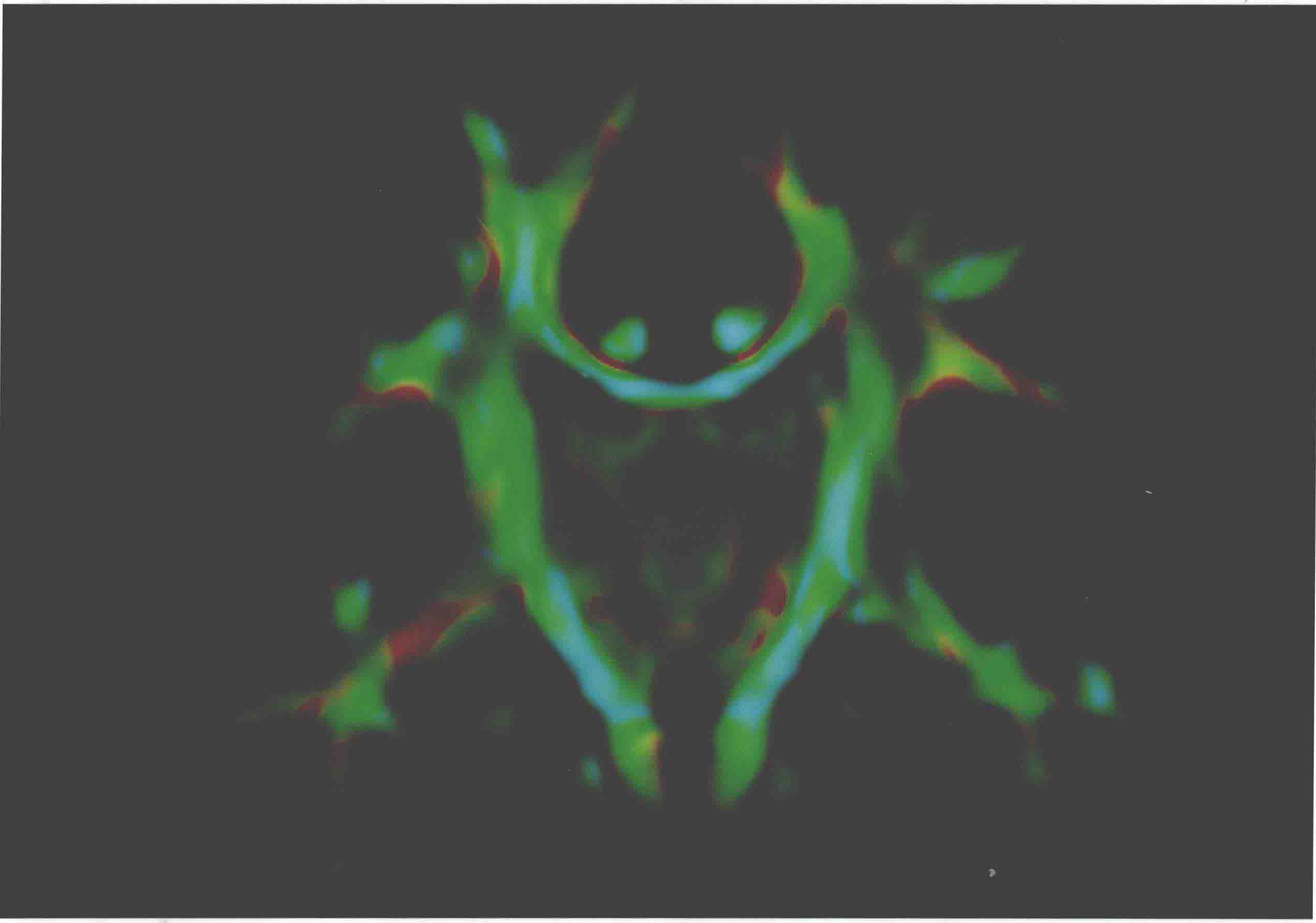
SECOND EDITION

Diffusion MRI

From Quantitative Measurement to *In-vivo* Neuroanatomy



EDITED BY

Heidi Johansen-Berg · Timothy E. J. Behrens

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HEIDI JOHANSEN-BERG

AND

TIMOTHY E.J. BEHRENS

Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB)
Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

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Foreword

If you want to know how an MP3 player works, the first thing you need to establish is how it is wired up. It is the same with the brain. Yet, as Crick and Jones commented in *Nature* in 1993 (Crick and Jones, 1993) it was lamentable how little we knew at that time about the connections of the human brain. All we could do was infer the connections indirectly from tracer studies in non-human primates. Yet it was only a year later that Basser *et al.* (1994) (see Chapter 1) showed that one could use MRI to measure the diffusion of water along axons, and in this way to visualize the major fiber tracts.

Anatomists were skeptical that much would come of the new methods. The reason is that their concern is with the fine details of the connections, rather than with the lie of the tracts. These fine details can be demonstrated by using the transport of tracers, and the method has been extensively used for the non-human primate brain (see Chapter 17). We currently have data for 7009 sites in the macaque brain, with 36 994 connections detailed (http://cocomac.g-node.org). But, unfortunately, though one can use MRI to visualize the transport of tracers (Saleem *et al.*, 2002), it is not ethical to inject tracers into the living brain. And so far, little progress has been made in using tracers in post-mortem brains. With current methods, dyes only diffuse at the rate of about 5 mm in 2 weeks (Kobbert *et al.*, 2000).

So to what extent can diffusion MRI provide similar information for the human brain? Fortunately, methods for tractography are steadily increasing in sophistication and although challenges remain it is now possible to estimate the probabilities of connections and to trace through regions of fiber complexity with some success (Chapter 19). Confidence in the exact site of termination will increase as the spatial resolution of MRI increases and it is possible to measure anisotropy within the gray matter. There are already hopeful signs. By use of a specialized coil array it has been possible to visualize thalamocortical fibers as they penetrate perpendicular to the pial surface and terminate in layer IV of occipital cortex (Jaermann *et al.*, 2008). And it has even been possible to measure laminar profiles of activity using fMRI (Ress *et al.*, 2007).

Given these tools, what can we use them for? First, we can check whether our inferences about connections from non-human primates are correct. Second, we can chart pathways that relate to abilities that are unique to humans, such as language. Third, we can establish the borders between neighboring cytoarchitectonic areas in the human brain, using the principle that each area has a unique pattern of inputs and outputs. Finally, we can make use of the *in vivo* nature of the measurements to examine how particular white matter connections contribute to individual variability in behavior, are subject to experience-dependent plasticity, and are affected in different disease states.

After introducing the key methods underlying diffusion imaging (Chapters 1 through 6), Section II of this book focuses on this last point: How can we make quantitative measurements of white matter connections in the living brain, and use these measurements as a probe in health and disease. In answering this question it is clearly important to know how the diffusion signal relates to the underlying biophysical properties of the axon—the real quantities of interest in white matter. Chapters 7 through 9 explore this issue in detail and examine what biological inferences we can already make from our diffusion data, and what new inferences we may be able to make in the near future. Chapters 10 through 15 then offer an essential guide to any scientist using these techniques to ask questions about white matter changes in health and disease. They start with a detailed and thorough guide to experimental design and data analysis techniques (Chapter 10), and then proceed with chapters giving key examples and highlighting important results from diffusion imaging in neurological and psychiatric disorders, in development and aging, and in behavioral neuroscience.

The first two sections of this book are therefore essential reading for scientists using diffusion imaging in their quantitative investigations, for those developing new methodologies for diffusion imaging, and for any clinicians and systems neuroscientists with an interest in white matter.

But there is an overarching reason why we need to know about the underlying architecture of connections in the human brain. The aim of neuroscience is to understand how the brain works as a whole, and the outstanding advantage of imaging methods (fMRI, EEG, MEG) is that they are whole-brain methods. Of course, we need to understand how each area performs its specific function, and for this we will need to resort to recording the electrical activity of cells, whether singly or in subpopulations. But tasks are not performed by single areas but by systems. And this means that we have to understand the interactions between areas within those systems. In imaging, measures of effective connectivity, whether structural equation modeling or dynamic causal modeling (Penny *et al.*, 2004), require the specification of a prior anatomical model for that system. This model need not include every synaptic stage in a circuit, but we do need to be confident that it holds for the human brain. Diffusion MRI promises to provide that model. This means that everyone who uses functional brain imaging needs to consult this book. In it they will find everything they need.

The last section provides an extensive account of the uses of diffusion MRI for neuroanatomy, and it is this section that those engaged in fMRI and MEG will need to consult. It starts with an overview of the emerging science of connectomics by Van Essen *et al.* and Sporns (Chapters 16 and 18) and an account of the related classical methods for tract tracing in animals by Morecraft and colleagues (Chapter 17). In Chapter 19, Behrens and colleagues give an introduction to probabilistic methods for tractography. In Chapter 20 Hubbard and Parker review the ways in which tractography has been validated. Klein *et al.* (Chapter 21) introduce the notion of connectional fingerprints (see also Chapter 19), and demonstrate that the pattern of connections can be used to distinguish between neighboring cytoarchitectonic areas. In Chapter 22, Catani and Budisavljević describe the language pathways in the human brain, and this chapter is followed by a discussion of the use of tractography in neurosurgical planning by Bartsch *et al.* (Chapter 23). In the next chapter, Rushworth *et al.* compare the frontal and parietal lobe connections in the macaque and human brain (Chapter 24). The last chapter (Chapter 25) is called "Imaging structure and function." That surely is the aim of all of those who use imaging to understand the workings of the human brain.

Richard Passingham
Professor of Cognitive Neuroscience, Department of Experimental Psychology, University of Oxford, UK

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Contributors

Daniel C. Alexander Department of Computer Science, University College London, UK

Jesper L.R. Andersson Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Yaniv Assaf Department of Neurobiology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel

Gareth Ball Centre for the Developing Brain, Department of Perinatal Imaging, Division of Imaging Sciences & Biomedical Engineering, St Thomas' Hospital, Kings College London, London, UK

Andreas J. Bartsch Department of Neuroradiology, University of Heidelberg, Heidelberg, Germany; Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Peter J. Basser Section on Tissue Biophysics and Biomimetics, PPITS, NICHD, National Institutes of Health, Bethesda, MD, USA

Christian Beaulieu Department of Biomedical Engineering, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

Timothy E.J. Behrens Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK; Department of Experimental Psychology, University of Oxford, Oxford, UK

Armin Biller Department of Neuroradiology, University of Heidelberg, Heidelberg, Germany

Benedetta Bodini Centre de recherche de l'institut du cerveau et de la moelle épinière, Université Pierre & Marie Curie, Hôpital Pitié Salpêtrière, Paris, France

Erie D. Boorman Department of Experimental Psychology, University of Oxford and Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Sanja Budisavljević Natbrainlab, Department of Forensic and Neurodevelopmental Science, Institute of Psychiatry, King's College London, London, UK

Marco Catani Natbrainlab, Department of Forensic and Neurodevelopmental Science, Institute of Psychiatry, King's College London, London, UK

Charles Chen Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

Olga Ciccarelli NMR Unit, Queen Square MS Centre, UCL Institute of Neurology, London, UK

Tim Coalson Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

Yoram Cohen School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv, Israel

Serena J. Counsell Centre for the Developing Brain, Department of Perinatal Imaging, Division of Imaging Sciences & Biomedical Engineering, St Thomas' Hospital, Kings College London, London, UK

Krikor Dikranian Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

Julia M. Edgar Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK; Department of Neurogenetics, Max Planck Institute of Experimental Medicine, Goettingen, Germany

A. David Edwards Centre for the Developing Brain, Department of Perinatal Imaging, Division of Imaging Sciences & Biomedical Engineering, St Thomas' Hospital, Kings College London, London, UK

Matthew F. Glasser Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

Ian R. Griffiths Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

John Harwell Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

György A. Homola Department of Neuroradiology, University of Würzburg, Würzburg, Germany

Penny L. Hubbard Centre for Imaging Sciences & Biomedical Imaging Institute, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

Saad Jbabdi Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Heidi Johansen-Berg Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Derek K. Jones Cardiff University Brain Research Imaging Centre (CUBRIC), School of Psychology, Cardiff University, UK

Gordon Kindlmann Department of Computer Science, University of Chicago, Chicago, IL, USA

Johannes C. Klein Department of Neurology, Goethe-University of Frankfurt, Frankfurt am Main, Germany; Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

M. Kubicki Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

José L. Lanciego Center for Applied Medical Research (CIMA and CIBERNED), Neurosciences Division, University of Navarra Medical College, Pamplona Navarra, Spain

Rogier B. Mars Department of Experimental Psychology, University of Oxford and Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Karla L. Miller Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Robert J. Morecraft Division of Basic Biomedical Sciences, Laboratory of Neurological Sciences, University of South Dakota, Sanford School of Medicine, Vermillion, South Dakota, USA

Evren Özarslan Section on Tissue Biophysics and Biomimetics, PPITS, NICHD, National Institutes of Health, Bethesda, MD, USA

Anand Pandit Centre for the Developing Brain, Department of Perinatal Imaging, Division of Imaging Sciences & Biomedical Engineering, St Thomas' Hospital, Kings College London, London, UK

Deepak N. Pandya Department of Anatomy and Neurobiology, Department of Neurology, Boston University School of Medicine, Boston, MA, USA

Geoffrey J.M. Parker Centre for Imaging Sciences & Biomedical Imaging Institute, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

O. Pasternak Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; Laboratory of Mathematics in Imaging, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Jim Pipe Keller Center for Imaging Innovation, Barrow Neurological Institute, Phoenix, Arizona, USA

Matthew F.S. Rushworth Department of Experimental Psychology, University of Oxford and Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

David H. Salat Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA; Massachusetts General Hospital Department of Radiology, Boston, MA, USA; Boston VA Healthcare System, Neuroimaging Research for Veterans Center, Boston, MA, USA

Jérôme Sallet Department of Experimental Psychology, University of Oxford and Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Jan Scholz Hospital for Sick Children, Toronto, Ontario, Canada

Kiran K. Seunarine Department of Computer Science, University College London, UK

M.E. Shenton Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; VA Boston Healthcare System, Brockton, MA, USA

Stephen M. Smith Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Stamatios N. Sotiropoulos Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Olaf Sporns Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA

Valentina Tomassini Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, University Hospital of Wales, Heath Park, Cardiff, UK

Gabriella Ugolini Neurobiologie et Developement, UPR3294 CNRS, Institut de Neurobiologie Alfred Fessard, Gif-sur-Yvette, France

David C. Van Essen Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA

C-F. Westin Laboratory of Mathematics in Imaging, Department of Radiology, Brighann and Women's Hospital, Harvard Medical School, Boston, MA, USA

Floris G. Wouterlood Department of Anatomy and Neurosciences, Vrije Universiteit Medical Center, Neuroscience Campus Amsterdam, Amsterdam, The Netherlands

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SECTION I

INTRODUCTION TO DIFFUSION MRI

CHAPTER

1

Introduction to Diffusion MR

Peter J. Basser, Evren Özarslan

Section on Tissue Biophysics and Biomimetics, PPITS, NICHD, National Institutes of Health, Bethesda, MD, USA

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1.1 WHAT IS DIFFUSION?

Diffusion is a mass transport process arising in nature, which results in molecular or particle mixing without requiring bulk motion. Diffusion should not be confused with convection or dispersion—other transport mechanisms that require bulk motion to carry particles from one place to another.

The excellent book by Howard Berg (1983) *Random Walks in Biology* describes a helpful Gedanken experiment that illustrates the diffusion phenomenon. Imagine carefully introducing a drop of colored fluorescent dye into a jar of water. Initially, the dye appears to remain concentrated at the point of release, but over time it spreads radially, in a spherically symmetric profile. This mixing process takes place without stirring or other bulk fluid motion. The physical law that explains this phenomenon is called Fick's first law (Fick, 1855a, 1855b), which relates the diffusive flux to any concentration difference through the relationship

$$\mathbf{J} = -D\nabla C, \tag{1.1}$$

where **J** is the net particle flux (vector), C is the particle concentration, and the constant of proportionality, D, is called the "diffusion coefficient." As illustrated in Figure 1.1, Fick's first law embodies the notion that particles flow from regions of high concentration to those of low concentration (hence the "−" sign in equation 1.1), just as heat flows from regions of high temperature to low temperature, as described in the earlier Fourier's law of heating on which Fick's law was based. In the case of diffusion, the flux is proportional to the concentration gradient as well as the diffusion coefficient. Unlike the flux vector or the concentration, the diffusion coefficient is an intrinsic property of the medium, and its value is determined by the size of the diffusing molecules and the temperature and microstructural features of the environment. The sensitivity of the diffusion coefficient on the local microstructure

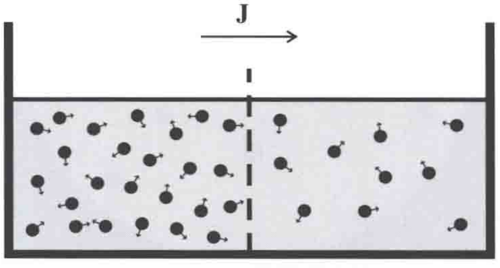

FIGURE 1.1 According to Fick's first law, when the specimen contains different regions with different concentrations of molecules, the particles will, on average, tend to move from high concentration regions to low concentration regions leading to a net flux (**J**).

enables its use as a probe of physical properties of biological tissue.

On a molecular level, diffusive mixing results solely from collisions between atoms or molecules in the liquid or gas state. Another interesting feature of diffusion is that it occurs even in thermodynamic equilibrium, for example, in a jar of water kept at a constant temperature and pressure. This is quite remarkable because the classical picture of diffusion, as expressed above in Fick's first law, implies that when the temperature or concentration gradients vanish, there is no net flux. There were many who held that diffusive mixing or energy transfer stopped at this point. We now know that although the net flux vanishes, there are still microscopic motions of molecules that persist; it is just that on average, there is no net molecular flux in equilibrium.

A framework that explains this phenomenon has its origins in the observations of Robert Brown, who is credited with being the first to report the random motions of pollen grains while studying them under the microscope (Brown, 1828) (Figure 1.2). Brown reported that particles moved randomly, without any apparent cause. He initially believed that there was some life force that was causing these motions, but disabused himself of this notion when he observed the same fluctuations when studying dust and other inorganic matter.

In the early part of the twentieth century, Albert Einstein, who was unaware of Brown's observation and seeking evidence that would undoubtedly imply the existence of atoms, came to the conclusion that "bodies of microscopically visible size suspended in a liquid will perform movements of such magnitude that they can be easily observed in a microscope" (Einstein, 1905; Fürth and Cowper, 1956). Einstein used a probabilistic framework to describe the motion of an ensemble of particles undergoing diffusion, which led to a coherent description of diffusion, reconciling the Fickian and Brownian pictures. He introduced the "displacement distribution" for this purpose, which quantifies the fraction of particles that will traverse a certain distance within a particular timeframe, or equivalently, the likelihood that a single given particle will undergo that displacement. For example, in free diffusion the displacement distribution is a Gaussian function whose width is determined by the diffusion coefficient, as illustrated in Figure 1.3. Gaussian diffusion will be treated in more detail in Chapter 5, whereas the more general case of non-Gaussianity will be tackled in Chapters 6 and 9.

Using the displacement distribution concept, Einstein was able to derive an explicit relationship between the mean-squared displacement of the ensemble, characterizing its Brownian motion, and the classical diffusion coefficient, D, appearing in Fick's law (Einstein, 1905, 1926), given by

$$\langle x^2 \rangle = 2D\Delta, \tag{1.2}$$

where $\langle x^2 \rangle$ is the mean-squared displacement of particles during a diffusion time Δ and D is the diffusion coefficient.

At around the same time as Einstein, Smoluchowski (1906) was able to reach the same conclusions using different means. Langevin improved upon Einstein's description of diffusion for ultra-short timescales in which there are few molecular collisions, but we are not able to probe this regime using MR diffusion measurements in water. Since a particle experiences about 10^{21} collisions every second in typical proton-rich solvents like water (Chandrasekhar, 1943), we generally do not concern ourselves with this correction in diffusion MR.

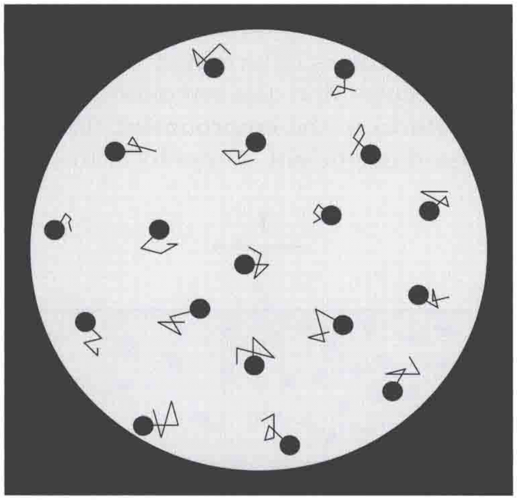

FIGURE 1.2 Robert Brown, a botanist working on the mechanisms of fertilization in flowering plants, noticed the perpetual motion of pollen grains suspended in water in 1827.

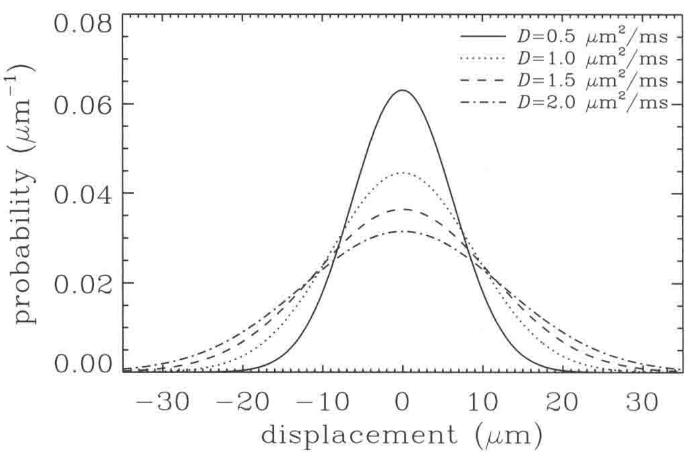

FIGURE 1.3 The Gaussian displacement distribution plotted for various values of the diffusion coefficient when the diffusion time was taken to be 40 ms. Larger diffusion coefficients lead to broader displacement probabilities, suggesting increased diffusional mobility.