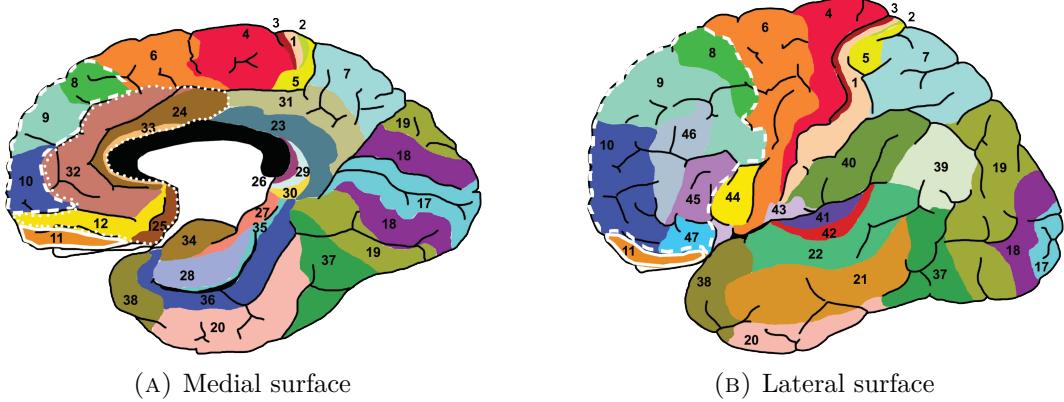


FIGURE 1.6: Brodmann map of functional partitions.

- Sensory areas:
  - Somatosensory cortex (areas 1-3): the post-central gyrus (Figure 1.5). It

is responsible for the body-wide sensory information processing, such as touch, temperature and pain.

- Visual cortex (areas 17-19): occipital lobe surface. It constitutes the center of processing of visual information, as received from the optic nerve.
- Auditory cortex (areas 41,42): rostral posterior part of the temporal lobe. It processes auditory information, identifying fundamental sound characteristics, such as frequency and loudness.
- Gustatory cortex (area 43): An area behind the temporal lobe, responsible for taste signals processing.
- Motor areas, that are related to movement planning and manifestation:
  - Primary motor cortex (area 4): The precentral gyrus (Figure 1.5). It is the center of voluntary movements execution, generating the electrical signals required for the neural impulses to be transmitted to the body muscles.
  - Premotor cortex and supplementary motor area cortex (area 6): rostral part of the frontal lobe, anterior to the primary motor cortex. They are the center of motion planning and control, determining the sequence of movements required for a simple task to be performed.
- Association areas, which are related to perception, memory and thought processes:
  - Prefrontal cortex (areas 8-14,24,25,32,44-47): anterior part of the surface of the frontal lobe. It is centrally involved in cognitive control functions, spanning attention, salience detection, inhibitory control, working memory (i.e. short-term temporarily stored memory, related to a certain task), cognitive flexibility, empathy and pain processing [79]. Areas 44 and 45, referred to as **Broca's region**, are responsible for speech production. Human prefrontal cortex remains one of the least functionally demystified parts of the cortex , presenting difficulties in every level of study, as it exhibits a higher relative size, higher cellular type variety, more complicated neuronal migration and denser connectivity patterns than other animals.[15]
  - Inferior temporal cortex (areas 20,21): caudal part of the temporal lobe cortex. It is responsible for the aggregation of the processed visual information towards a meaningful interpretation, supporting object recognition.
  - Posterior parietal cortex (areas 5,7): posterior part of the parietal lobe surface. It processes sensory information produced from all six senses to construct a semantic representation of the person's surroundings, leading to motion planning and spatial reasoning.
  - Cingulate gyrus (areas 23-24,28,33): an arch-like fold rostrally to corpus callosum. It is the conscious part of the **limbic system**, which is the center of emotions, instinct and reflex responses.

## 1. INTRODUCTION

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Recently, with the advance of imaging methods, maps have been manufactured, to automatically partition the MRI extracted three-dimensional (3D) cortical surface, based on morphological characteristics. One such gyral-based atlas, Desikan-Killiany (DK), is derived from the changes in curvature under an expert-driven model of gyri locations [25] and provides automatic **cortical parcellation**, aligned to the Brodmann functional partitioning (Figure 1.7). This atlas is going to be used throughout the proceeding analysis for the quality control of applied segmentation techniques.

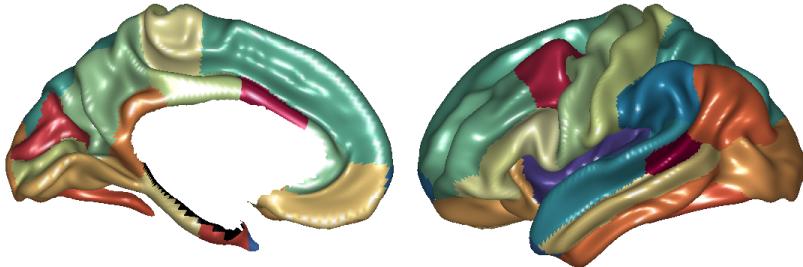


FIGURE 1.7: Desikan-Killiany atlas, mapped on the midthickness surface of the left hemisphere, with the medial (left) and the lateral (right) views displayed.[27] Different colors represent different partitions. The black region has not been mapped.

### 1.1.5 Evolutionary studies

From an evolutionary perspective, it is extremely rare for the right conditions to occur, in order for any soft tissue specimen to be preserved, across a considerable amount of time. The only known way is through mineralization [80]. This fact renders a mammal’s ancestor brain almost impossible to retrieve. Nevertheless, endocranial imprints have been used as a proxy to describe the relationships between hominids and their ancestors [7, 73]. The reason behind this phenotypic delegation is purely practical. The brain size and shape follow the container volume restrictions. Although such studies support the theory of propagating asymmetry among studied individuals, with the most evident signs in human skulls, little information about the surface shape can be retrieved, as only the convex hull shape of the brain can be delineated from such process. Through the association of brain asymmetry with DNA, a universal code among organisms, it becomes possible to deploy tools used by evolutionary geneticists, to identify the phylogenetic tree of this complex trait, locating conserved regions among organisms and their predicted divergence in time, under a pleiotropic model [58].

### 1.1.6 Reported general human cortex symmetry traits

Although human cortex exhibits roughly symmetric structure, the symmetry is systematically suppressed, not only due to the environment, with plasticity playing central role, but also because of genetic factors, as explained in the previous sections. An asymmetric pattern is manifested across adult individuals, irrelevantly of their upbringing, comprising, therefore, a characteristic of the human species, while general abnormalities in this pattern are related to the occurrence of mental disorders, such as autism or developmental language disorder [49, 61]. Some of the most prominent asymmetric traits across healthy individuals are the following:

- Yakovlevian torque (Figure 1.8): the right hemisphere prefrontal lobe and the left hemisphere occipital lobe tend to cross the midsagittal plane, extending towards the other hemisphere [62]. This creates a phenomenon of counter-clockwise warping, making the whole brain appear slightly leftwards rotated, while also making an impression on the inner part of the skull, called **petalia**. Increased left hemisphere occipital lobe extension, possibly caused by enlarged left lateral ventricle, is correlated with bipolar disorder[68]. Rising absence of the torque during aging is connected to schizophrenia and other mental disorders [84].
- Peri-Sylvian asymmetry: the left Sylvian (lateral) fissure is longer and sharper than the right one, while the right Sylvian fissure exhibits a more visible leftward curve, in the part where temporal lobe meets the parietal lobe, that is the auditory cortex, also called **planum temporale** [62]. The increased thickness of the right superior temporal lobe, that reduces the lateral fissure steepness, is attributed to increased white matter volume. Such trait has been reported to be gender-related, with males exhibiting greater asymmetry than females, as noted in previous studies, with steroid hormone receptor activity and steroid metabolic process related genes [45].
- Central sulcus asymmetry: the right hemisphere central sulcus is deeper and larger [62]. Larger asymmetry appears to be correlated with attention-deficit / hyperactivity-disorder (ADHD) [63].
- Motor areas asymmetry: the motor areas are generally larger on the left hemisphere.

Statistical modeling of the observed symmetry pattern can provide a hint on the significance of genetic and environmental factors contribution[56]. The current study focuses on the genetic component, which has been diversely investigated across literature.

## 1. INTRODUCTION

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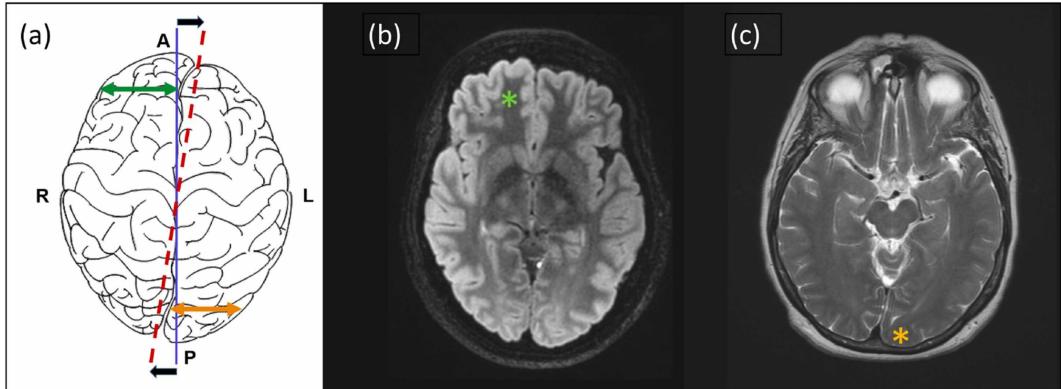


FIGURE 1.8: Yakovlevian torque schematically illustrated (a), along with its manifestation in different axial sections for a single individual (b,c) [62].

## 1.2 Genetics of multivariate quantitative traits

### 1.2.1 Multivariate genome-wide association study (mvGWAS)

Genome wide association studies (GWAS) aim to relate genetic information, usually extracted from single nucleotide polymorphisms (SNPs) markers arrays, with a phenotypic trait. When the trait is dichotomous, measured by its presence or absence, then GWAS are applied on a case-control fashion, where two cohorts, an affected (case) and an unaffected (control), are compared. [98] In the present work, the focus is directed to quantitative traits, whose measurement takes continuous values.

### 1.2.2 Single nucleotide polymorphism (SNP) identity and importance

Single nucleotide polymorphisms (SNPs) are characterized by single nucleotide base-pairs positions where two or more different alleles (i.e. variants of nucleotide bases) are observed, with the second most frequent allele appearing with a frequency, called minor allele frequency (MAF), higher than 1%, a property that sets this term apart from the more general notion of a single-nucleotide variant. Being the most common type of polymorphism in the human genome, SNPs were popularized on account of their considerable effect on influencing transcription. Apart from the direct case, where a SNP belongs to an exon and the alternate allele corresponds to a non-synonymous (the translated amino-acid differs) or a nonsense (the codon stops translation) mutation [82], the majority of registered SNPs (88%) reside in non-coding regions. They can have an impact on the physio-chemical properties and conformation of docking positions for DNA-binding enzymes, such as transcription factors (TFs), causing binding affinity changes, influencing transcription regulation and, ultimately, altering biological pathways relevant to dependent phenotypic traits [76]. As a matter of fact, 31% of the known DNA elements, as reported by the

ENCODE project, the human genome encyclopedia, appear to be part of TFs binding domains [29].

### 1.2.3 Linkage disequilibrium (LD) effect on SNPs

The genetic information for each individual is only represented by a certain amount of single nucleotide polymorphisms (SNPs), called **tag** SNPs, based upon the principle of high linkage disequilibrium (LD) [103, 8]. LD, the non random association between alleles at different loci, is attributed to mutations, genetic drift and, concomitantly, selection [103] that has rendered certain combinations of alleles, named **haplotypes**, more beneficial for the survival and reproduction of a population than others, increasing therefore its **fitness**. These combinations are also more likely to occur topologically close, with recombination events (i.e. events that cause DNA strands to break and recombine, altering the haplotype) being less frequent the smaller the genetic distance [103]. Tag SNPs reduce the amount of information required to process to observe pheno-to-geno associations, however the larger the effective population size(the part of the population that reproduces with viable offspring), the weaker the LD phenomenon [103].

### 1.2.4 Genetic association modeling

Phenotypic differences among individuals, described by the trait variance  $V_p$ , are the result of genetic variation  $V_g$ , known as **heritability**, environmentally induced variation  $V_e$  and developmental noise  $V_d$  (the deviations observed when environment and genetics are controlled), formally denoted as  $V_p = V_g + V_e + V_d$  [104]. The genetic information content  $V_g$  is *approximated* by the amount of variation in tag SNPs that is translated to variation in the studied trait properties. The presence of a minor allele signifies divergence from the general population characteristics, and hence implies that information is contained in that SNP. The relationship of each SNP with the phenotypic trait is statistically represented by a certain genetic model. Under the assumption of an **additive model**, if a certain minor allele occurs in both DNA strands, i.e the allele is homozygous at that locus, then its effect is double compared to the heterozygous case, independently of which strand is carrying it. This hypothesis requires no prior knowledge and makes no further assumptions regarding the alleles dynamics, that is the degree of dominance of each allelic variant. The described model, for a single quantitative trait (dependent variable) and a SNP with a single minor allele (assumed independent variable), assessed on a sample with size  $N$ , can be formulated using a univariate linear regression  $y = \mu + \beta x + \epsilon$ , with  $x$  the allele's occurrences number,  $y$  the phenotypic trait,  $\beta$  the SNP effect and  $\epsilon$  the part of non controllable factors, referring to environment and developmental noise.

### 1.2.5 Contradicting no association

A SNP is considered to be significant, if its effect contradicts the null hypothesis  $H_0$  of no association ( $\beta = 0$ ). For the subsequent analysis, under a biological setting,

## 1. INTRODUCTION

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it is assumed that the phenotypic trait follows a normal distribution. Under the reduced model of  $H_0$ , the residual sum of squares (RSS) equals  $RSS_R := \sum (y - \bar{y})^2$ , with  $\bar{y}$  the observed mean value of the phenotype, and the degrees of freedom (DOFs) being equal to  $N - 1$ . Under the full model of alternative hypothesis  $H_a$ , the RSS equals  $RSS_F := \sum (y - \hat{y})^2$  with  $\hat{y}$  the estimated trait, with  $N - 2$  DOFs. In an analysis of variance (ANOVA) setting, the F-statistic  $\frac{MSR}{MSE} := \frac{RSS_F - RSS_R}{RSS_R / (N - 2)}$  is defined, as MSR and MSE follow a  $\chi^2$  distribution with 1 DOF and N-2 DOFs respectively under  $H_0$ , which can be used to contradict the null hypothesis.

An alternative to the aforementioned hypothesis test can be made by considering an  $H_0$  that the coefficient  $\beta$ , scaled by the standard error (i.e. standard deviation), follows a standard normal distribution. The hypothesis then can be contradicted by comparing that quantity with the corresponding z-score. An advantage of the latter approach is that the distribution compared is two-sided, meaning that the effect can be given a positive or a negative sign. However, no consideration for the uncontrolled factors is made, a fact that could potentially influence the computed score and render it less interpretable, compared to the ANOVA case.

### 1.2.6 Measuring SNP significance

By assigning a minimal probability to the event that no association is observed, namely defining a p-value cutoff threshold, a SNP is found to be significant if the p-value from the corresponding F-test is less than the explicitly defined cutoff [3]. Greater sample size means lower MSE, larger F-statistic and, consequently, lower p-value. Thus, greater sample size increases the chance of discovering significant SNPs and low sample size raises the type I error of the detection, namely the presence of false negatives that actually confirm  $H_a$ .

The probability threshold is derived based on an empirical value, fixed to 0.05, corrected using the Bonferroni correction for multiple independent tests, hence  $\frac{0.05}{N_t}$  with  $N_t$  the number of SNPs. The method is rather conservative, therefore usually cutoffs are computed by replacing the number of tests with the amount of independent common SNPs for a given population. Based on the findings of the International Hapmap Project, this amounts approximately between 200,000 to 1 million tag SNPs [8]. Therefore, the cutoff threshold  $5 \times 10^{-8}$  is used. The p-values are most commonly converted to values proportional to significance, by applying the  $-\log_{10} p$  transformation. The LD phenomenon, being often locally observable, causes seemingly continuous p-value spikes to appear when plotting the data points, with the lead, or functional, SNP, that is the one with the greatest local significance (i.e. the lowest locally recorded p-value), being ‘supported’ by lesser significant SNP in its vicinity. The resulting scatter plot, with SNPs  $-\log_{10} p$  values uniformly placed on x axis (i.e. ignoring their actual positions in the genome), resembles the Manhattan city landscape (Figure 1.9b).

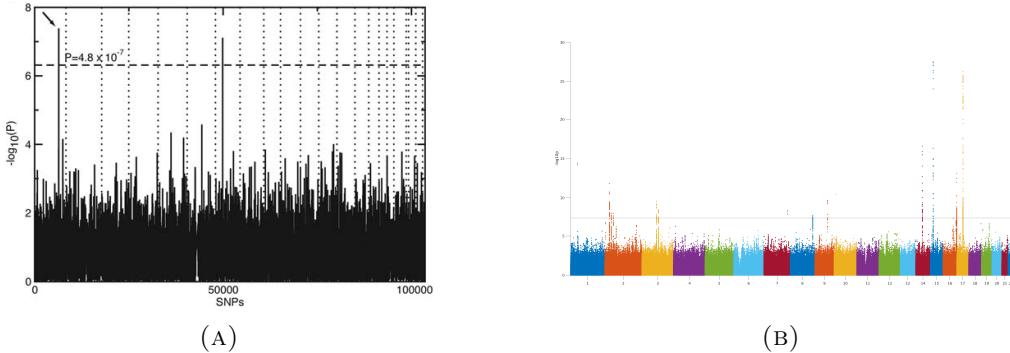


FIGURE 1.9: Examples of GWAS. In (A), the first recorded GWAS Manhattan plot [55] is displayed, where the SNP in chromosome 1 (black arrow) with the most significant effect, related to Complement H Factor Polymorphism, was identified to affect age-related macular degeneration disease propensity, one of the major causes of blindness among elderly. In (B), a GWAS scatter plot from the present work is shown, where the SNPs spikes signal, attributed to LD, is evident.

### 1.2.7 Major advantages and disadvantages of univariate GWAS

There are several design benefits and limitations of such a process. GWAS have been successful in revealing novel relationships between genes with known properties and a variety of observed phenotypic traits and clinical applications, presenting evidence of possible biological mechanisms related to genes with unknown function [94]. They also empower population-specific comparative studies, at the level of how ethnicity or other kinds of population stratification affect a certain trait, while accommodating the possibility to investigate the effect of an allele no matter how frequently it might appear in the studied sample [94]. On the other hand, it has been generally observed that each SNP can only explain a small part of the heritability of a certain trait, with a large amount of the signal hidden in gene-to-gene interactions, that are not captured in this method, and possibly in SNPs whose contribution has not been considered significant enough [94]. To remedy the latter issue, larger sample size is ideally required. Due to the fact that the largest amount of SNPs is located in intronic regions, it has also been difficult to assess the causality of those variants, which genes they affect and how they do it. Additionally, too many, possibly unrelated, hits may be involved in a GWAS result, due to LD. [94] Recent studies have deployed advanced post-GWAS statistical and machine learning (ML) approaches to account for identifying the causality and the functional behavior of significant SNP [75, 41].

### 1.2.8 Multivariate genome-wide association studies (mvGWAS)

When the analyzed phenotype is described by more than one measurements, as is the case in this work, where it is expressed as the combination of different 3D landmarks composing the cortex of each individual, GWAS require a methodological change to accommodate this fact, as univariate regression cannot be used as is. Also, a single

## 1. INTRODUCTION

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genetic locus may exhibit more than one minor allele. The goal, consequently, is to incorporate multi-allelic SNPs and, more importantly, multivariate phenotype, in a single hypothesis test per SNP, leading to what is called multivariate genome-wide association study (mvGWAS). In general, there is an abundance of strategies on how to perform a mvGWAS, ranging from direct methods, that approximate the inputs relation either in an unbiased manner or making certain educated guesses, to more complex techniques, that increase statistical power by transforming the inputs, at the expense of explanatory ability [40]. There are also methods that are based on the meta-analysis of outcomes from univariate studies, commonly used to juxtapose experiments from separate sources, for which the original data is missing, the experimental setup, mainly sample size, across studies varies, marking the studies data ‘incompatible’, or a single study is computationally intractable [98, 16]. These approaches combine the test-statistics produced from the individual studies and produce an estimate of the multiple trait test-statistic. Which approach performs best mainly lies on the dataset properties and the nature of the scientific question. Factors such as low sample size [91], genes pleiotropic effects [35] (i.e a gene affects multiple phenotypically independent biological pathways) or within-study variability [99, 51] tend to handicap the statistical modeling and increase the type I and II errors of the corresponding hypothesis tests. In this study, canonical correlation analysis (CCA) was chosen due to the high capacity in efficiently reducing the inputs dimensionality while preserving most information regarding their correlation, and the same sample size across analyzed traits, an approach that has provided successful results in similar efforts of brain shape and face shape analysis [17, 72]. An additional strength of this method is that a single test is performed per SNP, not requiring further multiple test correction over the number of phenotypic traits, thus having increased statistical power than meta-analysis techniques.

### 1.2.9 LD score regression (LDSC) analysis

The LD between two alleles  $A$  and  $B$  from different loci is generally quantified using one of the following values:

- the coefficient of linkage disequilibrium  $\mathcal{D}$ :

$$\mathcal{D} := p_{AB} - p_A p_B$$

with  $p_{AB}$  referring to the haplotype AB frequency and  $p_i$  to the allele i frequency. This coefficient is scaled by theoretical maximum  $\mathcal{D}$ ,  $\mathcal{D}_{max}$ , to render it independent of the per-pair frequencies magnitudes, producing  $\mathcal{D}'$ .

- the genetic correlation  $r^2$ , a proxy of the Pearson coefficient, defined by:

$$r^2 := \frac{\mathcal{D}}{p_A(1-p_A)p_B(1-p_B)}$$

Based on simulations, it has been shown that  $\mathcal{D}'$  is inflated when the sample size is small or the minor allele is rare [95], thus genetic correlation is generally preferred.

In a seminal research work from Bulik-Sullivan et al. [11], it was found that there is a closed mathematical expression that connects the allele  $j \chi^2$  expected value with the average heritability explained per SNP  $h$  and its LD score, defined by  $\sum_k r_{jk}^2$ ,  $r_{jk}$  being the  $r^2$  of the  $j$  with the  $k$  allele:

$$E[\chi^2|l_j] = \frac{Nh^2l_j}{M} + N\alpha + 1$$

$\alpha$  is the contribution of population-related effects, such as population stratification, that are not being controlled, known as confounding biases. The gains from this regression are dual; a measurement of heritability can be obtained by estimating the slope, and the confounding bias effect can be measured by the intercept. This formula, which originally referred to a univariate phenotype, was extended in [72] to incorporate D-dimensional multivariate traits:

$$E\left[\frac{\chi_j^2}{D\left(1 + \frac{\chi_j^2}{N}\right)}\right] = \frac{N-1}{P}\left(\frac{\sum_{d=1}^D h_d^2}{D}\right)l_j + 1 + O\left(\frac{1}{N}\right)$$

where  $O(1/N)$  term is corresponding to the confounding biases effect. The basic underlying assumptions, or limitations, of such a model are:

- The SNP heritability follows a uniform distribution, i.e. it is on average the same genome wide. Extensions have been made to relax this, generally wrong [97], assumption, by considering partitions of SNPs separately and doing what is known as stratified LDSC regression[38], based on existing chromatin activity profiles, the average suppression of genetic loci, per cell type. A further gene-specific development by Finucane et al. [39] was performed instead to incorporate gene expression profiles per cell type.
- Each SNP effect is assessed independently from the rest, therefore no between-SNPs interactions can be included in the computation.
- The covariance matrix of the phenotype equals the identity matrix multiplied by  $N$ , that is the studied traits are orthogonal to each other.

### 1.2.10 LDSC genetic correlation

Bulik-Sullivan et al. [10] also invented a way to utilize GWAS scores produced for two different traits as a proxy to relate the genetic correlation of these traits, namely the extent over which the two characteristics are being regulated by similar genetic drivers:

$$E[z_{1j}z_{2j}|l_j] = \frac{\sqrt{N_1N_2}\rho_g}{M}l_j + \frac{\rho N_s}{\sqrt{N_1N_2}}$$

The conversion between  $\chi^2$  with 1 DOF and  $z$  score values is straightforward, as, by definition, the square of a standard normal distribution follows the  $\chi^2$  one with 1 DOF. In other words, the equation above retrogresses to the LDSC regression

## 1. INTRODUCTION

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one, if traits 1 and 2 are considered the same. With LDSC correlation, seemingly independent phenotypes can be compared, testing for pleiotropic SNP effects and discovering novel biological pathways [10].

### 1.2.11 Generalizing to genes - Functional association

The next natural step to perform, once significant variants have been identified for a specific phenotype, is to investigate how such an association is realized, ultimately supporting and extending the assembly of the complex relationships graph between genetics and actual observations. No matter if there is effect on regulatory elements or on the gene product itself, this kind of venture is largely obfuscated, given the little amount of knowledge that exists to fill the relational path, which may include a great amount of steps and interactions. The majority of SNPs reside in intronic regions [8]. A great number of them is also likely to exhibit *cis*-acting effects. Surprising is also the event that SNPs mapped on an exon of a known gene can be actually manifesting significant correlation with a trait, such as obesity [18], through the interaction with a different gene. Resolution of GWAS in discovering causal genes is also being limited by the number of studied individuals, the genotyping arrays technologies and the existence of LD [28], with the lead SNPs not necessarily being the functional source of the association signal. Even by ignoring the ambiguous relationships and by knowing the start and end of an association path, the probabilities are thin that the exact trajectory, implicating selective messenger RNA translation throughout development, can be derived.

Nevertheless, active research is being performed, to approximate and model the underlying dynamics. Highly trait-specific and exhaustive wet-lab ablation studies, that include genome editing, can profoundly reduce the functional analysis complexity, particularly when little evolutionary and ethical barriers exist, and the analyzed trait has low dimensionality [83]. In the general case, though, modeling and approximations need to be performed, in order to deal with the task. Population stratification and ethnic group variation has shown little interference in common variants analyses [103], at least when considering GWAS on various diseases, a fact that points to highly frequent and widely distributed causal alleles and may support a form of simplification for the described, seemingly physically and computationally intractable task, possibly allowing for the unification of results from diverse ethnicity experiments. In addition, a gradual incorporation of multiple knowledge sources is taking place to support this undertake; findings from RNA expression profiling (such as RNAseq and scRNAseq), also known as eQTL analysis, [112, 115] or epigenetic regulation studies (such as ATACseq and CHIPseq) [22, 50], that could potentially provide snapshots of genes expression during development, are cross-tested against GWAS. Through identification of cell types by genetic expression profiles clustering and association between tissues and identified clusters, localized analyses can be more accurate in extracting SNP-to-gene relationships [12].

The key approximation required to combine information is to map the underlying data onto the same space. The most elementary jointly studied structure in these relational analyses is genes, due to the recurring need for actual, known, gene

product concentrations to be detected. For the generalization from SNP to gene, the intermediate detection of lead SNPs needs to take place, as aforementioned, under a process called **fine-mapping** [88], which is tackled in various ways, from application of basic heuristics to regression and bayesian modeling, by incorporating priors fitted on the data. It is frequent practice to assume that lead SNPs reside in the captured and imputed data, therefore overlooking the event of no registration, when investigating rather common phenotypic traits. In such a case, a simple metric, utilized in the current study, to detect lead SNPs is to use the genetic relationship matrix (GRM), that is the symmetric matrix produced by computing  $r^2$  for each SNP pair, to identify independent significant variants, using an arbitrary cutoff, over an explicitly defined genetic distance [109]. Once the lead SNPs have been pinpointed, they are matched to existing maps of annotated genes, after also considering surrounding non coding regions, such as the transcription start sites, as well as other information, retrieved from curated databases [107, 69]. A great part of the generalization is susceptible to underlying biases, with each gene having distinctly different size and possibly overlapping with others [108].

Functional association is then made possible under the framework of gene set enrichment analysis (GSEA) [92]. Being a well-established and extensively used method by a variety of different bioinformatics tools [14, 109, 64], with its first application dating back to 2003 [71], GSEA is realized by considering gene expression or epigenetic profiles, namely sets of significantly up and down-regulated genes, from different cell types or tissues, and statistically comparing the relation degree, i.e. enrichment, with the genes identified in GWAS. This process can also be applied ubiquitously, from deriving connections with literature-specific gene annotated knowledge, such as gene ontology (GO) terms [4] and publications [93], to back-projecting the GWAS results to identify shared regulatory domains [52] or enriched TFs motifs [47]. Main disadvantage of GSEAs, other than the great number of assumptions required to retrieve GWAS gene sets, is the fact that the compared genes are lacking any prioritization or score, so their contribution is assumed uniform [108].

### 1.3 Related studies

The current work is meant to complement existing literature on the derivation of a statistical and genetic basis of cortical surface asymmetry on reportedly healthy individuals [90, 59, 60, 114]. However, the deployed methods are largely correlated with what has been done by Naqvi et al. [72] and Claes et al. [17]. The main comparison is made with the work of Sha et al. [90], being by far the most similar. There, DK atlas parcellation was used to extract widely-used asymmetry phenotypic features, called asymmetry indices (AIs) [43, 85, 59, 87, 116], that are calculated as the scaled difference of the contra-lateral segments areas or volumes, depending on the nature of the research. The described quantity, for surface studies, is mathematically formulated as:

$$AI_i = \frac{S_{li} - S_{ri}}{S_{li} + S_{ri}}$$

## 1. INTRODUCTION

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with  $S_{li}$  and  $S_{ri}$  being the areas of the left and right hemispheric i-th segment respectively. Although the application of this method has brought forward plausible and promising results, regarding, for example, blood flow discrepancies [43], sex preference studies [87], Alzheimer's disease effect evaluation [85], or depression phenotypic traits detection [116], it has also been met with skepticism, relatively to the implied assumptions statistical validity [19]. Sha et al. [90] considered only the regions with significant SNP heritability ( $FDR > 0.05$ ), as calculated using restricted maximum likelihood estimation [113], while at the same time controlling for age, ethnicity, data collection and covariates. Subsequently, they performed a multivariate GWAS using a meta-analysis tool, called MetaPhat [65], on the filtered areas. MetaPhat joins the univariate GWAS per AI results, through the application of CCA, extracting the first canonical correlation coefficient  $r_i$ , along with a p-value of the hypothesis of all CCA coefficients being 0. The steps of snp-to-gene and functional annotation were performed using FUMA toolbox [109], that makes use of a large variety of databases and other tools, such the SNP annotation tool ANNOVAR [107] and the gene-set enrichment tool, MAGMA [23]. The lead SNPs filtering and functional characterization was specifically done with brain-related provided eQTL and chromatin datasets [90]. Additional temporal developmental analysis was made feasible, again through FUMA, and the authors identified high genetic enrichment during the early weeks of brain development, albeit with limitations in the dataset size and time resolution [54]. From the described pipeline, Sha et al. [90] were able to identify 21 genetic loci, implicated in microtubule organization and prenatal brain development. Furthermore, SNP-level significant similarities were identified with regards to schizophrenia, autism and educational attainment[90]. Because of the fact that multivariate GWAS were applied, the authors argue that no LD score analysis could be performed. However, based on the work of Naqvi et al. [72], published the same year, a connection with multivariate studies can be, as aforementioned, successfully established. The dataset used to perform GWAS was the self-proclaimed white European cohort of UK Biobank, amounting to 32256 individuals [66].

In the work of Kong et al. [59], the performed phenotypic measurements remained similar, enhanced with cortical thickness asymmetry statistics. However, the target goal did not implicate genetic factors at all and was conversely related to the first part of the current study, that is the statistical understanding of asymmetry across partition segments. The authors identified high AI dependency on age, sex and intercranial volume, raising awareness about the need of such covariates control. They managed to validate, through their analysis, global patterns of asymmetry in the inferior frontal gyrus, transverse temporal gyrus, parahippocampal gyrus, and entorhinal cortex [59], sub-regions of the inferior temporal and prefrontal cortices. Kong et al. [60] extended their research in performing GWAS on a global proxy of asymmetry, the Yakovlevian torque effect as measured using the skewness coefficients extracted from the 3D affine transformation matrix required to align a real asymmetric brain shape onto a template symmetric cortex, by merging a variety of different datasets, including UK Biobank. The authors were able to identify significant associations, without considering underlying genetics, between handedness and horizontal or vertical brain skewness, strengthening the position

that functional lateralization follows structural asymmetry. Skewness also showed significant correlations with cognitive ability, behavior, language skills and mental health. The place and the country of birth appeared highly correlated with the observed asymmetry, without them being controlled prior to the correlation analysis. BMI was also found to be considerably associated. On a genetic basis, Kong et al. [60] identified high polygenicity, low heritability and genetic overlaps with autism spectrum disorder (ASD), though without detecting any significant genetic correlation with skewness.

By far the most complete reported study on cortical asymmetry was performed by Zhao et al. [114]. They focused on local geometrical features and the alteration of brain torque during development, by considering contiguous brain slices along with skewness coefficients and average landmark asymmetry differences on regions defined by automatic parcellation Destrieux atlas [26], collecting 348 features per individual. To handle the temporal factor, specialized datasets for studying brain development during adolescence, ABCD [105], PING [53] and PNC [86], came into play [114]. By using meta-analysis applied on univariate GWAS, they were able to identify only 2 significant lead SNPs, in chromosomes 1 and 10, from the originally discovered 86 lead SNPs, after adjusting p-values for the number of traits under a strict Bonferroni threshold. Without considering this adjustment, they identified significant genetic correlations; under moderately high positive  $r_g$  ( $>0.2$ ), with Alzheimer's disease (AD), ADHD, and under negative  $r_g$  ( $<-0.2$ ) with bipolar disorder, educational attainment, intelligence and schizophrenia [114].



# Chapter 2

# Materials and Methods

In figure ?? a brief overview of the processes applied in this work is displayed. In the coming sections, each compartment will be separately analyzed.

## 2.1 General

## 2.2 Data description

In this study, targeted on humans, a cross section between the dependent cerebral asymmetry and the independent genetic factors is performed, in an effort to discover affiliated genetic regions and provide a novel understanding of the related genes cooperation. With the advent of technology capable to collect and process genomes from different individuals in relatively high speed, vast databases have been constructed. One of the main players in the data collection has been UK Biobank; a large-scale database from a randomized consortium of 500,000 individuals, whose genome has been collected, from whom 48,000 subjects had also participated in brain MRI collection process, as of December 2020 [66]. In this thesis, we exploit this newly acquired dataset to identify the key loci that are related to the human brain surface symmetry. Only healthy self-proclaimed white European individuals were considered. A large dataset of 19,654 individuals was used as the main, discovery dataset, while a smaller one, coming from a different batch, of 16,342 individuals was used as a replication dataset during GWAS.

## 2.3 Phenotype

## 2.4 MRI Shapes Normalization

The current work applies principles from general symmetry studies to model cortical asymmetry. For any of these analyses to occur, the preprocessing of 3D shapes content...

## 2. MATERIALS AND METHODS

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produced from MRI scans needs to be considered. MRI output is affected by the subject positioning and technical error [111]. Volumetric differences also increase the level of discrepancies among MRI samples. To prevent positioning and volume deviations from gravely affecting shape comparisons, a normalization is required[56]. The samples are represented as a set of landmarks  $\mathcal{G}$  of predefined dimensionality, joined together with predefined edges  $\mathcal{V}$ , forming a multiple-connected structure  $S$ , that is a graph in which there is at least one path joining any two vertices. The normalization is performed through the application of generalized Procrustes analysis (GPA). GPA is an algorithm that iteratively performs translation, scaling and rotation on a given set of structures  $S$ , given a reference  $S_0$ , aiming to minimize the euclidean distance of corresponding points. The transformed samples then belong to what it has been coined as Kendall Space [56]. Under the framework of symmetry analysis, a single hemisphere is considered to be one of the  $S$  structures. To apply any symmetry analysis, therefore, one of the individual hemispheres needs to be mirrored on the other side of the midsagittal plane, and then GPA is applied to align all hemispheres at once.

### 2.5 Shapes Partitioning

TO BE FIXED / CONTINUED The present work evaluates the brain asymmetry genetic landscape in a coarse-to-fine segmentation. The technique has been used in a number of different related studies [17][72], yielding results that are in accordance with the underlying anatomic features. The main reason behind this partitioning is the intrinsic complexity of the studied phenotype, eliciting expected differences in the genomic profiles of each cerebral cortex region. The basic assumption made is that topologically close landmarks share similar genetic background. In general though, this type of distance-based clustering is governed by the least quantity of assumptions, regarding the shape or form of the cluster [106]. The partitions' genetic juxtaposition is valuable for identifying which regions share similar significant genetic loci, highlighting the corresponding genes contribution, or showcasing the specialization of certain regions that share little to no similarities with their neighbors. Identifying the latter provides a way of mapping the developmental activation of each locus, bringing forth the opportunity to augment the results of related developmental studies [101]. Hierarchical spectral clustering (HSC) is an unsupervised method of iterative partitioning, that makes use of the distance matrix eigenvectors [74]. It results into a binary tree structure (i.e. each parent shape is partitioned into two children). In the current study, a level-4 partitioning is performed, resulting into 31 partitions. Subsequently, they are transformed to the corresponding principal components that explain 80% of the variance, not only for reasons of further dimensionality reduction, but also to ensure that the resulting traits are orthogonal, and therefore compatible for LDSC analyses

## 2.6 Symmetry Statistical analysis

Bilateral asymmetry is mainly described using three components in literature [57][102]. Directional asymmetry (DA), the main focus of this study, corresponds to the hemispheric side effect, namely how the intrinsic (i.e. genetic) properties of the studied population are manifesting across individuals. Antisymmetry, which is related to the effect where sidedness is random in a population (i.e. left-right pattern is mirrored to a right-left pattern), is not observed in the human cerebral cortex, in contrast to other internal organs positions, or organisms [73]. The third component, fluctuating asymmetry (FA), encompasses any random developmental and environmental effects, that cannot be explained with the existing knowledge. The observed deviations can be statistically linearly modeled as products of two effects, the hemisphere side studied and the individual specimen analyzed, as well as their interaction [57]. Formally, based on [100] assuming the presence of replications for each observation per individual, to account for technical error, a mixed linear model representing the aforementioned dependencies is defined as:

$$Y_{ijk} = \mu + \beta + I_i + S_{ij} + E_{ijk} \quad (2.1)$$

where  $Y_{ijk}$  is the phenotype of the  $i$ -th individual, from the  $j$ -th side, under the  $k$ -th replication,  $\mu$  and  $\beta$  are the fixed intercept and fixed side effect respectively,  $I_i \sim \mathcal{N}(0, \sigma_{ind}^2)$  is the random individual effect,  $S_{ij} \sim \mathcal{N}(0, \sigma_{FA}^2)$  is the random side and individual specific effect, matched to FA, and  $E_{ijk} \sim \mathcal{N}(0, \sigma_{ME}^2)$  is the measurement error. Replications are necessary in such analyses, in order to distinguish FA effect from measurement error. Given this definition, a way to measure the statistical significance is performed through an F-test applied on 2-way ANOVA, to relate the RSS ratios of effects to observable error terms, and of fluctuating effect to the measurement error. Extra care needs to be given on the determination of the DOF of each term, given the preprocessing applied to bring the hemispheres surfaces into Kendall shape space [57]. Given that the analysis is performed on a pair of symmetric objects, and not on a single symmetric object, this configuration is named **matching asymmetry analysis**.



## Chapter 3

# Data Preprocessing



## **Chapter 4**

# **Asymmetry Phenotypic Analysis**



## Chapter 5

# Asymmetry Genetic Analysis

### 5.1 Post-Processing

### 5.2 Meta-Analysis



# **Chapter 6**

## **Discussion**



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