NEUROMETHODS

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Brain Morphometry

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Preface to the Series

Experimental life sciences have two basic foundations: concepts and tools. The *Neuromethods* series focuses on the tools and techniques unique to the investigation of the nervous system and excitable cells. It will not, however, shortchange the concept side of things as care has been taken to integrate these tools within the context of the concepts and questions under investigation. In this way, the series is unique in that it not only collects protocols but also includes theoretical background information and critiques which led to the methods and their development. Thus, it gives the reader a better understanding of the origin of the techniques and their potential future development. The *Neuromethods* publishing program strikes a balance between recent and exciting developments like those concerning new animal models of disease, imaging, in vivo methods, and more established techniques, including immunocytochemistry and electrophysiological technologies. New trainees in neurosciences still need a sound footing in these older methods in order to apply a critical approach to their results.

Under the guidance of its founders, Alan Boulton and Glen Baker, the *Neuromethods* series has been a success since its first volume published through Humana Press in 1985. The series continues to flourish through many changes over the years. It is now published under the umbrella of Springer Protocols. While methods involving brain research have changed a lot since the series started, the publishing environment and technology have changed even more radically. *Neuromethods* has the distinct layout and style of the Springer Protocols program, designed specifically for readability and ease of reference in a laboratory setting.

The careful application of methods is potentially the most important step in the process of scientific inquiry. In the past, new methodologies led the way in developing new disciplines in the biological and medical sciences. For example, physiology emerged out of anatomy in the nineteenth century by harnessing new methods based on the newly discovered phenomenon of electricity. Nowadays, the relationships between disciplines and methods are more complex. Methods are now widely shared between disciplines and research areas. New developments in electronic publishing make it possible for scientists who encounter new methods to quickly find sources of information electronically. The design of individual volumes and chapters in this series takes this new access technology into account. Springer Protocols makes it possible to download single protocols separately. In addition, Springer makes its print-on-demand technology available globally. A print copy can therefore be acquired quickly and for a competitive price anywhere in the world.

Saskatoon, Canada ***Wolfgang Walz***

Preface

The structure and function of the human brain are the result of numerous biochemical and biophysical processes interacting across multiple scales in space and time. Variation in total gray and white matter volumes of the human brain is initially genetically determined. Most of the genes known to control these processes during brain development, maturation, and aging are highly conserved and participate to a complex process that leads the brain, during development, to a dramatic transformation from a simple tubular structure to a highly convoluted shape. However, this does not necessarily mean that genes influence different focal brain structures in the same manner and that a common genetic origin associated with general cognition and behavior is shared by all structures. In addition, life events and experiences during childhood impact directly on neurodevelopment. In line with this, a variety of studies have linked early and late events with brain morphology and disrupted neurodevelopment.

Pronounced differences, both at the morphological and at the cognitive/behavioral levels, abound among individuals. Macroscopic variations in brain anatomy are sufficiently maintained to grant comparative investigations. Indeed, morphological analyses that compare brains at different healthy or pathological stages can reveal important information about the progression of normal or abnormal development. Characterizing focal brain morphology and its association with development, functioning, and age-related neurodegenerative processes in healthy humans as well as local morphological alterations as found in psychiatric disorders and neurological diseases is crucial for the development of modern neuroscience.

Brain morphometry as a discipline is mainly concerned with the development of tools and strategies for the measurement of brain structural properties according to the kind of imaging data used, whether ontogenetic, pathological, or phylogenetic issues are targeted, and the spatial scales of interest. Further, shape feature comparisons have long been constrained to simple and mainly volume- or slice-based measures but benefited enormously from the digital revolution, as now all sorts of shapes in any number of dimensions can be handled numerically.

Magnetic resonance imaging (MRI), the state of the art of structural neuroimaging, provides a spatial representation of the brain and its components and allows for the calculation of several parameters of interest, related to the morphological features of brain regions. The fast evolution in terms of spatial resolution and signal-to-noise ratio in MRI scanners and the improvements on new imaging techniques and data processing algorithms have helped in developing studies able to detect and to quantify initially gross but even subtle structural abnormalities that appear when comparing different populations.

The most popular MRI-based approaches typically used to investigate morphological properties of gray matter structures both in healthy people and in patients are voxel-based morphometry (VBM), deformation-based morphometry (DBM), pattern-based morphometry (PBM), and surface-based morphometry (SBM). Analogously, the axonal architecture of white matter is generally obtained by diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI) fiber-tracking techniques. All of these methods are able to discriminate, noninvasively, the different tissues of the brain, thanks either to their molecular composition (i.e., local magnetic properties) or to their intercellular organization (i.e.,

local hydrodynamic regimes). In fact, if on one hand the first four approaches are performed commonly using the image contrast between water and fat (T1-weighted images), on the other hand, the second two aim to identify the molecular diffusion processes of water occurring along dominant axonal tracts.

Brain morphometric studies clarified that the largest changes within an individual generally occur during early development, more subtle ones follow during adulthood, and, again, dramatic changes occur in the last part of the human life: the aging. Currently, however, most applications of MR-based brain morphometry have a clinical target. They help to diagnose and monitor neuropsychiatric disorders. In fact, advances in neuroimaging progressively moved the scientific community toward a new understanding of neurological diseases as well as of psychiatric disorders based on their underlying neurobiology, facilitating the diagnostic classification, improving our ability to predict treatment outcome, and enhancing our understanding of the genetic and environmental causes of these disorders.

The rationale behind the realization of this book has been to offer to a broad audience, from expert neuroscientists to neuroimaging beginners, an overview of the state of the art of gray matter morphometry, as it can be derived from magnetic resonance images. Firstly, the book takes on the main topics about the technical procedures that underlie a morphometric study, from the registration and segmentation steps to the statistical analysis of structural parameters, passing through the most advanced methods for the measurement of cortical shaping and its multilayered structure. Subsequently, we intended to go through clinical and nonclinical applications. The nonclinical part of the book includes the characterization of normal development, aging, and the interplay between morphometry and genetics. Advanced approaches for the cytoarchitectonic description of brain structures and the impact that multicenter studies can have on morphometry results thanks to the inclusion of massively large cohorts are presented together with possible integrations with functional MRI data. The clinical part highlights the importance of brain morphometry in the improvement of the neurobiological characterization of major psychiatry disorders (schizophrenia, bipolar disorder, unipolar depression, obsessive-compulsive disorder, personality disorders, and suicide) and neuropsychiatric/neurological diseases (Alzheimer disease, non-Alzheimer dementias, Parkinson disease, multiple sclerosis, traumatic brain injury, and epilepsy).

The strength of the present book lies not only in the collection of the up-to-date methodological approaches thought to improve the characterization of the human brain structural properties and of a consistent coverage of brain dysfunctional and non-dysfunctional neuroanatomical variations but also in the multi-register harmonization obtained across its chapters. In fact, the final product is suitable for a specific update at the student, clinician, and researcher levels.

As it happens for every scientific approach to the study of a system, morphometry is a discipline in continuous evolution. Certainly, the access to high-performance informatics has notably improved the quality of results, as well as the technological amelioration of MRI signals equalized data reliability and stimulated the production of sophisticated algorithms for analysis. However, there is a long road ahead, with the connection between the microscopic and the mesoscopic levels of our knowledge about the structure of the brain still distant. Some basis has been placed, with the introduction of ultra-high-field MRI, which not only allows for the detection of structures at the micron scale but will open also the chance to use novel sources of contrast. Contemporarily, a better understanding of brain physiology due to the development of techniques able to detect, noninvasively, spatially precise local tissue metabolism will benefit the characterization of shapes, thickness, and

gyrification of cortex also in terms of their role in the whole system. Finally, the recent application of complex network science to clinical and nonclinical aspects of neuroscience will surely help the characterization of structural differences across age, medication, or dysfunction at the population level, thanks to its ability in unearthing elusive patterns and trends in big data.

We give our thanks to all the authors of the chapters in this book. They are leading investigators in their respective fields and kindly offered their insights into different aspects of brain morphometry. It goes without saying that, without their help, this book would not exist.

Rome, Italy

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