

Preface

For centuries, we have wanted to know how the human brain works. How do we build, store, and retrieve memories? How do we understand spoken and written language? Are such different functions localized in distinct brain regions that differ in some special properties? If so, what are those properties?

In the past 50-plus years, we have been able to answer many of these questions and, in general, have gained an amazing amount of knowledge about the structural and functional organization of the human brain. In the process, we have also started asking questions about distal causes of the apparent variability manifested by *healthy* brains. Do the brain cells of a pianist differ from those of a person who has never played a musical instrument? Is Einstein's brain different from Bach's? And what about the mother's diet during pregnancy: does it support the growth of certain elements in the brain without affecting others? And peers during adolescence: do they leave a long-lasting signature in the social brain? Does the way we live in our middle years affect how our brains age?

To answer these and many other questions, we can now turn to population neuroscience. With in vivo imaging we are able to ask what shapes the brain, both from within (genes) and from without (social and physical environment). There are two main reasons for doing so. First, it is likely that by uncovering sources of inter-individual variability in the (healthy) human brain, we will acquire knowledge about *processes* leading to a particular *state* of brain structure and function. Second, by gaining insights into a process, we get closer to *prediction*. This is because individuals with a particular constellation of distal causes, and the ensuing developmental cascades, will likely differ in the state of their brains at a particular time in their life and, by extension, in their risk for developing a brain disorder. Thus, over the long term, understanding distal causes and associated processes will lay down the foundations for personalized preventive medicine.

Can these goals be achieved? The human brain is a large and complex organ: 1,300 cm³ of tissue, 100 billion neurons, and 176,000 km of axons. Our genome is equally complex: ~20,000 genes with tissue-specific patterns of expression, regulated through multiple mechanisms, including epigenetic ones. Add to these a mind-boggling number of possible social and physical environments the individual encounters from conception onwards—further affected, perhaps, through

environment-induced epigenetic modifications of his/her ancestors' genes—and clearly we have a very complex array of factors in the shaping of a human brain.

How can we deal with such a level of complexity? As outlined in this book, one possible approach is that of population neuroscience, where detailed information about the individual's envirome, genome and epigenome, and (brain) phenome is collected simultaneously in a large, population-based sample. Subsequently, these multi-level datasets are combined in analytical models to gain new knowledge about the process, thus enabling prediction of the individual's risk of a brain disorder. By its nature, this work can be carried out only by teams of scientists with a wide range of expertise, including epidemiology, genetics, cognitive neuroscience and brain imaging, engineering, computational science, bioinformatics and mathematics, as well psychiatry and neurology, behavioral sciences, law and ethics. By introducing the relevant vocabulary, concepts, and tools, this book aspires to prepare students and practitioners of these diverse disciplines to join such multi-disciplinary teams.

The book is laid out as follows. In [Chap. 1](#), the reader will learn about the key terms and concepts used in epidemiology (e.g., “exposures” and “outcomes”), genetics (e.g., genome, transcriptome, proteome), and cognitive neuroscience (regional specialization, structural and functional connectivity, development and plasticity). We will also introduce the concepts of envirome and phenome, and point out the needs for triangulation in enviromics and multi-level high-throughput approaches in phenomics. The reader will then learn about developmental cascades as a model for thinking about multi-factorial traits emerging over time. This chapter will end by introducing the concept of personalized preventive medicine.

Next, in order to help practitioners of one discipline understand the ways of thinking common in another, [Chap. 2](#) will provide brief historical accounts of epidemiology, genetics, and cognitive neuroscience, the three disciplines that form the foundation of population neuroscience. In the five chapters that follow, the reader will learn about diverse measurements and tools used to acquire them, which are available to researchers in order to characterize an individual's envirome ([Chap. 3](#)), genome([Chap. 4](#)), epigenome ([Chap. 5](#)), molecular phenome ([Chap. 6](#)), and systems-level (brain) phenome ([Chap. 7](#)).

[Chapter 8](#) will describe in brief a number of population-based imaging studies, in order to illustrate the use of some of the tools mentioned in the previous chapters; we will consider here both birth cohorts and prospective population-based studies initiated during childhood and adulthood. In [Chap. 9](#), the reader will discover some key challenges and their possible solutions. We will review ways in which we can construct hypotheses through meta-analyses, address the key issue of association versus causality and discuss the need for going beyond the “MR brain”.

Finally, [Chap. 10](#) will return to personalized preventive medicine and speculate about possible ways of using the knowledge gained in population-based studies of the human brain for moderating the individual's risk and resilience vis-à-vis common brain disorders. We will talk here about healthy life expectancy, the cost of common chronic disorders, risk profiling, and possible tools for transmitting

personalized high-tech information to the “client.” We will close with a hypothetical scenario that points out the social and economic costs of Alzheimer’s Disease and offers possible solutions for delaying the onset of this disease through personalized preventive medicine.

This book brings together knowledge gained through many years of my work on the human brain, first as a cognitive neuroscientist and later as a population neuroscientist. Over the past 30 years, I have been fortunate to have wonderful mentors and colleagues—starting with Miloš Kukleta during my medical studies in the Czech Republic, going on to Brenda Milner, Michael Petrides, and Alan Evans during my years at the Montreal Neurological Institute, and also many colleagues on both sides of the Atlantic, who worked with us on a number of MR-based population-based studies of the brain and body. My students and fellows have inspired me to find answers to their questions—thus pushing me to a clearer understanding of my own words and concepts. Their input has been invaluable and I am indebted to them for it.

This book would not have been possible without Zdenka Pausova, my partner in both work and life. Over more than 20 years, Zdenka has provided me the inspiration and knowledge necessary for embarking on studies in genetics and epidemiology. Together, we built the Saguenay Youth Study, which provides the template of most of the ideas and concepts described in this book. And I also want to thank our daughter, Veronika, for her positive energy and patience with the “science talk” while driving to school or camping.

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