

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

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Thesis submitted for the degree of  
Master of Science in Bioinformatics

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Academic year 2022

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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 . . . . .	11
1.3 Phenotypic trait analysis . . . . .	17
1.4 Breaking the complexity into parts . . . . .	18
1.5 Searching for the origin . . . . .	18
1.6 Data description . . . . .	18
1.7 Novelties based on related literature . . . . .	18
<b>2 Materials and Methods</b>	21
2.1 General . . . . .	21
2.2 Phenotype . . . . .	21
2.3 Magnetic resonance imaging (MRI) Shapes Normalization . . . . .	21
2.4 Symmetry Statistical analysis . . . . .	22
2.5 Genome . . . . .	22
<b>3 Data Preprocessing</b>	23
<b>4 Asymmetry Phenotypic Analysis</b>	25
<b>5 Asymmetry Genetic Analysis</b>	27
5.1 Post-Processing . . . . .	27
5.2 Meta-Analysis . . . . .	27
<b>6 Discussion</b>	29
<b>Bibliography</b>	31

# List of Figures

1.1	Bilateria clade [36]	2
1.2	Human cerebrum brain asymmetry	4
1.3	A classical model of radial glial cells division processes [59]	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 [44]	11
1.9	Examples of GWAS Manhattan plots [39]	14

# List of Tables

# Abbreviations

**3D** three-dimensional

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

**ANOVA** analysis of variance

**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

**GPA** generalized Procrustes analysis

**GWAS** genome wide association studies

**HSC** hierarchical spectral clustering

**L-R** left-right

**LD** linkage disequilibrium

**LDSC** LD score regression

**MAF** minor allele frequency

**ML** machine learning

**LIST OF TABLES**

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- 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. Further comparisons with other past human phenotypic characteristics studies are lastly applied.



# 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 [15, 16], 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 [28], 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 [35]. 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** [24]. 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 [5]. 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 [4]. 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 [33]. Their movement is by construction asymmetric, causing a leftward flow of extraembryonic fluid and, subsequently, asymmetric distribution of exogenously introduced proteins [56]. Both studied phenomena point to early initiation of asymmetric genes expression.

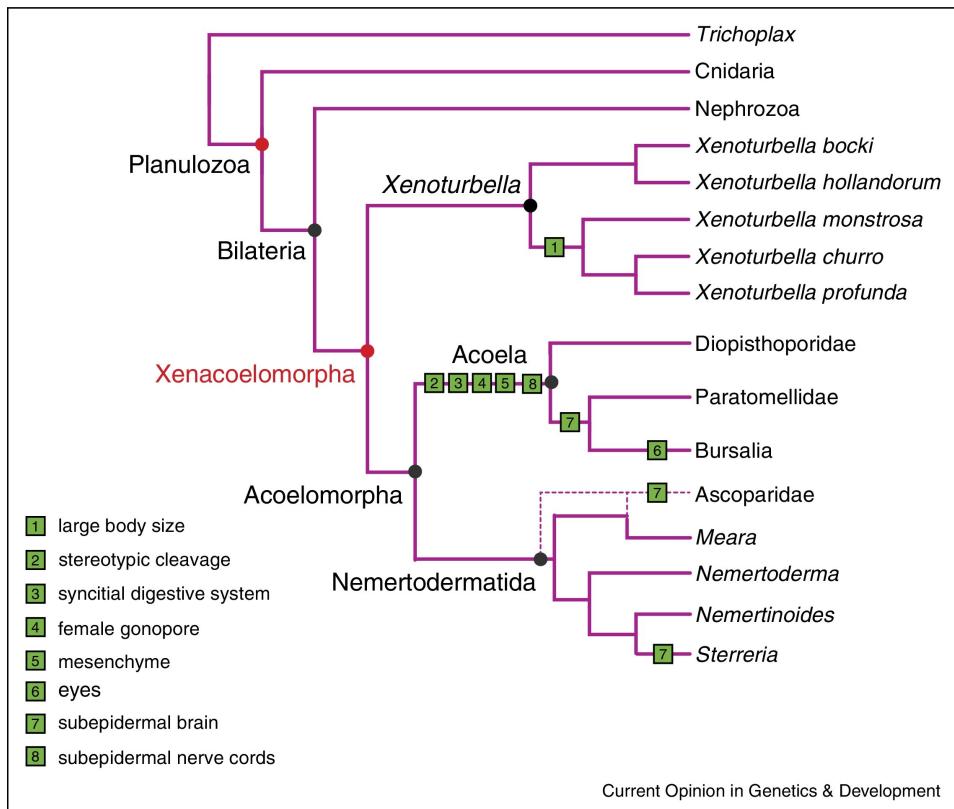


FIGURE 1.1: Species phylogenetic tree subset, displaying bilateria clade, its sister clade, Cnidaria, and the direct children[36]. Of great importance on the evolutionary studies of bilateral symmetry is the Xenacoelomorpha clade.

### 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 [24]. 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** [25]. 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 [67]. Such an asymmetry manifestation in a macroscopic level, therefore, may be the progenitor of other forms of asymmetry at a later developmental stage [62], 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 [62, 16]. 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[49].

## 1. INTRODUCTION

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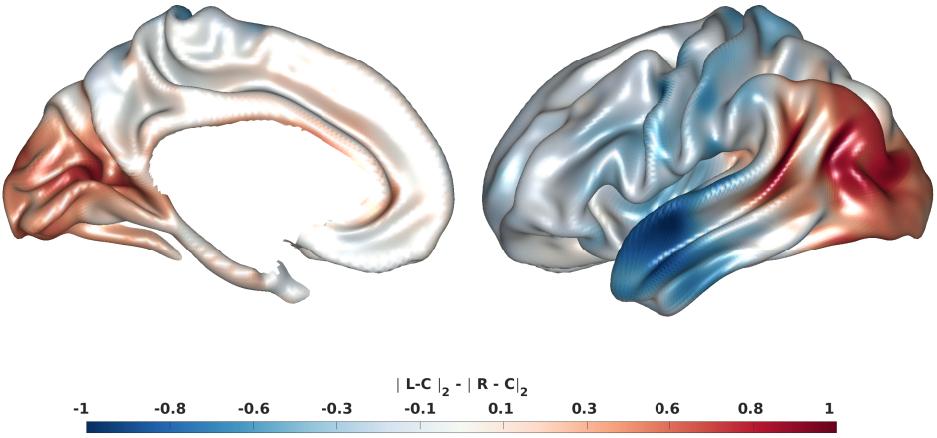


FIGURE 1.2: Illustration of human cerebrum brain asymmetry. Normalized differences of the distances of each hemisphere rescaled, rotated and averaged surface landmarks from the center of mass. See section 1.3 for more details on the preprocessing.

### 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) [32]. 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 [55], 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**[32]. 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**[59]. 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 [49]. 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 [55] and affecting the way new layers are formed. Human neurogenesis extends to the third gestation trimester, being suppressed in case of premature birth [47]. Postnatal neurogenesis is therefore presumed to be quite limited for primates [22], 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 [21]. 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 [62, 11]. 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 [77, 17]. 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 [11]. 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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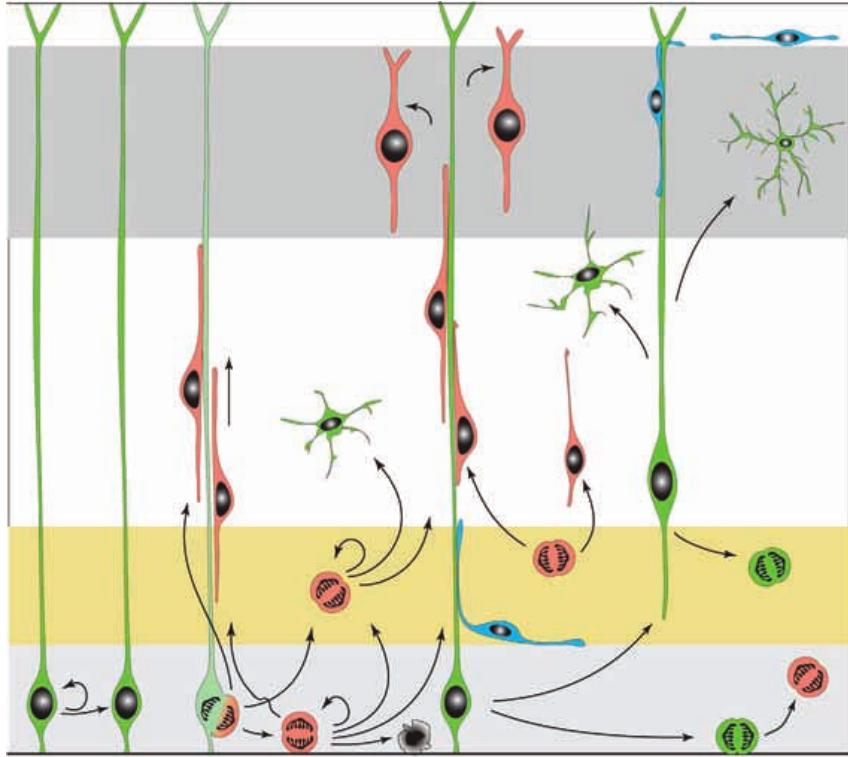


FIGURE 1.3: Illustration of a classical model of radial glial cells complex nonlinear division processes and neuronal migration [59]. From left to right: NPCs (green) originally divide symmetrically; During differentiation, NPCs become RGCs, which divide asymmetrically, generating neurons or neural progenitor 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 [23] and functional [27] 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.

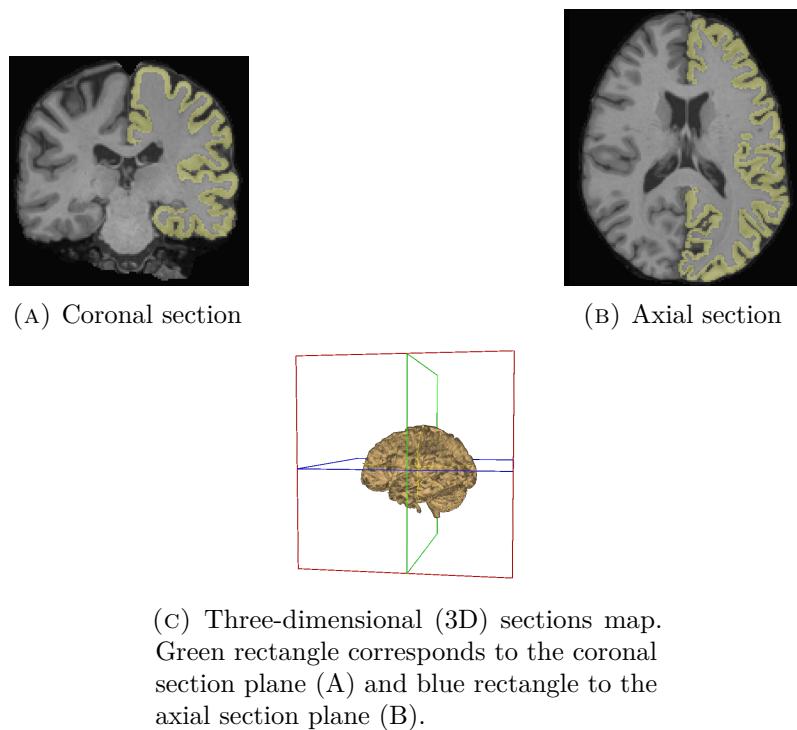


FIGURE 1.4: Gray and white matter as seen from different sections, in an MRI screening, as retrieved from Freesurfer freeview routine. The gray matter is annotated with yellow color in the right hemisphere. Non brain regions have been removed.

## 1. INTRODUCTION

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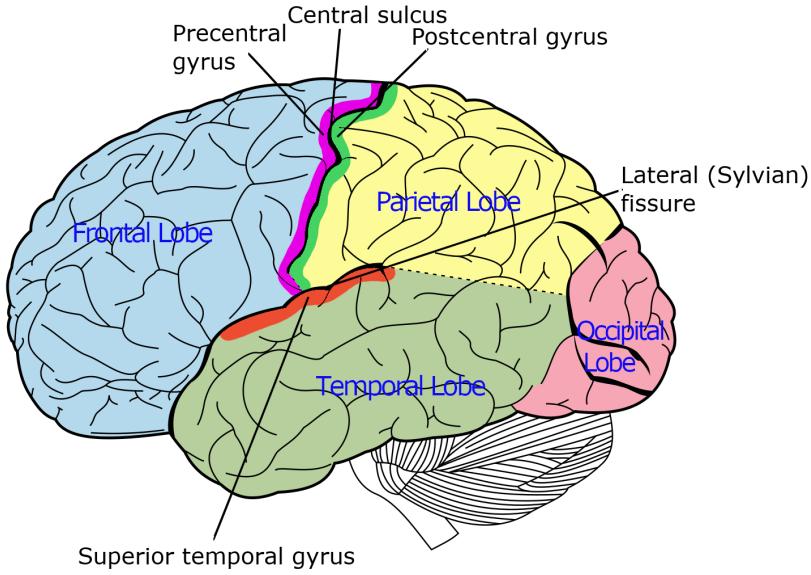


FIGURE 1.5: Cerebrum lobes (blue font) and main gyri, sulci and fissures approximate positions (black font).

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 [8] (Figure 1.6). The main regions identified are:

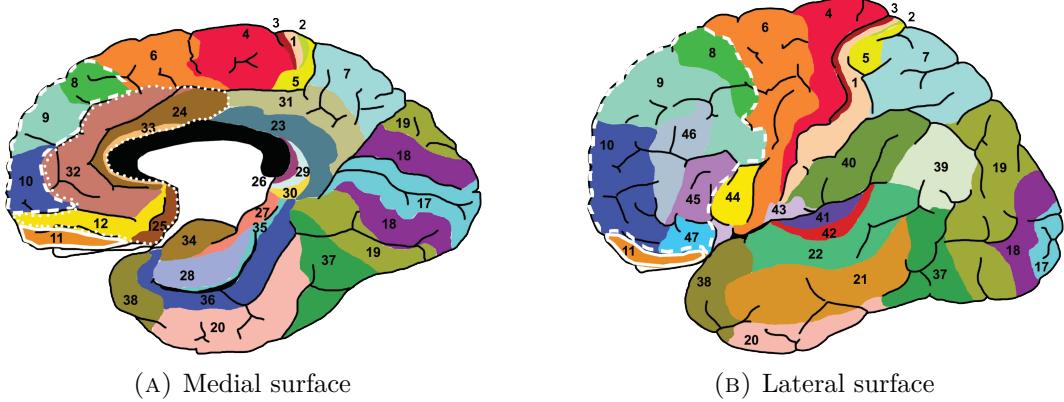


FIGURE 1.6: Brodmann map of functional partitions.

- 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 [57]. 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.[12]
  - 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 [18] 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.

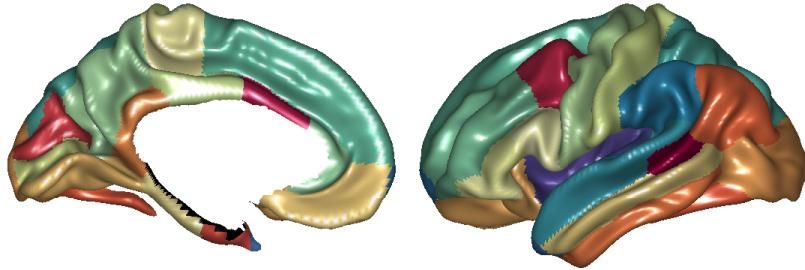


FIGURE 1.7: Desikan-Killiany atlas, mapped on the midthickness surface of the left hemisphere, with the medial (left) and the lateral (right) views displayed.[19] Different colors represent different partitions. The black region has not been mapped.

### 1.1.5 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 [37][43]. 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 [44]. 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[48]. Rising absence of the torque during aging is connected to schizophrenia and other mental disorders [61].

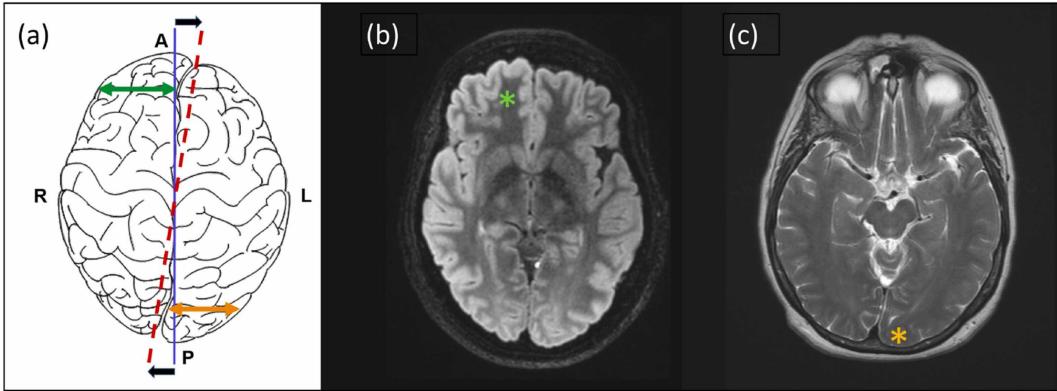


FIGURE 1.8: Yakovlevian torque schematically illustrated (a), along with its manifestation in different axial sections for a single individual (b,c) [44].

- 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** [44]. 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 [34].
- Central sulcus asymmetry: the right hemisphere central sulcus is deeper and larger [44]. Larger asymmetry appears to be correlated with attention-deficit / hyperactivity-disorder (ADHD) [45].
- 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[40]. The current study focuses on the genetic component, which has been diversely investigated across literature.

## 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. [69] In the present work,

## 1. INTRODUCTION

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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 [60], 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 deoxyribonucleic acid (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 [54]. 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 [20].

### 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) [74, 7]. LD, the non random association between alleles at different loci, is attributed to mutations, genetic drift and, concomitantly, selection [74] 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 [74]. 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 [74].

### 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  $V_p = V_g + V_e + V_d$  [75]. 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, 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

## 1. INTRODUCTION

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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 [7]. 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).

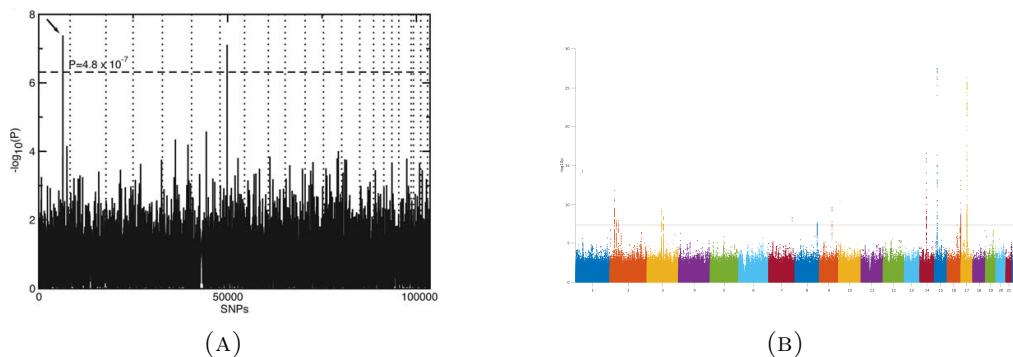


FIGURE 1.9: Examples of GWAS. In (A), the first recorded GWAS Manhattan plot [39] is displayed, where the SNP in chromosome 1 (black arrow) with the most significant effect, related to Complement H Factor Polymorphism, was identified to affect age-related macular degeneration disease propensity, one 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 [65]. 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 [65]. 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 [65]. 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. [65] 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 [53, 31].

### 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 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 [30]. 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 [69, 13]. 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 [64], genes pleiotropic effects [26] (i.e a gene affects multiple phenotypically independent biological pathways) or within-study variability [70, 38] 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 [14, 50].

### 1.2.9 LD score regression (LDSC) analysis

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 [66]. In a seminal research work from Bulik-Sullivan et al. [10], 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:

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

$\alpha$  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 [50] to incorporate D-dimensional multivariate traits:

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

The basic underlying assumptions 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 [68], assumption, by considering partitions of SNP separately and doing what is known as stratified LDSC regression. [29]
- Each SNP effect is assessed independently from the rest.
- 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. [9] 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:

$$E[z_{1j}z_{2j}|l_j] = \frac{\sqrt{N_1 N_2} \rho_g}{M} l_j + \frac{\rho N_s}{\sqrt{N_1 N_2}}$$

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 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 [9].

### 1.2.11 Generalizing to genes

### 1.2.12 Functional association

The analysis outcome requires further processing, as explained in section 5.1, to account for the main weakness of this method, that it does not consider the SNP-to-SNP effect, tackled using as proxy the notion of LD, and subsequently to topologically and functionally enhance the filtered findings. Once this additional step has been performed, a cross-trait analysis is applied, described in section 5.2, where the directional asymmetry (DA) genetic signature is compared with the signatures of phenotypic traits, analyzed in a similar study [50], the cerebral and facial shapes.

## 1.3 Phenotypic trait analysis

### 1.3.1 Summary on cortex anatomy

### 1.3.2 Dataset Description

The current study focuses on identifying the genetic landscape that composes the observed symmetry pattern, hence, subsequently, a brief introduction into how the genetic variations are being statistically modeled is provided.

Sha et al. [63]

### 1.3.3 Phenotypic partitioning

Hierarchical spectral clustering (HSC) is an unsupervised method of iterative partitioning, that makes use of the distance matrix eigenvectors [52]. 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, for reasons of further dimensionality reduction. TO BE CONTINUED

## 1. INTRODUCTION

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### 1.4 Breaking the complexity into parts

#### TO BE EXPANDED

The present work evaluates the brain asymmetry genetic landscape in a coarse-to-fine segmentation, through the application of HSC[52], discussed in subsection 1.3.3. The technique has been used in a number of different related studies [14][50], 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 [76]. 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 [72].

### 1.5 Searching for the origin

#### TO BE EXPANDED

The genomic studies are performed under the framework of SNP-by-SNP CCA.

### 1.6 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 [46]. 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.

### 1.7 Novelties based on related literature

Due to the biological importance of cerebral bilateral asymmetry, it is a subject that has been rigorously studied from multiple viewpoints.

### 1.7.1 Evolution

From an evolutionary stand, 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 [58]. 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 [6][51]. 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 of DA 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 [42].

### 1.7.2 Clinical studies



# Chapter 2

## Materials and Methods

### 2.1 General

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.

### 2.2 Phenotype

### 2.3 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 produced from MRI scans needs to be considered. MRI output is affected by the subject positioning and technical error [78]. 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[40]. 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 [40]. 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. MATERIALS AND METHODS

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### 2.4 Symmetry Statistical analysis

Bilateral asymmetry is mainly described using three components in literature [41][73]. 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 [51]. 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 [41]. Formally, based on [71] 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 [41]. 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**.

### 2.5 Genome

## 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**



# Bibliography

- [1] Eeva Aaku-Saraste, Björn Oback, Andrea Hellwig, and Wieland B. Huttner. Neuroepithelial cells downregulate their plasma membrane polarity prior to neural tube closure and neurogenesis. *Mechanisms of Development*, 69(1-2):71–81, dec 1997. ISSN 0925-4773. doi: 10.1016/S0925-4773(97)00156-1.
- [2] Reem S. Abu-Rustum, M. Fouad Ziade, and Sameer E. Abu-Rustum. Reference Values for the Right and Left Fetal Choroid Plexus at 11 to 13 Weeks. *Journal of Ultrasound in Medicine*, 32(9):1623–1629, sep 2013. ISSN 1550-9613. doi: 10.7863/ULTRA.32.9.1623. URL <https://onlinelibrary.wiley.com/doi/full/10.7863/ultra.32.9.1623>  
<https://onlinelibrary.wiley.com/doi/abs/10.7863/ultra.32.9.1623>  
<https://onlinelibrary.wiley.com/doi/10.7863/ultra.32.9.1623>.
- [3] David Alejandro Gonzalez-Chica, João Luiz Bastos, Rodrigo Pereira Duquia, Renan Rangel Bonamigo, and Jeovany Martínez-Mesa. EPIDEMIOLOGY AND BIOSTATISTICS APPLIED TO DERMATOLOGY. *An Bras Dermatol*, 90(4):523–531, 2015. doi: 10.1590/abd1806-4841.20154289. URL <http://dx.doi.org/10.1590/abd1806-4841.20154289>.
- [4] Sherry Aw and Michael Levin. Is left-right asymmetry a form of planar cell polarity? *Development*, 136(3):355–366, feb 2009. ISSN 0950-1991. doi: 10.1242/DEV.015974. URL <https://journals.biologists.com/dev/article/136/3/355/65515/Is-left-right-asymmetry-a-form-of-planar-cell>.
- [5] Sherry Aw, Dany S. Adams, Dayong Qiu, and Michael Levin. H,K-ATPase protein localization and Kir4.1 function reveal concordance of three axes during early determination of left-right asymmetry. *Mechanisms of Development*, 125(3-4):353–372, mar 2008. ISSN 0925-4773. doi: 10.1016/J.MOD.2007.10.011.
- [6] Antoine Balzeau, Emmanuel Gilissen, and Dominique Grimaud-Hervé. Shared Pattern of Endocranial Shape Asymmetries among Great Apes, Anatomically Modern Humans, and Fossil Hominins. *PLoS ONE*, 7(1):e29581, jan 2012. ISSN 1932-6203. doi: 10.1371/JOURNAL.PONE.0029581. URL <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0029581>.
- [7] John W. Belmont, Paul Hardenbol, Thomas D. Willis, Fuli Yu, Huanming Yang, Lan Yang Ch'Ang, Wei Huang, Bin Liu, Yan Shen, Paul Kwong Hang Tam,

## BIBLIOGRAPHY

---

Lap Chee Tsui, Mary Miu Yee Waye, Jeffrey Tze Fei Wong, Changqing Zeng, Qingrun Zhang, Mark S. Chee, Luana M. Galver, Semyon Kruglyak, Sarah S. Murray, Arnold R. Oliphant, Alexandre Montpetit, Fanny Chagnon, Vincent Ferretti, Martin Leboeuf, Michael S. Phillips, Andrei Verner, Shenghui Duan, Denise L. Lind, Raymond D. Miller, John Rice, Nancy L. Saccone, Patricia Taillon-Miller, Ming Xiao, Akihiro Sekine, Koki Sorimachi, Yoichi Tanaka, Tatsuhiko Tsunoda, Eiji Yoshino, David R. Bentley, Sarah Hunt, Don Powell, Houcan Zhang, Ichiro Matsuda, Yoshimitsu Fukushima, Darryl R. Macer, Eiko Suda, Charles Rotimi, Clement A. Adebamowo, Toyin Aniagwu, Patricia A. Marshall, Olayemi Matthew, Chibuzor Nkwodimma, Charmaine D.M. Royal, Mark F. Leppert, Missy Dixon, Fiona Cunningham, Ardavan Kanani, Gudmundur A. Thorisson, Peter E. Chen, David J. Cutler, Carl S. Kashuk, Peter Donnelly, Jonathan Marchini, Gilean A.T. McVean, Simon R. Myers, Lon R. Cardon, Andrew Morris, Bruce S. Weir, James C. Mullikin, Michael Feolo, Mark J. Daly, Renzong Qiu, Alastair Kent, Georgia M. Dunston, Kazuto Kato, Norio Niikawa, Jessica Watkin, Richard A. Gibbs, Erica Sodergren, George M. Weinstock, Richard K. Wilson, Lucinda L. Fulton, Jane Rogers, Bruce W. Birren, Hua Han, Hongguang Wang, Martin Godbout, John C. Wallenburg, Paul L'Archevêque, Guy Bellemare, Kazuo Todani, Takashi Fujita, Satoshi Tanaka, Arthur L. Holden, Francis S. Collins, Lisa D. Brooks, Jean E. McEwen, Mark S. Guyer, Elke Jordan, Jane L. Peterson, Jack Spiegel, Lawrence M. Sung, Lynn F. Zacharia, Karen Kennedy, Michael G. Dunn, Richard Seabrook, Mark Shillito, Barbara Skene, John G. Stewart, David L. Valle, Ellen Wright Clayton, Lynn B. Jorde, Aravinda Chakravarti, Mildred K. Cho, Troy Duster, Morris W. Foster, Maria Jasperse, Bartha M. Knoppers, Pui Yan Kwok, Julio Licinio, Jeffrey C. Long, Pilar Ossorio, Vivian Ota Wang, Charles N. Rotimi, Patricia Spallone, Sharon F. Terry, Eric S. Lander, Eric H. Lai, Deborah A. Nickerson, Gonçalo R. Abecasis, David Altshuler, Michael Boehnke, Panos Deloukas, Julie A. Douglas, Stacey B. Gabriel, Richard R. Hudson, Thomas J. Hudson, Leonid Kruglyak, Yusuke Nakamura, Robert L. Nussbaum, Stephen F. Schaffner, Stephen T. Sherry, Lincoln D. Stein, and Toshihiro Tanaka. The International HapMap Project. *Nature* 2004 426:6968, 426(6968):789–796, dec 2003. ISSN 1476-4687. doi: 10.1038/nature02168. URL <https://www.nature.com/articles/nature02168>.

- [8] K Brodmann. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Johann Ambrosius Barth, Leipzig, 1909.
- [9] Brendan Bulik-Sullivan, Hilary K. Finucane, Verner Anttila, Alexander Gusev, Felix R. Day, Po Ru Loh, Laramie Duncan, John R.B. Perry, Nick Patterson, Elise B. Robinson, Mark J. Daly, Alkes L. Price, and Benjamin M. Neale. An atlas of genetic correlations across human diseases and traits. *Nature Genetics* 2015 47:11, 47(11):1236–1241, sep 2015. ISSN 1546-1718. doi: 10.1038/ng.3406. URL <https://www.nature.com/articles/ng.3406>.

- [10] Brendan Bulik-Sullivan, Po Ru Loh, Hilary K. Finucane, Stephan Ripke, Jian Yang, Nick Patterson, Mark J. Daly, Alkes L. Price, Benjamin M. Neale, Aiden Corvin, James T.R. Walters, Kai How Farh, Peter A. Holmans, Phil Lee, David A. Collier, Hailiang Huang, Tune H. Pers, Ingrid Agartz, Esben Agerbo, Margot Albus, Madeline Alexander, Farooq Amin, Silviu A. Bacanu, Martin Begemann, Richard A. Belliveau, Judit Bene, Sarah E. Bergen, Elizabeth Bevilacqua, Tim B. Bigdeli, Donald W. Black, Richard Bruggeman, Nancy G. Buccola, Randy L. Buckner, William Byerley, Wiepke Cahn, Guiqing Cai, Murray J. Cairns, Dominique Campion, Rita M. Cantor, Vaughan J. Carr, Noa Carrera, Stanley V. Catts, Kimberly D. Chambert, Raymond C.K. Chan, Ronald Y.L. Chen, Eric Y.H. Chen, Wei Cheng, Eric F.C. Cheung, Siow Ann Chong, C. Robert Cloninger, David Cohen, Nadine Cohen, Paul Cormican, Nick Craddock, Benedicto Crespo-Facorro, James J. Crowley, David Curtis, Michael Davidson, Kenneth L. Davis, Franziska Degenhardt, Jurgen Del Favero, Lynn E. DeLisi, Ditte Demontis, Dimitris Dikeos, Timothy Dinan, Srdjan Djurovic, Gary Donohoe, Elodie Drapeau, Jubao Duan, Frank Dudbridge, Naser Durmishi, Peter Eichhammer, Johan Eriksson, Valentina Escott-Price, Laurent Essioux, Ayman H. Fanous, Martilius S. Farrell, Josef Frank, Lude Franke, Robert Freedman, Nelson B. Freimer, Marion Friedl, Joseph I. Friedman, Menachem Fromer, Giulio Genovese, Lyudmila Georgieva, Elliot S. Gershon, Ina Giegling, Paola Giusti-Rodríguez, Stephanie Godard, Jacqueline I. Goldstein, Vera Golimbet, Srihari Gopal, Jacob Gratten, Lieuwe De Haan, Christian Hammer, Marian L. Hamshere, Mark Hansen, Thomas Hansen, Vahram Haroutunian, Annette M. Hartmann, Frans A. Henskens, Stefan Herms, Joel N. Hirschhorn, Per Hoffmann, Andrea Hofman, Mads V. Hollegaard, David M. Hougaard, Masashi Ikeda, Inge Joa, Antonio Juliá, René S. Kahn, Luba Kalaydjieva, Sena Karachanak-Yankova, Juha Karjalainen, David Kavanagh, Matthew C. Keller, Brian J. Kelly, James L. Kennedy, Andrey Khrunin, Yunjung Kim, Janis Klovins, James A. Knowles, Bettina Konte, Vaidutis Kucinskas, Zita Ausrele Kucinskiene, Hana Kuzelova-Ptackova, Anna K. Kähler, Claudine Laurent, Jimmy Lee Chee Keong, S. Hong Lee, Sophie E. Legge, Bernard Lerer, Miaoxin Li, Tao Li, Kung Yee Liang, Jeffrey Lieberman, Svetlana Limborska, Carmel M. Loughland, Jan Lubinski, Jouko Lönnqvist, Milan Macek, Patrik K.E. Magnusson, Brion S. Maher, Wolfgang Maier, Jacques Mallet, Sara Marsal, Manuel Mattheisen, Morten Mattingsdal, Robert W. McCarley, Colm McDonald, Andrew M. McIntosh, Sandra Meier, Carin J. Meijer, Bela Melegh, Ingrid Melle, Raquelle I. Mesholam-Gately, Andres Metspalu, Patricia T. Michie, Lili Milani, Vihra Milanova, Younes Mokrab, Derek W. Morris, Ole Mors, Kieran C. Murphy, Robin M. Murray, Inez Myint-Germeys, Bertram Müller-Myhsok, Mari Nelis, Igor Nenadic, Deborah A. Nertney, Gerald Nestadt, Kristin K. Nicodemus, Liene Nikitina-Zake, Laura Nisenbaum, Annelie Nordin, Eadbhard O'Callaghan, Colm O'Dushlaine, F. Anthony O'Neill, Sang Yun Oh, Ann Olincy, Line Olsen, Jim Van Os, Christos Pantelis, George N. Papadimitriou, Sergi Papiol, Elena Parkhomenko, Michele T. Pato, Tiina Paunio, Milica Pejovic-Milovancevic, Diana O. Perkins, Olli Pietiläinen, Jonathan Pimm, Andrew J. Pocklington, John Powell, Ann E. Pulver,

## BIBLIOGRAPHY

---

- Shaun M. Purcell, Digby Quested, Henrik B. Rasmussen, Abraham Reichenberg, Mark A. Reimers, Alexander L. Richards, Joshua L. Roffman, Panos Roussos, Douglas M. Ruderfer, Veikko Salomaa, Alan R. Sanders, Ulrich Schall, Christian R. Schubert, Thomas G. Schulze, Sibylle G. Schwab, Edward M. Scolnick, Rodney J. Scott, Larry J. Seidman, Jianxin Shi, Engilbert Sigurdsson, Teimuraz Silagadze, Jeremy M. Silverman, Kang Sim, Petr Slominsky, Jordan W. Smoller, Hon Cheong So, Chris C.A. Spencer, Eli A. Stahl, Hreinn Stefansson, Stacy Steinberg, Elisabeth Stogmann, Richard E. Straub, Eric Strengman, Jana Strohmaier, T. Scott Stroup, Mythily Subramaniam, Jaana Suvisaari, Dragan M. Svrankic, Jin P. Szatkiewicz, Erik Söderman, Srinivas Thirumalai, Draga Toncheva, Paul A. Tooney, Sarah Tosato, Juha Veijola, John Waddington, Dermot Walsh, Dai Wang, Qiang Wang, Bradley T. Webb, Mark Weiser, Dieter B. Wildenauer, Nigel M. Williams, Stephanie Williams, Stephanie H. Witt, Aaron R. Wolen, Emily H.M. Wong, Brandon K. Wormley, Jing Qin Wu, Hualin Simon Xi, Clement C. Zai, Xuebin Zheng, Fritz Zimprich, Naomi R. Wray, Kari Stefansson, Peter M. Visscher, Rolf Adolfsson, Ole A. Andreassen, Douglas H.R. Blackwood, Elvira Bramon, Joseph D. Buxbaum, Anders D. Børglum, Sven Cichon, Ariel Darvasi, Enrico Domenici, Hannelore Ehrenreich, Tõnu Esko, Pablo V. Gejman, Michael Gill, Hugh Gurling, Christina M. Hultman, Nakao Iwata, Assen V. Jablensky, Erik G. Jönsson, Kenneth S. Kendler, George Kirov, Jo Knight, Todd Lencz, Douglas F. Levinson, Qingqin S. Li, Jianjun Liu, Anil K. Malhotra, Steven A. McCarroll, Andrew McQuillin, Jennifer L. Moran, Preben B. Mortensen, Bryan J. Mowry, Markus M. Nöthen, Roel A. Ophoff, Michael J. Owen, Aarno Palotie, Carlos N. Pato, Tracey L. Petryshen, Danielle Posthuma, Marcella Rietschel, Brien P. Riley, Dan Rujescu, Pak C. Sham, Pamela Sklar, David St Clair, Daniel R. Weinberger, Jens R. Wendland, Thomas Werger, Patrick F. Sullivan, and Michael C. O'Donovan. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics* 2015 47:3, 47(3):291–295, feb 2015. ISSN 1546-1718. doi: 10.1038/ng.3211. URL <https://www.nature.com/articles/ng.3211>.
- [11] Monica Laura Cara, Ioana Streată, Ana Maria Bugă, and Dominic Gabriel Iliescu. Developmental Brain Asymmetry. The Good and the Bad Sides. *Symmetry* 2022, Vol. 14, Page 128, 14(1):128, jan 2022. ISSN 2073-8994. doi: 10.3390/SYM14010128. URL <https://www.mdpi.com/2073-8994/14/1/128> [htmhttps://www.mdpi.com/2073-8994/14/1/128](https://www.mdpi.com/2073-8994/14/1/128).
- [12] Mattia Chini and Ileana L. Hanganu-Opatz. Prefrontal Cortex Development in Health and Disease: Lessons from Rodents and Humans. *Trends in Neurosciences*, 44(3):227–240, mar 2021. ISSN 0166-2236. doi: 10.1016/J.TINS.2020.10.017.
- [13] Anna Cichonska, Juho Rousu, Pekka Marttinen, Antti J. Kangas, Pasi Soininen, Terho Lehtimäki, Olli T. Raitakari, Marjo Riitta Järvelin, Veikko Salomaa, Mika Ala-Korpela, Samuli Ripatti, and Matti Pirinen. metaCCA: summary statistics-based multivariate meta-analysis of genome-wide association studies

- using canonical correlation analysis. *Bioinformatics*, 32(13):1981–1989, jul 2016. ISSN 1367-4803. doi: 10.1093/BIOINFORMATICS/BTW052. URL <https://academic.oup.com/bioinformatics/article/32/13/1981/1742730>.
- [14] Peter Claes, Jasmien Roosenboom, Julie D White, Tomek Swigut, Dzemila Sero, Jiarui Li, Myoung Keun Lee, Arslan Zaidi, Brooke C Mattern, Corey Liebowitz, Laurel Pearson, Tomás González, Elizabeth J Leslie, Jenna C Carlson, Ekaterina Orlova, Paul Suetens, Dirk Vandermeulen, Eleanor Feingold, Mary L Marazita, John R Shaffer, Joanna Wysocka, Mark D Shriver, and Seth M Weinberg. Genome-wide mapping of global-to-local genetic effects on human facial shape. *Nature Genetics*, 50(3):414–423, 2018. ISSN 1546-1718. doi: 10.1038/s41588-018-0057-4. URL <https://doi.org/10.1038/s41588-018-0057-4>.
  - [15] Miguel L. Concha, Isaac H. Bianco, and Stephen W. Wilson. Encoding asymmetry within neural circuits. *Nature Reviews Neuroscience* 2012 13:12, 13(12):832–843, nov 2012. ISSN 1471-0048. doi: 10.1038/nrn3371. URL <https://www.nature.com/articles/nrn3371>.
  - [16] Michael C. Corballis. The evolution and genetics of cerebral asymmetry. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 364 (1519):867, 2009. ISSN 14712970. doi: 10.1098/RSTB.2008.0232. URL <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2666079/>.
  - [17] Örjan de Manzano and Fredrik Ullén. Same Genes, Different Brains: Neuroanatomical Differences Between Monozygotic Twins Discordant for Musical Training. *Cerebral Cortex*, 28(1):387–394, jan 2018. ISSN 1047-3211. doi: 10.1093/CERCOR/BHX299. URL <https://academic.oup.com/cercor/article/28/1/387/4608057>.
  - [18] Rahul S. Desikan, Florent Ségonne, Bruce Fischl, Brian T. Quinn, Bradford C. Dickerson, Deborah Blacker, Randy L. Buckner, Anders M. Dale, R. Paul Maguire, Bradley T. Hyman, Marilyn S. Albert, and Ronald J. Killiany. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, 31(3):968–980, jul 2006. ISSN 1053-8119. doi: 10.1016/J.NEUROIMAGE.2006.01.021.
  - [19] Erin W. Dickie, Alan Anticevic, Dawn E. Smith, Timothy S. Coalson, Mathuvanthy Manogaran, Navona Calarco, Joseph D. Viviano, Matthew F. Glasser, David C. Van Essen, and Aristotle N. Voineskos. ciftify: A framework for surface-based analysis of legacy MR acquisitions. *NeuroImage*, 197:818, aug 2019. ISSN 10959572. doi: 10.1016/J.NEUROIMAGE.2019.04.078. URL [/pmc/articles/PMC6675413//pmc/articles/PMC6675413/?report=abstract](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6675413/)<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6675413/>.
  - [20] Ian Dunham, Anshul Kundaje, Shelley F. Aldred, Patrick J. Collins, Carrie A. Davis, Francis Doyle, Charles B. Epstein, Seth Frietze, Jennifer Harrow, Rajinder Kaul, Jainab Khatun, Bryan R. Lajoie, Stephen G. Landt, Bum Kyu Lee,

## BIBLIOGRAPHY

---

Florencia Pauli, Kate R. Rosenbloom, Peter Sabo, Alexias Safi, Amartya Sanyal, Noam Shores, Jeremy M. Simon, Lingyun Song, Nathan D. Trinklein, Robert C. Altshuler, Ewan Birney, James B. Brown, Chao Cheng, Sarah Djebali, Xianjun Dong, Jason Ernst, Terrence S. Furey, Mark Gerstein, Belinda Giardine, Melissa Greven, Ross C. Hardison, Robert S. Harris, Javier Herrero, Michael M. Hoffman, Sowmya Iyer, Manolis Kellis, Pouya Kheradpour, Timo Lassmann, Qunhua Li, Xinying Lin, Georgi K. Marinov, Angelika Merkel, Ali Mortazavi, Stephen C.J. Parker, Timothy E. Reddy, Joel Rozowsky, Felix Schlesinger, Robert E. Thurman, Jie Wang, Lucas D. Ward, Troy W. Whitfield, Steven P. Wilder, Weisheng Wu, Hualin S. Xi, Kevin Y. Yip, Jiali Zhuang, Bradley E. Bernstein, Eric D. Green, Chris Gunter, Michael Snyder, Michael J. Pazin, Rebecca F. Lowdon, Laura A.L. Dillon, Leslie B. Adams, Caroline J. Kelly, Julia Zhang, Judith R. Wexler, Peter J. Good, Elise A. Feingold, Gregory E. Crawford, Job Dekker, Laura Elnitski, Peggy J. Farnham, Morgan C. Giddings, Thomas R. Gingeras, Roderic Guigó, Timothy J. Hubbard, W. James Kent, Jason D. Lieb, Elliott H. Margulies, Richard M. Myers, John A. Stamatoyannopoulos, Scott A. Tenenbaum, Zhiping Weng, Kevin P. White, Barbara Wold, Yanbao Yu, John Wrobel, Brian A. Risk, Harsha P. Gunawardena, Heather C. Kuiper, Christopher W. Maier, Ling Xie, Xian Chen, Tarjei S. Mikkelsen, Shawn Gillespie, Alon Goren, Oren Ram, Xiaolan Zhang, Li Wang, Robbyn Issner, Michael J. Coyne, Timothy Durham, Manching Ku, Thanh Truong, Matthew L. Eaton, Alex Dobin, Andrea Tanzer, Julien Lagarde, Wei Lin, Chenghai Xue, Brian A. Williams, Chris Zaleski, Maik Röder, Felix Kokocinski, Rehab F. Abdelhamid, Tyler Alioto, Igor Antoshechkin, Michael T. Baer, Philippe Batut, Ian Bell, Kimberly Bell, Sudipto Chakrabortty, Jacqueline Chrast, Joao Curado, Thomas Derrien, Jorg Drenkow, Erica Dumais, Jackie Dumais, Radha Duttagupta, Megan Fastuca, Kata Fejes-Toth, Pedro Ferreira, Sylvain Foissac, Melissa J. Fullwood, Hui Gao, David Gonzalez, Assaf Gordon, Cédric Howald, Sonali Jha, Rory Johnson, Philipp Kapranov, Brandon King, Colin Kingswood, Guoliang Li, Oscar J. Luo, Eddie Park, Jonathan B. Preall, Kimberly Presaud, Paolo Ribeca, Daniel Robyr, Xiaoan Ruan, Michael Sammeth, Kuljeet Singh Sandhu, Lorain Schaeffer, Lei Hoon See, Atif Shahab, Jorgen Skancke, Ana Maria Suzuki, Hazuki Takahashi, Hagen Tilgner, Diane Trout, Nathalie Walters, Huaien Wang, Yoshihide Hayashizaki, Alexandre Reymond, Stylianos E. Antonarakis, Gregory J. Hannon, Yijun Ruan, Piero Carninci, Cricket A. Sloan, Katrina Learned, Venkat S. Malladi, Matthew C. Wong, Galt P. Barber, Melissa S. Cline, Timothy R. Dreszer, Steven G. Heitner, Donna Karolchik, Vanessa M. Kirkup, Laurence R. Meyer, Jeffrey C. Long, Morgan Maddren, Brian J. Raney, Linda L. Grasfeder, Paul G. Giresi, Anna Battenhouse, Nathan C. Sheffield, Kimberly A. Showers, Darin London, Akshay A. Bhinge, Christopher Shestak, Matthew R. Schaner, Seul Ki Kim, Zhuzhu Z. Zhang, Piotr A. Mieczkowski, Joanna O. Mieczkowska, Zheng Liu, Ryan M. McDaniell, Yunyun Ni, Naim U. Rashid, Min Jae Kim, Sheera Adar, Zhancheng Zhang, Tianyuan Wang, Deborah Winter, Damian Keefe, Vishwanath R. Iyer, Meizhen Zheng, Ping Wang, Jason Gertz, Jost Vielmetter, E. Christopher Partridge, Katherine E. Varley, Clarke Gasper, Anita Bansal, Shirley Pepke,

## BIBLIOGRAPHY

---

Preti Jain, Henry Amrhein, Kevin M. Bowling, Michael Anaya, Marie K. Cross, Michael A. Muratet, Kimberly M. Newberry, Kenneth McCue, Amy S. Ne-smith, Katherine I. Fisher-Aylor, Barbara Pusey, Gilberto DeSalvo, Stephanie L. Parker, Sreeram Balasubramanian, Nicholas S. Davis, Sarah K. Meadows, Tracy Eggleston, J. Scott Newberry, Shawn E. Levy, Devin M. Absher, Wing H. Wong, Matthew J. Blow, Axel Visel, Len A. Pennachio, Hanna M. Petrykowska, Alexej Abyzov, Bronwen Aken, Daniel Barrell, Gemma Barson, Andrew Berry, Alexandra Bignell, Veronika Boychenko, Giovanni Bussotti, Claire Davidson, Gloria Despacio-Reyes, Mark Diekhans, Iakes Ezkurdia, Adam Frankish, James Gilbert, Jose Manuel Gonzalez, Ed Griffiths, Rachel Harte, David A. Hendrix, Toby Hunt, Irwin Jungreis, Mike Kay, Ekta Khurana, Jing Leng, Michael F. Lin, Jane Loveland, Zhi Lu, Deepa Manthravadi, Marco Mariotti, Jonathan Mudge, Gaurab Mukherjee, Cedric Notredame, Baikang Pei, Jose Manuel Rodriguez, Gary Saunders, Andrea Sboner, Stephen Searle, Cristina Sisu, Catherine Snow, Charlie Steward, Electra Tapanari, Michael L. Tress, Marijke J. Van Baren, Stefan Washietl, Laurens Wilming, Amonida Zadissa, Zhengdong Zhang, Michael Brent, David Haussler, Alfonso Valencia, Nick Addleman, Roger P. Alexander, Raymond K. Auerbach, Suganthi Balasubramanian, Keith Bettinger, Nitin Bhardwaj, Alan P. Boyle, Alina R. Cao, Philip Cayting, Alexandra Charos, Yong Cheng, Catharine Eastman, Ghia Euskirchen, Joseph D. Fleming, Fabian Grubert, Lukas Habegger, Manoj Hariharan, Arif Harmanci, Sushma Iyengar, Victor X. Jin, Konrad J. Karczewski, Maya Kasowski, Phil Lacroute, Hugo Lam, Nathan Lamarre-Vincent, Jin Lian, Marianne Lindahl-Allen, Renqiang Min, Benoit Miotto, Hannah Monahan, Zarmik Moqtaderi, Xinmeng J. Mu, Henriette O'Geen, Zhengqing Ouyang, Dorrelyn Patacsil, Debasish Raha, Lucia Ramirez, Brian Reed, Minyi Shi, Teri Slifer, Heather Witt, Linfeng Wu, Xiaoqin Xu, Koon Kiu Yan, Xinqiong Yang, Kevin Struhl, Sherman M. Weissman, Luiz O. Penalva, Subhradip Karmakar, Raj R. Bhanvadia, Alina Choudhury, Marc Domanus, Lijia Ma, Jennifer Moran, Alec Victorsen, Thomas Auer, Lazaro Centanin, Michael Eichenlaub, Franziska Gruhl, Stephan Heermann, Burkhard Hoeckendorf, Daigo Inoue, Tanja Kellner, Stephan Kirchmaier, Claudia Mueller, Robert Reinhardt, Lea Schertel, Stephanie Schneider, Rebecca Sinn, Beate Wittbrodt, Jochen Wittbrodt, Gaurav Jain, Gayathri Balasundaram, Daniel L. Bates, Rachel Byron, Theresa K. Canfield, Morgan J. Diegel, Douglas Dunn, Abigail K. Ebersol, Tristan Frum, Kavita Garg, Erica Gist, R. Scott Hansen, Lisa Boatman, Eric Haugen, Richard Humbert, Audra K. Johnson, Ericka M. Johnson, Tattyana V. Kutyavin, Kristen Lee, Dimitra Lotakis, Matthew T. Maurano, Shane J. Neph, Fiedencio V. Neri, Eric D. Nguyen, Hongzhu Qu, Alex P. Reynolds, Vaughn Roach, Eric Rynes, Minerva E. Sanchez, Richard S. Sandstrom, Anthony O. Shafer, Andrew B. Stergachis, Sean Thomas, Benjamin Vernot, Jeff Vierstra, Shinny Vong, Hao Wang, Molly A. Weaver, Yongqi Yan, Miaohua Zhang, Joshua M. Akey, Michael Bender, Michael O. Dorschner, Mark Groudine, Michael J. MacCoss, Patrick Navas, George Stamatoyannopoulos, Kathryn Beal, Alvis Brazma, Paul Flieck, Nathan Johnson, Margus Lukk, Nicholas M. Luscombe, Daniel Sobral, Juan M. Vaquerizas, Serafim Batzoglou,

## BIBLIOGRAPHY

---

- Arend Sidow, Nadine Hussami, Sofia Kyriazopoulou-Panagiotopoulou, Max W. Libbrecht, Marc A. Schaub, Webb Miller, Peter J. Bickel, Balazs Banfai, Nathan P. Boley, Haiyan Huang, Jingyi Jessica Li, William Stafford Noble, Jeffrey A. Bilmes, Orion J. Buske, Avinash D. Sahu, Peter V. Kharchenko, Peter J. Park, Dannon Baker, James Taylor, and Lucas Lochovsky. An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012 489:7414, 489(7414):57–74, sep 2012. ISSN 1476-4687. doi: 10.1038/nature11247. URL <https://www.nature.com/articles/nature11247>.
- [21] Laura I. Van Dyck and Eric M. Morrow. Genetic control of postnatal human brain growth. *Current opinion in neurology*, 30(1):114, 2017. ISSN 14736551. doi: 10.1097/WCO.00000000000000405. URL [/pmc/articles/PMC5340196/](https://pmc.ncbi.nlm.nih.gov/pmc/articles/PMC5340196/)?report=abstract<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5340196/>.
  - [22] Aurélie Ernst and Jonas Frisén. Adult Neurogenesis in Humans—Common and Unique Traits in Mammals. *PLoS Biology*, 13(1), 2015. ISSN 15457885. doi: 10.1371/JOURNAL.PBIO.1002045. URL [/pmc/articles/PMC4306487/](https://pmc.ncbi.nlm.nih.gov/pmc/articles/PMC4306487/)?report=abstract<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4306487/>.
  - [23] Mark F. Bear, Barry W. Connors, and Michael A. Paradiso. Appendix: An illustrated guide to human neuroanatomy. In *Exploring the brain*, chapter 7, pages 205–262. Wolters Kluwer, 4th edition, 2016. ISBN 0781778174.
  - [24] Mark F. Bear, Barry W. Connors, and Michael A. Paradiso. Formation of the Neural Tube—Three Primary Brain Vesicles. In *Exploring the brain*, chapter 7, pages 193–196. Wolters Kluwer, 4th edition, 2016. ISBN 0781778174.
  - [25] Mark F. Bear, Barry W. Connors, and Michael A. Paradiso. Differentiation of the Forebrain. In *Exploring the brain*, chapter 7, pages 196–199. Wolters Kluwer, 4th edition, 2016. ISBN 0781778174.
  - [26] Samuel B. Fernandes, Kevin S. Zhang, Tiffany M. Jamann, and Alexander E. Lipka. How Well Can Multivariate and Univariate GWAS Distinguish Between True and Spurious Pleiotropy? *Frontiers in Genetics*, 11:1747, jan 2021. ISSN 16648021. doi: 10.3389/FGENE.2020.602526/BIBTEX.
  - [27] Alice Ferng and Dimitrios Mytilinaios. Brodmann areas: Anatomy and functions | Kenhub, 2022. URL <https://www.kenhub.com/en/library/anatomy/brodmann-areas>.
  - [28] John R. Finnerty. The origins of axial patterning in the metazoa: how old is bilateral symmetry? *International Journal of Developmental Biology*, 47 (7-8):523–529, dec 2003. ISSN 0214-6282. doi: 10.1387/IJDB.14756328. URL <http://www.ijdb.ehu.es/web/paper/14756328>.

- 
- [29] Hilary K. Finucane, Brendan Bulik-Sullivan, Alexander Gusev, Gosia Trynka, Yakir Reshef, Po Ru Loh, Verner Anttila, Han Xu, Chongzhi Zang, Kyle Farh, Stephan Ripke, Felix R. Day, Shaun Purcell, Eli Stahl, Sara Lindstrom, John R.B. Perry, Yukinori Okada, Soumya Raychaudhuri, Mark J. Daly, Nick Patterson, Benjamin M. Neale, and Alkes L. Price. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nature Genetics* 2015 47:11, 47(11):1228–1235, sep 2015. ISSN 1546-1718. doi: 10.1038/ng.3404. URL <https://www.nature.com/articles/ng.3404>.
  - [30] Tessel E. Galesloot, Kristel Van Steen, Lambertus A.L.M. Kiemeney, Luc L. Janss, and Sita H. Vermeulen. A comparison of multivariate genome-wide association methods. *PLoS ONE*, 9(4), apr 2014. ISSN 19326203. doi: 10.1371/JOURNAL.PONE.0095923.
  - [31] Michael D. Gallagher and Alice S. Chen-Plotkin. The Post-GWAS Era: From Association to Function. *The American Journal of Human Genetics*, 102(5):717–730, may 2018. ISSN 0002-9297. doi: 10.1016/J.AJHG.2018.04.002.
  - [32] Magdalena Götz and Wieland B Huttner. The cell biology of Neurogenesis. *Nat Rev Mol Cell Biol*, 6:777–788, 2005. doi: 10.1038/nrm1739. URL [www.nature.com/articles/nrm1739](http://www.nature.com/articles/nrm1739).
  - [33] Daniel T. Grimes and Rebecca D. Burdine. Left-right patterning: breaking symmetry to asymmetric morphogenesis. *Trends in genetics : TIG*, 33(9):616, sep 2017. ISSN 13624555. doi: 10.1016/J.TIG.2017.06.004. URL [/pmc/articles/PMC5764106/](https://pmc/articles/PMC5764106/)?report=abstract&https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5764106/.
  - [34] Tulio Guadalupe, Marcel P. Zwiers, Katharina Wittfeld, Alexander Teumer, Alejandro Arias Vasquez, Martine Hoogman, Peter Hagoort, Guillen Fernandez, Jan Buitelaar, Hans van Bokhoven, Katrin Hegenscheid, Henry Völzke, Barbara Franke, Simon E. Fisher, Hans J. Grabe, and Clyde Francks. Asymmetry within and around the human planum temporale is sexually dimorphic and influenced by genes involved in steroid hormone receptor activity. *Cortex; a journal devoted to the study of the nervous system and behavior*, 62:41–55, jan 2015. ISSN 1973-8102. doi: 10.1016/J.CORTEX.2014.07.015. URL <https://pubmed.ncbi.nlm.nih.gov/25239853/>.
  - [35] Peter Heger, Wen Zheng, Anna Rottmann, Kristen A. Pan Lio, and Thomas Wiehe. The genetic factors of bilaterian evolution. *eLife*, 9:1–45, jul 2020. ISSN 2050084X. doi: 10.7554/ELIFE.45530.
  - [36] Andreas Hejnol and Kevin Pang. Xenacoelomorpha’s significance for understanding bilaterian evolution. *Current Opinion in Genetics And Development*, 39:48–54, aug 2016. ISSN 0959-437X. doi: 10.1016/J.GDE.2016.05.019.
  - [37] M R Herbert, D A Ziegler, C K Deutsch, L M O’Brien, D N Kennedy, P A Filipek, A I Bakardjiev, J Hodgson, M Takeoka, N Makris, and V S Caviness Jr.

## BIBLIOGRAPHY

---

- Brain asymmetries in autism and developmental language disorder: a nested whole-brain analysis. *Brain*, 128(1):213–226, jan 2005. ISSN 0006-8950. doi: 10.1093/brain/awh330. URL <https://doi.org/10.1093/brain/awh330>.
- [38] Dan Jackson, Richard Riley, and Ian R. White. Multivariate meta-analysis: Potential and promise. *Statistics in Medicine*, 30(20):2481, sep 2011. ISSN 02776715. doi: 10.1002/SIM.4172. URL [/pmc/articles/PMC3470931/](https://pmc.ncbi.nlm.nih.gov/pmc/articles/PMC3470931/)?report=abstract<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3470931/>.
- [39] Robert J. Klein, Caroline Zeiss, Emily Y. Chew, Jen Yue Tsai, Richard S. Sackler, Chad Haynes, Alice K. Henning, John Paul SanGiovanni, Shrikant M. Mane, Susan T. Mayne, Michael B. Bracken, Frederick L. Ferris, Jurg Ott, Colin Barnstable, and Josephine Hoh. Complement factor H polymorphism in age-related macular degeneration. *Science*, 308(5720):385–389, apr 2005. ISSN 00368075. doi: 10.1126/SCIENCE.1109557/SUPPL\_FILE/KLEIN\_SOM.PDF. URL <https://www.science.org/doi/abs/10.1126/science.1109557>.
- [40] Christian Peter Klingenberg. Walking on Kendall’s Shape Space: Understanding Shape Spaces and Their Coordinate Systems. *Evolutionary Biology*, 47(4):334–352, dec 2020. ISSN 19342845. doi: 10.1007/S11692-020-09513-X/FIGURES/9. URL <https://link.springer.com/article/10.1007/s11692-020-09513-x>.
- [41] Christian Peter Klingenberg, Marta Barluenga, and Axel Meyer. Shape analysis of symmetric structures: Quantifying variation among individuals and asymmetry. *Evolution*, 56(10):1909–1920, 2002. ISSN 00143820, 15585646. URL <http://www.jstor.org/stable/3094634>.
- [42] Evan M. Koch and Shamil R. Sunyaev. Maintenance of Complex Trait Variation: Classic Theory and Modern Data. *Frontiers in Genetics*, 12:2198, nov 2021. ISSN 16648021. doi: 10.3389/FGENE.2021.763363/BIBTEX.
- [43] Xiang-Zhen Kong, Merel C Postema, Tulio Guadalupe, Carolien de Kovel, Premika S W Boedhoe, Martine Hoogman, Samuel R Mathias, Daan van Rooij, Dick Schijven, David C Glahn, Sarah E Medland, Neda Jahanshad, Sophia I Thomopoulos, Jessica A Turner, Jan Buitelaar, Theo G M van Erp, Barbara Franke, Simon E Fisher, Odile A van den Heuvel, Lianne Schmaal, Paul M Thompson, and Clyde Francks. Mapping brain asymmetry in health and disease through the ENIGMA consortium. *Human Brain Mapping*, 43(1):167–181, jan 2022. ISSN 1065-9471. doi: <https://doi.org/10.1002/hbm.25033>. URL <https://doi.org/10.1002/hbm.25033>.
- [44] Frank Kuo and Tarik F. Massoud. Structural asymmetries in normal brain anatomy: A brief overview. *Annals of Anatomy - Anatomischer Anzeiger*, 241:151894, apr 2022. ISSN 0940-9602. doi: 10.1016/J.AANAT.2022.151894.

- [45] Shuyu Li, Shaoyi Wang, Xinwei Li, Qiongling Li, and Xiaobo Li. Abnormal surface morphology of the central sulcus in children with attention-deficit/hyperactivity disorder. *Frontiers in Neuroanatomy*, 9(AUGUST):114, aug 2015. ISSN 16625129. doi: 10.3389/FNANA.2015.00114/BIBTEX.
- [46] Thomas J. Littlejohns, Jo Holliday, Lorna M. Gibson, Steve Garratt, Niels Oesingmann, Fidel Alfaro-Almagro, Jimmy D. Bell, Chris Boultwood, Rory Collins, Megan C. Conroy, Nicola Crabtree, Nicola Doherty, Alejandro F. Frangi, Nicholas C. Harvey, Paul Leeson, Karla L. Miller, Stefan Neubauer, Steffen E. Petersen, Jonathan Sellors, Simon Sheard, Stephen M. Smith, Cathie L.M. Sudlow, Paul M. Matthews, and Naomi E. Allen. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nature Communications* 2020 11:1, 11(1):1–12, may 2020. ISSN 2041-1723. doi: 10.1038/s41467-020-15948-9. URL <https://www.nature.com/articles/s41467-020-15948-9>.
- [47] Sabrina Malik, Govindaiah Vinukonda, Linnea R. Vose, Daniel Diamond, Bala B.R. Bhimavarapu, Furong Hu, Muhammad T. Zia, Robert Hevner, Nada Zecevic, and Praveen Ballabh. Neurogenesis continues in the third trimester of pregnancy and is suppressed by premature birth. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 33(2):411–423, jan 2013. ISSN 1529-2401. doi: 10.1523/JNEUROSCI.4445-12.2013. URL <https://pubmed.ncbi.nlm.nih.gov/23303921/>.
- [48] Jerome J. Maller, Rodney Anderson, Richard H. Thomson, Jeffrey V. Rosenfeld, Zafiris J. Daskalakis, and Paul B. Fitzgerald. Occipital bending (Yakovlevian torque) in bipolar depression. *Psychiatry Research: Neuroimaging*, 231(1):8–14, jan 2015. ISSN 0925-4927. doi: 10.1016/J.PSCYCHRESNS.2014.11.008.
- [49] Zoltán Molnár, Gavin J. Clowry, Nenad Šestan, Ayman Alzu’bi, Trygve Bakken, Robert F. Hevner, Petra S. Hüppi, Ivica Kostović, Pasko Rakic, E. S. Anton, David Edwards, Patricia Garcez, Anna Hoerder-Suabedissen, and Arnold Kriegstein. New insights into the development of the human cerebral cortex. *Journal of Anatomy*, 235(3):432, 2019. ISSN 14697580. doi: 10.1111/JOA.13055. URL [/pmc/articles/PMC6704245/](https://pmc/articles/PMC6704245/)?report=abstract&https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6704245/.
- [50] Sahin Naqvi, Yoeri Sleyp, Hanne Hoskens, Karlijne Indencleef, Jeffrey P Spence, Rose Bruffaerts, Ahmed Radwan, Ryan J Eller, Stephen Richmond, Mark D Shriver, John R Shaffer, Seth M Weinberg, Susan Walsh, James Thompson, Jonathan K Pritchard, Stefan Sunaert, Hilde Peeters, Joanna Wysocka, and Peter Claes. Shared heritability of human face and brain shape. *Nature Genetics*, 53(6):830–839, 2021. ISSN 1546-1718. doi: 10.1038/s41588-021-00827-w. URL <https://doi.org/10.1038/s41588-021-00827-w>.
- [51] Simon Neubauer, Philipp Gunz, Nadia A. Scott, Jean Jacques Hublin, and Philipp Mitteroecker. Evolution of brain lateralization: A shared hominid

## BIBLIOGRAPHY

---

- pattern of endocranial asymmetry is much more variable in humans than in great apes. *Science Advances*, 6(7):9935–9949, 2020. ISSN 23752548. doi: 10.1126/SCIADV.AAX9935/SUPPL\_FILE/AAX9935\_SM.PDF. URL <https://www.science.org/doi/abs/10.1126/sciadv.aax9935>.
- [52] Andrew Y. Ng, Michael I. Jordan, and Yair Weiss. On spectral clustering: Analysis and an algorithm. In *Advances in Neural Information Processing Systems*, 2002.
  - [53] Hannah L. Nicholls, Christopher R. John, David S. Watson, Patricia B. Munroe, Michael R. Barnes, and Claudia P. Cabrera. Reaching the End-Game for GWAS: Machine Learning Approaches for the Prioritization of Complex Disease Loci. *Frontiers in Genetics*, 11:350, apr 2020. ISSN 16648021. doi: 10.3389/FGENE.2020.00350/BIBTEX.
  - [54] Sierra S. Nishizaki, Natalie Ng, Shengcheng Dong, Robert S. Porter, Cody Morterud, Colten Williams, Courtney Asman, Jessica A. Switzenberg, and Alan P. Boyle. Predicting the effects of SNPs on transcription factor binding affinity. *Bioinformatics*, 36(2):364–372, jan 2020. ISSN 1367-4803. doi: 10.1093/BIOINFORMATICS/BTZ612. URL <https://academic.oup.com/bioinformatics/article/36/2/364/5543098>.
  - [55] Tomasz J. Nowakowski, Alex A. Pollen, Carmen Sandoval-Espinosa, and Arnold R. Kriegstein. Transformation of the Radial Glia Scaffold Demarcates Two Stages of Human Cerebral Cortex Development. *Neuron*, 91(6):1219–1227, sep 2016. ISSN 10974199. doi: 10.1016/J.NEURON.2016.09.005/ATTACHMENT/5FB07326-F8FF-4C17-9374-553AF90F6D57/MMC2.XLSX. URL [http://www.cell.com/article/S0896627316305645/fulltexthttp://www.cell.com/article/S0896627316305645/abstracthttps://www.cell.com/neuron/abstract/S0896-6273\(16\)30564-5](http://www.cell.com/article/S0896627316305645/fulltexthttp://www.cell.com/article/S0896627316305645/abstracthttps://www.cell.com/neuron/abstract/S0896-6273(16)30564-5).
  - [56] Yasushi Okada, Sen Takeda, Yosuke Tanaka, Juan Carlos Izpisúa Belmonte, and Nobutaka Hirokawa. Mechanism of Nodal Flow: A Conserved Symmetry Breaking Event in Left-Right Axis Determination. *Cell*, 121(4):633–644, may 2005. ISSN 0092-8674. doi: 10.1016/J.CELL.2005.04.008.
  - [57] Wei Yi Ong, Christian S. Stohler, and Deron R. Herr. Role of the Prefrontal Cortex in Pain Processing. *Molecular Neurobiology*, 56(2):1137, feb 2019. ISSN 15591182. doi: 10.1007/S12035-018-1130-9. URL [/pmc/articles/PMC6400876/](https://pmc/articles/PMC6400876/) pmc/articles/PMC6400876/?report=abstracthttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC6400876/.
  - [58] Mark A. Purnell, Philip J.C. Donoghue, Sarah E. Gabbott, Maria E. McNamara, Duncan J.E. Murdock, and Robert S. Sansom. Experimental analysis of soft-tissue fossilization: opening the black box. *Palaeontology*, 61(3):317–323, may 2018. ISSN 1475-4983. doi: 10.1111/PALA.12360. URL <https://onlinelibrary.wiley.com/doi/full/10.1111/pala.12360https://onlinelibrary.wiley.com/doi/full/10.1111/pala.12360>

- //onlinelibrary.wiley.com/doi/abs/10.1111/pala.12360https://onlinelibrary.wiley.com/doi/10.1111/pala.12360.
- [59] P. Rakic. Radial glial cells: Brain functions. In *Encyclopedia of Neuroscience*, volume R, pages 15–21. Elsevier Ltd, 2009. ISBN 9780080450469. doi: 10.1016/B978-008045046-9.01021-4.
  - [60] Vasily Ramensky, Peer Bork, and Shamil Sunyaev. Human non-synonymous SNPs: server and survey. *Nucleic Acids Research*, 30(17):3894–3900, sep 2002. ISSN 0305-1048. doi: 10.1093/NAR/GKF493. URL <https://academic.oup.com/nar/article/30/17/3894/2376118>.
  - [61] Michele Ribolsi, Zafiris J Daskalakis, Alberto Siracusano, and Giacomo Koch. Abnormal Asymmetry of Brain Connectivity in Schizophrenia , 2014. URL <https://www.frontiersin.org/article/10.3389/fnhum.2014.01010>.
  - [62] Judith Schmitz, Onur Güntürkün, and Sebastian Ocklenburg. Building an asymmetrical brain: The molecular perspective. *Frontiers in Psychology*, 10 (APR):982, 2019. ISSN 16641078. doi: 10.3389/FPSYG.2019.00982/BIBTEX.
  - [63] Zhiqiang Sha, Dick Schijven, Amaia Carrion-Castillo, Marc Joliot, Bernard Mazoyer, Simon E. Fisher, Fabrice Crivello, and Clyde Francks. The genetic architecture of structural left-right asymmetry of the human brain. *Nature Human Behaviour* 2021 5:9, 5(9):1226–1239, mar 2021. ISSN 2397-3374. doi: 10.1038/s41562-021-01069-w. URL <https://www.nature.com/articles/s41562-021-01069-w>.
  - [64] Jinhua Sheng, Luyun Wang, Hu Cheng, Qiao Zhang, Rougang Zhou, and Yuchen Shi. Strategies for multivariate analyses of imaging genetics study in Alzheimer’s disease. *Neuroscience Letters*, 762:136147, sep 2021. ISSN 0304-3940. doi: 10.1016/J.NEULET.2021.136147.
  - [65] Vivian Tam, Nikunj Patel, Michelle Turcotte, Yohan Bossé, Guillaume Paré, and David Meyre. Benefits and limitations of genome-wide association studies. *Nature Reviews Genetics* 2019 20:8, 20(8):467–484, may 2019. ISSN 1471-0064. doi: 10.1038/s41576-019-0127-1. URL <https://www.nature.com/articles/s41576-019-0127-1>.
  - [66] M. D. Teare, A. M. Dunning, F. Durocher, G. Rennart, and D. F. Easton. Sampling distribution of summary linkage disequilibrium measures. *Annals of human genetics*, 66(Pt 3):223–233, 2002. ISSN 0003-4800. doi: 10.1017/S0003480002001082. URL <https://pubmed.ncbi.nlm.nih.gov/12174213/>.
  - [67] Lauren N. Telano and Stephen Baker. Physiology, Cerebral Spinal Fluid. *StatPearls*, jul 2021. URL <https://www.ncbi.nlm.nih.gov/books/NBK519007/>.
  - [68] Gosia Trynka, Cynthia Sandor, Buhm Han, Han Xu, Barbara E. Stranger, X. Shirley Liu, and Soumya Raychaudhuri. Chromatin marks identify critical

## BIBLIOGRAPHY

---

- cell types for fine mapping complex trait variants. *Nature genetics*, 45(2):124–130, feb 2013. ISSN 1546-1718. doi: 10.1038/NG.2504. URL <https://pubmed.ncbi.nlm.nih.gov/23263488/>.
- [69] Emil Uffelmann, Qin Qin Huang, Nchangwi Syntia Munung, Jantina de Vries, Yukinori Okada, Alicia R Martin, Hilary C Martin, Tuuli Lappalainen, and Danielle Posthuma. Genome-wide association studies. *Nature Reviews Methods Primers*, 1:59, 2021. ISSN 2662-8449. doi: 10.1038/s43586-021-00056-9. URL <https://doi.org/10.1038/s43586-021-00056-9>.
- [70] Takuji Usui, Malcolm R. Macleod, Sarah K. McCann, Alistair M. Senior, and Shinichi Nakagawa. Meta-analysis of variation suggests that embracing variability improves both replicability and generalizability in preclinical research. *PLOS Biology*, 19(5):e3001009, may 2021. ISSN 1545-7885. doi: 10.1371/JOURNAL.PBIO.3001009. URL <https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3001009>.
- [71] S. Van Dongen, G. Molenberghs, and E. Matthysen. The statistical analysis of fluctuating asymmetry: REML estimation of a mixed regression model. *Journal of Evolutionary Biology*, 12(1):94–102, jan 1999. ISSN 1010061X. doi: 10.1046/J.1420-9101.1999.00012.X.
- [72] Nandita Vijayakumar, Nicholas B. Allen, George Youssef, Meg Dennison, Murat Yücel, Julian G. Simmons, and Sarah Whittle. Brain development during adolescence: A mixed-longitudinal investigation of cortical thickness, surface area, and volume. *Human Brain Mapping*, 37(6):2027–2038, jun 2016. ISSN 10970193. doi: 10.1002/HBM.23154.
- [73] Guy Vingerhoets, Robin Gerrits, and Helena Verhelst. Atypical Brain Asymmetry in Human Situs Inversus: Gut Feeling or Real Evidence? *Symmetry 2021, Vol. 13, Page 695*, 13(4):695, apr 2021. ISSN 2073-8994. doi: 10.3390/SYM13040695. URL <https://www.mdpi.com/2073-8994/13/4/695> <https://www.mdpi.com/2073-8994/13/4/695>.
- [74] Peter M. Visscher, Matthew A. Brown, Mark I. McCarthy, and Jian Yang. Five Years of GWAS Discovery. *The American Journal of Human Genetics*, 90(1):7–24, jan 2012. ISSN 0002-9297. doi: 10.1016/J.AJHG.2011.11.029.
- [75] Günter Vogt. Disentangling the environmentally induced and stochastic developmental components of phenotypic variation. *Phenotypic Switching: Implications in Biology and Medicine*, pages 207–251, jan 2020. doi: 10.1016/B978-0-12-817996-3.00010-4.
- [76] Ulrike Von Luxburg. A tutorial on spectral clustering. *Statistics and Computing 2007 17:4*, 17(4):395–416, aug 2007. ISSN 1573-1375. doi: 10.1007/S11222-007-9033-Z. URL <https://link.springer.com/article/10.1007/s11222-007-9033-z>.

## BIBLIOGRAPHY

---

- [77] Tonya White, Nancy C. Andreasen, and Peggy Nopoulos. Brain Volumes and Surface Morphology in Monozygotic Twins. *Cerebral Cortex*, 12(5):486–493, may 2002. ISSN 1047-3211. doi: 10.1093/CERCOR/12.5.486. URL <https://academic.oup.com/cercor/article/12/5/486/318712>.
- [78] Mandy Melissa Jane Wittens, Gert Jan Allemeersch, Diana Maria Sima, Maarten Naeyaert, Tim Vanderhasselt, Anne Marie Vanbinst, Nico Buls, Yannick De Brucker, Hubert Raeymaekers, Erik Fransen, Dirk Smeets, Wim van Hecke, Guy Nagels, Maria Bjerke, Johan de Mey, and Sebastiaan Engelborghs. Inter- and Intra-Scanner Variability of Automated Brain Volumetry on Three Magnetic Resonance Imaging Systems in Alzheimer’s Disease and Controls. *Frontiers in Aging Neuroscience*, 13:641, oct 2021. ISSN 16634365. doi: 10.3389/FNAGI.2021.746982/BIBTEX.