Ethics and Clinical Neuroinnovation

Fundamentals, Stakeholders, Case Studies, and Emerging Issues

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Foreword

> At a gathering of brain scientists and philosophers, participants zeroed in on one portion of the world of worry about unbridled science called "neuroethics." It deals with the benefits and dangers of treating and manipulating our minds.
>
> William Safire (2002)[1]

Fascination with our minds, and ethical questions concerning them, can be traced back for millennia. The exploration of the physical brain as the source of the mind began in full force in seventeenth century England.[2] But "neuroethics," in its contemporary sense, was born in May 2002 at a conference in San Francisco sponsored by the Dana Foundation and co-hosted by Stanford University and the University of California at San Francisco.[3] At the same time, William Safire, former Nixon White House speechwriter and chairman of the board of the Dana Foundation popularized the use of the term "neuroethics" when he featured it in his New York Times column.

The past 20 years have seen great growth in the field of neuroethics, with the formation of an international scholarly society[4] in 2006, the subsequent creation of at least two scholarly journals[5] and the addition of neuroethics components to several national or regional projects or organizations.[6] They have also seen a rise in sustained grant funding for academic research into neuroethics. The BRAIN Initiative of the United States National Institutes of Health (NIH) began awarding

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[1] William Safire, *The But-What-If Factor*, NY Times (May 16, 2002), available at https://www.nytimes.com/2002/05/16/opinion/the-but-what-if-factor.html.

[2] Carl Zimmer, Soul Made Flesh (Free Press, 2004)

[3] Neuroethics: Mapping the Field (ed. Steven J. Markus, The Dana Press, 2002)

[4] The International Neuroethics Society, https://www.neuroethicssociety.org.

[5] AJOB Neuroscience, https://www.tandfonline.com/toc/uabn20/12/4, and Neuroethics, https://www.springer.com/journal/12152.

[6] These include at least the Neuroethics Working Group of the NIH BRAIN® Initiative, https://braininitiative.nih.gov/about/neuroethics-working-group, the ethics components of the European Union's Human Brain Project, https://www.humanbrainproject.eu/en/social-ethical-reflective/about/, the International Brain Initiative, https://www.internationalbraininitiative.org, and the Global Neuroethics Summit, https://globalneuroethicssummit.com.

research grants for the study of neuroethics issues in 2016. This volume is one early result.

I generally view the role of a foreword in a book as akin to an appetizer at a meal, or, better, an amuse-bouche, a very small taste of what is to come. And so I will keep this foreword short and use it to do two things: First, I want to give you a sense of the book that lies in front of you. And second, I hope to try to place this book into its context in the field of neuroethics, both past and present.

The immediate source of this book was a 2017 NIH grant to Stanford University, entitled "Enabling Ethical Participation in Innovative Neuroscience on Mental Illness and Addiction: Towards a New Screening Tool Enhancing Informed Consent for Transformative Research on the Human Brain," with Professor Laura Weiss Roberts as the principal investigator.[7] But, in fact, as Chap. 12 makes clear, its genesis lies much deeper in the past, with work on informed consent done by co-investigator Laura Dunn in the early 2000s, joined by Laura Weiss Roberts in the early 2010s. Although the book covers much other useful and important ground, at its core is a synthesis of some of the fascinating work done under the BRAIN Initiative grant.

ETHICS AND CLINICAL NEUROINNOVATION comes in three parts. The first provides background information on mental illness, neuroscience, and neuroethics. The second looks in depth at several aspects of neuroethics and innovative neurotechnologies. And the third lays out the unprecedented work completed by Dr. Roberts' team under the BRAIN Initiative grant to understand better what the stakeholders in the innovative neurotechnologies—patients, neuroscience researchers, ethicists, and others—think about these issues.

The initial part contains six chapters. The first lays out, in painful numbers, the vast amount of human suffering created by psychiatric, addiction-related, co-occurring, and behavioral disorders. If you do not know of a friend, family member, or loved one whose life has been blighted by one (or more) of these conditions, just wait—you will. The second chapter is the longest in the book but one of the best, as it lays out the history and current status of neuroscience, neuroimaging, and other forms of neuroinnovation. It does so with impressive panache and some humor— "Transcranial Electrical Stimulation, which … directly stimulates cortical tissue with high voltage electric shocks to the scalp (it's as painful as it sounds)." The third chapter looks at the basic approaches of neuroethics and how they may apply to machine learning algorithms and brain–machine interfaces.

Chapter 4 looks at changes in the context of innovation, from the ubiquity of digital data and its problems, to blurred lines between clinical care, research, and commerce, and the growing impact of both patient and patient advocacy organizations and other non-scientist communities on innovation. Chapter 5 analyzes what makes innovation in the brain different from general medical innovation, with a focus on the brain's special role as the source of consciousness—people would be much less concerned about, say, gall bladder innovation. And the last chapter in

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[7] The grant is described at https://reporter.nih.gov/project-details/9419223.

section one reviews the NIH's "Brain Research Through Advancing Innovative Neurotechnologies" or BRAIN® (yes, the acronym is trademarked) Initiative, its neuroethics component, and the grant from NIH that resulted in the project described in this book.

The second part of the book comprises five chapters that dive into neuroethics issues in particular settings. Chapter 7 looks at the ethics of neurostimulation via neurosurgery as a way to treat intractable, dangerous obesity. The eighth chapter focuses on the fascinating question of "covert consciousness": how neurotechnologies have been and may be used to detect consciousness in unresponsive patients and what we should worry about in those efforts. Chapter 9 examines the ethics of human studies with psychedelic drugs, their substantial promise, and their equally large challenges. The tenth chapter analyzes the criminal justice system's uses of neuroscience technologies, especially in three ways: looking back at the time of the crime, support for a clinical diagnosis and evidence to bolster a claim of diminished capacity, while the third looks at the present for immediate issues like a witness's truthfulness, the validity of eyewitness identification, and implicit biases. Chapter 11, the last chapter of this section, emphasizes how innovation is skipping over academic labs and happening directly in firms, and the implications of that shift.

Part three is the core of this book. It describes many of the results of the empirical research projects undertaken by its chapters' authors as part of their BRAIN Initiative neuroethics grant. Chapter 12, its initial chapter, describes the genesis and development of the project and its two main components. The first component, aim 1 of the grant, uses semi-structured interviews with stakeholders to identify what distinctive ethical questions are raised by innovative neuroscience research in mental illness and addiction. The second, aim 2, uses a large survey of possible research participants to seek to understand what affects decisions whether or not to participate in such research. The survey seeks to test and refine the Roberts Valence Model for Ethical Engagement in Research, a tool that members of the group have been building over several years.

The remaining chapters of part three further describe this work. The next four cover the semi-structured interviews, beginning with Chap. 13, which details who was asked what, and how (and, importantly, how the answers were coded for analysis). The three chapters that follow, Chaps. 14, 15, and 16, analyze the interviews with 44 professional stakeholders—neuroscience researchers, IRB members, and ethicists. They probe the stakeholders' views on, respectively, ethical considerations in innovative neuroscience research involving human participants; the contexts in which research occurs and the special effects those contexts have on psychiatry and neuroscience research; and clinical innovation in psychiatry and neuroscience. As far as I know, these chapters and the work behind them make up a unique resource for understanding how they are engaged in, or overseeing, neuroscience research and what they are doing. They will provide valuable insights to inform this kind of research going forward.

The final chapter deals with the survey aspect of the project. Chapter 17 is an interesting and enlightening look at Mechanical Turk (widely known as "MTurk"), the Amazon survey tool that, because of its ease and low cost, has become

widespread in research, both academic and otherwise. As someone who has read much research using MTurk, I was delighted finally to understand how it works—and particularly taken by the ethical questions the chapter raises about MTurk itself. Chapter 17 is followed by an Appendix that sets out some of the survey results. These are not results from the full 1000-person survey planned, but from one pilot survey of 151 people. Although pilot studies only, they provide some novel and interesting findings, and leave me eager to read the results of the full survey.

This is a useful and interesting book, but how does it fit into today's neuroethics? And, at least as importantly, just what *is* neuroethics today?

It may be useful to look back two decades to William Safire's op-ed. In it he raises many possibilities: drugs to enhance memory or alertness, technical manipulation of memories, neuroscientific lie detection, combining our heads' "wetware" with computers, and "a kind of Botox for the brain to smooth out wrinkled temperaments." Neuroethics analyzed, and argued about, all of these issues and more for years, convinced that if they were not already reality, they soon would be. I wrote about most of them myself. But 20 years later, they remain hypotheticals—still intriguing and still unreal, or, at least, unrealized. Astounded by rapid neuroscience progress, particularly using functional magnetic resonance imaging (fMRI), we were too optimistic—or, from some perspectives, pessimistic—about what the future would bring, and how soon. (Interestingly, at the same time, two other high profile bioscience fields, genomics and stem cell research, created similarly inflated hopes and fears.)

All of Safire's issues may well yet come to pass, but it turns out we did not need FDA regulation of fMRI-based lie detection in 2005 in spite of an article I wrote that year urging it.[8] The tools we had were astounding and excellent at giving us a much better understanding of "the human brain" than ever before. But usually that understanding was of group averages, not of individual brains, and did not provide the detail needed to understand *your* brain or *mine*. In some ways, the big lesson of the last 20 years in neuroscience is that human brains are even more complicated than we imagined.

So, until the next, and better, generation of tools—the creation of which is the main goal of the BRAIN Initiative—neuroethics is more usefully deployed in questioning the tools that are closer to hand, and the research being done to improve them. ETHICS AND CLINICAL NEUROINNOVATION does just that. This kind of neuroethics is less likely to show up in headlines, or in nightmares, but it is, for now, much more useful—useful as one part of the morally compelling effort to relieve the vast human suffering caused by diseases of the brain…very much a "neuroethical" goal.

<div align="right">
Henry T. Greely
Stanford Law School
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[8] Henry T. Greely, *Premarket Approval Regulation for Lie Detection: An Idea Whose Time May Be Coming*, AM. J. BIOETHICS, 5(2):50–52 (March-April 2005)

Preface

Necessity is the mother of invention. Necessity inspires creativity and novel approaches to consequential challenges. Necessity, unfortunately, is also the mother of failure (when solutions do not exist), expedience and compromise (when resources are costly, out of reach, or insufficient), and of neglect and stigma (when needs are simply too overwhelming).

The needs experienced by people living with mental illness and addiction throughout history have been immense and, for the most part, unmet. Failure, expedience, compromise, neglect, and stigma have been common themes. In recent decades, however, these needs have been increasingly recognized by society and have become an inspiration for pioneers—pioneers in the neurosciences, clinical medicine, and health professions—policy makers, and scholars. Invention, creativity, and novel approaches related to brain disorders and brain health have brought along their companions, promise, hope, and compassion.

This book covers this rich array of issues, broadly conceived under the notion of neuroethics in relation to innovation for the purpose of advancing the health and well-being of people living with mental illnesses, including addiction. The book embraces existing scholarship and, more importantly, qualitative and early quantitative data drawn from stakeholders with vastly different experiences. The book embraces this complexity, with areas of commonality and diversity, congruence, and contradiction, in an effort to help illuminate ethically salient dimensions of neuroinnovation in society at this moment.

This moment is exceptional in that we are living in a time of technological advance, scientific brilliance, and accelerated impact of entrepreneurialism in society. We are living in a time of pandemic and heightened realization of the connections amongst all people, past, present, and future. And we are living in a time of dynamic societal attitudes that are rapidly consolidating based on a variety of influences, in which skepticism in science seems equal to the greater need for belief in science as a path toward health and a better future. As we note in Chapter 1, this book is intended to bring forward a variety of perspectives for deeper consideration. Many impressions shared in this text may be corrected and many new findings may emerge in the coming years that serve to reinforce or to revise the ideas presented

here. Through this book, we intend to strengthen the foundations of neuroethics during a time of immense change.

I thank people with lived experience of illness for sharing their invaluable and often neglected insights to this book, I thank the research professionals and IRB members who spoke with us for their perspectives and expertise, and I thank my wonderful colleagues for their great work and partnership. My sincere thanks to the National Institute of Mental Health for funding this project; to our Program Officer James Churchill; to my colleagues at Springer, Richard Lansing, Diane Lamsback, and Anila Vijayan, for seeing the value in our proposal and publishing this unique book; to our intrepid contributors who wrote and revised chapters of this book even in the midst of a novel global pandemic; to Hank Greely for the foreword; to our stakeholders for sharing their words with us; and to my team, including Max Kasun, Gabriel Termuehlen, and especially Jodi Paik, MFA, who helped shepherd this project.

Palo Alto, CA, USA   Laura Weiss Roberts

Contents

Part I
Foundations of Ethics in Clinical Neuroinnovation

Chapter 1
The Case for Neuroinnovation: Health Burdens Associated with Psychiatric, Addiction-Related, and Co-occurring Disorders

Laura Weiss Roberts and Katie Ryan

The Global Burden of Mental Illness and Addiction

Mental, neurological, and substance use disorders are a source of great personal suffering for hundreds of millions of individuals across the globe. These disorders—the causes of which are often a combination of genetic, environmental, biological, and societal factors—have historically been stigmatized, underfunded, and undertreated. As an increasingly globalized world has allowed for unprecedented connectivity and insights, the devastating consequences of mental illness and addiction on both personal and socioeconomic scales have become fully apparent.

People in every nation, community, and family are affected by the direct and indirect burdens of mental illness. One in five American adults experience some form of mental illness in any given year, while one in every 20 lives with a serious mental illness [1]. This pattern holds true for populations across the globe—it is estimated that one in four individuals globally will experience mental illness in their lifetime [2]. Over 12 billion working days are lost to mental illness every year, and mental illness is estimated to cost the world $16 trillion by 2030 [3].

The mental health repercussions of the SARS-CoV-2 pandemic are incalculable and far-reaching, with anticipated impact for generations [4]. Psychosocial dimensions of the pandemic include isolation, loneliness, grief, family disruption, and poor coping, including use of addictive substances [5]. People living with mental disorders experienced disproportionate burden of infection and diminished access to appropriate physical and mental health services [6–8]. The full spectrum of neuropsychiatric sequelae of viral infections of the brain is just beginning to be recognized, with heightened risk for mortality and enduring morbidity [9]. The

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superimposed effects of the pandemic atop the opioid and substance epidemics felt in multiple nations are immense [10].

Although the global disease burden for mental illness is often cited as accounting for around 23% of years lived with disability (YLDs) [11] and 7.4% of disability-adjusted life years (DALYs) [12], Vigo et al. [13] argue that these are vast underestimates. Using published data, they estimate that mental illness accounts for 32.4%—nearly one-third—of YLDs across the globe, and 13.0% of DALYs. Comprehensive pandemic-related data assessing mental health consequences have yet to be gathered. Given these updated estimates, mental illness is the resounding leading cause of global burden of disease in terms of YLDs and historically has been as debilitating as cardiovascular and circulatory disease when it comes to DALYs.

Unlike many physical illnesses which primarily affect older adults, the burden of mental illness and substance use disorders is unfortunately shared amongst individuals across the lifespan. Mental illness and substance use disorders account for 25% of all YLDs in children and youth and are the leading cause of disability in children and youth globally [14]. Furthermore, mental illness and addiction are responsible for 5.7% of DALYs amongst children and are the sixth leading cause of DALYs amongst children [14].

While economically established nations have seen improvements in the identification, prevention, and eradication of many communicable and non-communicable diseases, mental illness and addiction remain common and undertreated. Despite the prevalence of mental illness and addiction and its documented impact on overall health and quality of life, as many as two-thirds of people who live with a mental illness in the United States may not receive any form of treatment [15].

The Individual Burden of Mental Illness and Addiction

While the socioeconomic burden of mental illness and addiction is immense, the impact of these disorders at the individual level is equally overwhelming. Living with mental illness or addiction can impact nearly all aspects of one's life, from personal and familial relationships, to career prospects and opportunities, to physical well-being and health outcomes. In the United States, individuals who live with a mental illness or addiction are significantly more likely than the general population to experience homelessness at some point in their lifetime [16]. Unemployment is also more common among those with a mental illness or addiction [17]. People with severe mental illness are also more likely to suffer from a range of physical illnesses when compared to the general population [18] and experience excess mortality two to three times greater than the general population, leading to a shortened life expectancy by 10–25 years [19]. During the pandemic, though initially underrecognized, people with mental disorders including addiction were disproportionately affected by infections and experienced greater mortality than other individuals [20, 21].

Adding to this tragedy, many living with mental disorders or addiction are victimized for their conditions and become targets of stigma and discrimination. Approximately 60% of people express an unwillingness to work closely with a person with a severe mental illness or addiction, and a similar percentage of people believe that those with mental illness or addiction are violent [22]. In reality, individuals with severe mental illness are more likely to be the victims of violence than other community members [23]. This stigmatization and victimization can lead individuals with mental illness and addiction to self-stigmatize and can ultimately discourage them from seeking appropriate care and treatment [24]. The negative impact of isolation during the pandemic was felt greatly by people living with mental disorders, in part because their social networks and resources are intrinsically more fragile [25–28].

Beyond the facts and figures, the nature of these types of disorders qualitatively impacts the day-to-day life of individuals in ways that are very difficult, if not impossible, to measure quantitatively. By definition, mental disorders involve a decline in one's capacity to function well and with fulfillment and joy. It is thus unsurprising that mental, neurological, and substance use disorders are serious risk factors for premature death. Of people who commit suicide, 45% have a known mental health condition [29].

Progress and the Ongoing Burden

Over the past decades, efforts to reduce the burden of mental illness and addiction have been initiated at local, national, and international levels. In 2015, the United Nations General Assembly adopted the World Health Organization's Sustainable Development Goals (SDGs), which addressed global health targets for the upcoming 15 years. This adoption of the SDGs was the first time that world leaders promoted mental health as a health priority within the global development agenda and declared it an integral piece of sustainable development [30]. Beyond promoting the reduction of premature mortality through increased mental health care and treatment, the SDGs also targeted strengthening the prevention and treatment of substance abuse disorder.

At a national level, the United States' National Institute of Health launched the BRAIN Initiative in 2013, with the goal of developing innovative tools and technologies necessary to better understanding the structure and functioning of the brain. As of the start of 2020, the BRAIN Initiative has awarded over $1.3 billion to over 700 investigators. Similar initiatives have emerged across the globe, and in 2017, a Declaration of Intent for an International Brain Initiative was announced, with representation from Japan, Korea, Europe, the United States, Australia, Canada, and China [31].

At state and local levels, awareness of mental health issues has increased through community outreach programs, marketing campaigns, and the use of social media. In 2013, the state of California launched a large-scale social marketing campaign

that was intended to reduce stigma surrounding mental health issues. Preliminary findings show that individuals who were mentally ill who were exposed to the campaign were more likely to receive treatment for their illness, and it was estimated that if all Californians with a mental illness had been exposed to the campaign, the number of those seeking treatment may have increased by one-third [32].

Although this progress is extremely promising for the future of treating mental illness and addiction, the known number of individuals living with serious mental illness continues to increase [2]. Due to the complexity of mental illness, treatments that are effective for some do not provide any benefit to others, and access to effective care and treatment often remains limited to those who do not have adequate resources or support. In the context of the pandemic, which led to nearly 5.5 million deaths world-wide as of December 2021, many health resources were redirected to respond to the overwhelming crisis of infection with the SARS-CoV-2 virus. In addition, many health care providers tragically died as a result of the pandemic, and the workforce was further diminished by physical and psychological risk, burnout, compassion fatigue, and exhaustion associated with prolonged and unrelenting effort and exposures in health care activities. This shift and reduction in resources have been felt greatly by people with chronic and co-occurring conditions, including many with mental disorders. While scientific progress in all medical fields is a slow, concerted effort, the complexity of the brain and the difficulty involved in accessing it create additional challenges that can further impede advancement in the fields of mental health, neuroscience, and psychiatry.

Relief Through Innovation

As researchers, doctors, governments, and individuals continue to gain a more nuanced understanding about how mental illness and substance abuse impact individuals, families, and communities, we turn toward increasingly innovative and novel research on these conditions in hopes that progress toward a healthier and less-burdened world is possible. Recent advancements in technology, computing power, and public understanding of mental illness and addiction have set the stage for major developments toward the understanding of the human brain and the treatment of various of major mental illnesses.

These advancements have occurred, and continue to occur, across all levels of psychiatry and neuroscience. For example, since its discovery in 2005, the field of optogenetics has flourished, leading to unprecedented discoveries about how clusters of individual neurons communicate [33] and how the brain changes after a stroke [34], in addition to allowing for more precise mapping of the brain [35]. Advancements in cloud computing and internet speeds have allowed for the development of open-source data-sharing databases such as OpenfMRI, which permit researchers from across the globe to share neuroscience data, with the goal of increasing data validity and replication in order to better address questions

regarding human brain structure and function, and ultimately to better treat mental illnesses [36–38].

Advances in basic science and technology have additionally moved beyond the laboratory and into the lives of patients who suffer from mental illness and addiction. Deep brain stimulation (DBS), a neurosurgical procedure where an implantable pulse generator is placed directly against relevant structures in the brain, is approved as a treatment for advanced Parkinson's disease and dystonia and is currently being studied as a therapeutic intervention for obesity and obsessive-compulsive disorder [39]. Within the past decades, developments in the non-invasive procedure of transcranial magnetic stimulation (TMS) have allowed 30–40% of patients with treatment-resistant depression to experience remission of depressive symptoms, with fewer side effects than antidepressant medications [40, 41]. Certain specific types of TMS, administered in novel ways, have led to dramatic recovery in even very treatment-resistant individuals [42, 43]. The FDA approval of intranasal ketamine in 2019 has provided a similar cohort of patients with an opportunity to ameliorate their symptoms [44]. Innovation in telehealth and the use of algorithms and precision psychiatry strategies to identify individuals who would most benefit from intervention have led to scalable opportunities that are unprecedented in the field of mental health [45].

Neuroethics and the Foundation for this Book

There is great hope that, through continued innovation in neuroscience, the global burden of mental illness and addiction can be relieved. With this hope and advancement, however, it is important to recognize the unique and important circumstances of the people and populations affected by brain disorders with mental health, addiction, behavioral, and psychosocial dimensions.

Mental illness in particular "affects aspects of life that we define as fundamental to being human," and the treatment of mental illness "involves techniques that require exploration of intimate aspects of patients' lives and interventions that in some cases may limit the freedoms of patients" [46, p. 3–4]. These distinctive aspects of mental illness, and brain disorders more broadly, paired with the misunderstanding, isolation, and stigmatization that often come hand-in-hand, form a population of individuals who may be exceptionally vulnerable in research and medical contexts.

As research involving populations with mental illness and addiction continues to progress into more innovative and hopefully more beneficial realms, it is important to keep in mind concerns related to the nature of these illnesses, stigma, lack of resources, and public trust in research institutions and researchers. Investigation of the place of neuroinnovation and clinical neuroscience in society, including the ethical dimensions of these domains and safeguards that undergird public trust, is imperative.

Table 1.1 Examples of funded grant proposals related to research ethics led by Dr. Laura Weiss Roberts (Principal Investigator), 1997-present

Years	Grant proposal title	Funder
2018–2020	*Enabling ethical participation in innovative neuroscience on Alzheimer's Disease and Related Dementias* (administrative supplement to R01 MH114856)	National Institutes of Health
2017–2021	*Enabling ethical participation in innovative neuroscience on mental illness and addiction: towards a new screening tool enhancing informed consent for transformative research on the brain* (R01 MH114856)	National Institutes of Health
2014–2015	*Ethical implications of excluding the mentally ill from medical treatment research*[a]	Greenwall Foundation
2008–2010	*Research for a healthier tomorrow—program development fund*	A component of the advancing a healthier Wisconsin endowment at the Medical College of Wisconsin
2006–2012	*Ethics and safeguards in genetics research* (R01 MH074080)	National Institute of Mental Health and National Human Genome Research Institute
2004–2007	*Genetics and ethics: worker perspectives* (DE-FG02-04ER63772)	U.S. Department of Energy
2002–2004	*Barriers to care for rural runaway youth* (administrative supplement to DA013139)	National Institute on Drug Abuse
2000–2002	*Healthy, ill, and working individuals' perspectives on ethical, legal, and social implications in complex genetic disorders* (ER63018–2387)	U.S. Department of Energy
1999–2004	*Stigma and rurality: drug abuse, HIV/STD and mental illness* (R01 DA013139)	National Institute on Drug Abuse
1999–2004	*The ethics of psychiatric research: Science and safeguards* (K02 MH001918)	National Institute of Mental Health
1999–2002	*Informed consent and surrogate decision-making in schizophrenia: perspectives of patients and their families*	National Alliance for research on schizophrenia and depression
1997–2000	*Vulnerability and informed consent in clinical research* (R01 MH058102)	National Institute of Mental Health and National Institute on Drug Abuse

[a]Laura Weiss Roberts served as Co-Principal Investigator, Keith Humphreys served as Principal Investigator, Philip Lavori served as Co-Investigator

This central concern is the impetus for the research led by one of us (LWR) over decades (see Table 1.1) and represents the fundamental premise of this book on neuroinnovation and ethics. **By anticipating, eliciting, and addressing the ethical issues that may emerge alongside innovative research on conditions originating in or affecting the brain, public trust in clinical neuroscience and psychiatry can be strengthened. By being rigorous, honest, self-observing, and deeply connected to the ecology of neuroscience and psychiatry, we can work**

collaboratively with stakeholders across society to ensure that the greatest benefits possible can be reaped from scientific advancement and at the same time do our best to ensure that the greatest harms and risks are identified and avoided.

The intention of this book is thus to further understanding of the developing field of neuroethics, specifically in the context of innovation and scientific inquiry related to clinical neurosciences. This first section, *Foundations of Ethics in Clinical Neuroinnovation*, lays the groundwork for further discussion by exploring the historical, ethical, and contextual roots of the subject. Specific use cases of neuroinnovation, and the ethical issues they may reveal, are discussed in section two, *Special Topics in Clinical Neuroinnovation.* In section three, *Neuroethics and Innovation: Inquiry informed by the Roberts Valence Model,* we document our team's research into better understanding the ethically salient perspectives of various stakeholders involved in neuroinnovative projects.

The scope of this book is limited to foundational and special topics in clinical neuroinnovation and the framework and qualitative phase of our project on neuroethics funded by the National Institutes of Health BRAIN Initiative. We have also included an introduction to the quantitative work associated with the pilot portion of our project in an Appendix (see Appendix 1). The full quantitative findings of our project and our related competitive supplement project on Alzheimer's disease and innovation are beyond what is possible to cover in this book.

The editor (LWR), authors, and research team who have developed this book may not agree with everything that appears in the chapters that follow. And many impressions may be corrected and many facts may emerge in the coming years. This book documents a spectrum of views and findings. We consider this work to be a "snapshot" that captures many different viewpoints, including, very importantly, perspectives of people living with mental health concerns and addiction, investigators, ethicists, scholars, policymakers, and thought leaders, at this time. The content of this book is, by its nature, complex and newly emerging. Shared understanding, principles, and societal congruence regarding neuroethics does not yet exist but we hope that work, such as recorded here, will help create this new foundation. These chapters, and the varied perspectives and the data proffered, will help define an ethical framework for clinical neuroinnovation. Further elucidation of this framework is critical if the benefits of highly innovative neuroscience are to be realized.

Key Points
1. Mental disorders account for nearly one-third of years lived with disability (YLD) across the globe, and 13.0% of disability-adjusted life years (DALY), making them the resounding leading cause of global burden of disease in terms of YLDs and level with cardiovascular and circulatory disease when it comes to DALYs.
2. Especially in light of the mental health and neuropsychiatric impact, including regarding addiction, of the COVID-19 pandemic, these estimates are low and insufficient to capture the true impact of mental illness.

3. The need to better understand, prevent, and treat mental illness has gained traction politically, with specific commitments toward focus and funding from the United Nations, the World Health Organization, and, nationally, the U.S. Government's BRAIN Initiative.
4. Highly innovative neuroscience has great transformative potential in reducing the burden of mental illness and related disorders.
5. Ethical frameworks that specifically address innovative research in the context of neuroscience are fundamental requirements to fully realize the potential of clinical neuroinnovation.

Questions to Consider
1. How has globalization influenced our understanding of mental illness and its effects?
2. How does innovation in the realm of neuroscience compare to innovation in other sectors (technology, medicine, etc.)? Where are the ethical concerns similar and where might they diverge?
3. What distinctive characteristics of mental illness affect our understanding of ethics in research?

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Further Reading

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Chapter 2
Neuroinnovation in Medicine: History and Future

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Neuroscience is currently in a golden age [1] made possible by the ever-accelerating pace of new tool development. On the one hand, advances in neuroimaging techniques such as diffusion tensor imaging (DTI) have enabled researchers to elucidate high-resolution wiring blueprints of the human brain [2]. On the other hand, the development of fundamental interventional tools such as optogenetics [3], deep brain stimulation (DBS) [4], and transcranial magnetic stimulation (TMS) [5] have allowed researchers to probe and modulate brain circuits with unprecedented precision. Increasingly, insights derived from basic research are being translated into clinical therapeutics. We are entering an era in which neuroinnovation-driven advances in knowledge of the brain are sophisticated enough to allow for development of effective, rationally designed treatments for a large and increasing number of psychiatric conditions (such as major depressive disorder (MDD) and obsessive-compulsive disorder (OCD)), giving rise to the new field of interventional psychiatry [6]. This has not always been the case.

A Historical Perspective

For most of history, the origin and causes of mental illnesses were unknown, and descriptions of mental illnesses were based on behavioral observations and subjective reports. A limited understanding of the neurobiological basis of mental disorders resulted in many individuals subjected to questionable treatments such as surgical frontal lobotomy [7]. Psychiatry lacked a neuroscientific

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foundation on which to appropriately diagnose and treat patients due to limited knowledge and insufficient tools to visualize, probe, and manipulate brain activity.

Things began to change in the twentieth century when innovations in neuroscience provided a framework for characterizing and treating mental illnesses. The development of the microscope led to pioneering work by Camillo Golgi and Santiago Ramon y Cajal, leading to the elucidation of the neuron as the fundamental unit of the nervous system [8]. Advances in biochemistry and electrophysiology helped characterize the chemical and electrical properties of neurons, establishing the molecular basis of neurotransmission. This in turn gave rise to the field of psychopharmacology and the development of modern psychiatric drugs. To this day, the vast majority of psychiatric treatments involve medications, such as selective serotonin reuptake inhibitors (SSRIs), whose fundamental mechanism of action appears to be modulation of neurotransmission at the synapse, although other theories have been proposed [9, 10].

As advanced and useful as psychotropic medications may be, one persistent problem has been the nonspecific distribution and action of such medications throughout the entire brain, leading to side effects. For example, most antipsychotic medications are thought to exert antipsychotic effects by blocking dopamine-2 (D2) receptors in areas of the brain responsible for cognition and perception but may also cause motor side effects (so-called extrapyramidal symptoms) by blockage of the same D2 receptors in the basal ganglia [11]. Another problem is treatment resistance; up to 30% of patients with major depressive disorder fail to remit with standard pharmaceutical interventions [12], indicating the need to develop alternative modalities of treatment.

Developing more precise and effective brain treatments required an increasing understanding of the neural basis of disease and the development of interventional tools to safely modulate brain activity. Prior to the advent of modern neuroimaging, establishing correlations between brain and behavior was slow, painstaking work. Neuroanatomists had long observed relationships between localized brain lesions and distinctive psychological and behavioral abnormalities (for example, Broca and Wernicke's work in the mid-nineteenth century [13]), but progress was slow due to the invasive nature of then-available analysis tools of autopsy and gross examination of the post-mortem brain.

The advent of noninvasive neuroimaging, first detailing brain structure, then elucidating brain activity, vastly accelerated the knowledge of human brain–behavior relationships, and with it our understanding of the neural basis of psychiatric and neurologic illness, setting the stage for the subsequent development of neuroinnovative treatments.

A Brief History of Neuroimaging

For much of the twentieth century, medicine actively sought search a noninvasive, high-resolution method to image the living human brain.

The discovery of X-rays by Wilhelm Roentgen in 1895 revolutionized medical imaging but unfortunately did little to shed light on brain structure, which remained a largely invisible "dark continent" [14]; X-ray technology at the time could not distinguish between different soft tissues. In 1918, the neurosurgeon Walter Dandy hit upon the idea of introducing contrast materials such as air into the ventricles (*air ventriculography*) of his patients, allowing for crude X-ray visualization of the ventricular system. Later, in 1927, the Portuguese neurologist Egaz Moniz pioneered and subsequently refined the technique of *cerebral angiography*, which allowed indirect visualization of brain structures via the introduction of contrast medium into the cerebral vasculature [14].

The development of computerized axial tomography (CAT) by Godfrey Hounsfield in the 1960s revolutionized brain imaging. Hounsfield's insight, based on principles developed by Alan Cormack, was that X-ray images taken from numerous angles ("axial") could be reconstructed by computer algorithms ("computed tomography") to generate three-dimensional images that could distinguish between various types of soft tissues. In 1968, he produced the first picture of a human brain (encased in lucite) that could distinguish gray matter from white matter [14]. Because of it's obvious potential, the British Medical Research Council helped fund the rapid development of a prototype that could scan a living human head. The first scan of a living patient was conducted on October 1, 1971 at Atkinson Morley's Hospital in London. Although the resulting brain image was crude by today's standards (the image was only 80 by 80 pixels), it was good enough to visualize a frontal brain tumor in the patient, which was promptly resected. Within 5 years, 475 CT scanners were in use in US hospitals, and by 1981 CT scanners were installed in 46% of all large hospitals in the US [14].

As impressive as CT brain scans were at the time, they could only visualize brain structure, not brain activity. Researchers soon realized, however, that principles of computed tomography could be applied to visualize the distribution of radioactive tracers injected into the brain's blood supply, and the positron emission tomography (PET) scan was born [15]. PET scans are based on the principle that radionuclide tracers injected into the bloodstream concentrate in areas of increased neural activity. Radionuclides, which are unstable, emit positrons as they spontaneously decay. These positrons travel an average distance of 2–3 mm before eventually colliding with an electron, resulting in mutual annihilation and the generation of a pair of gamma rays which are detected by an array of gamma ray detectors arranged around the head. By applying principles of computed tomography, a 3-dimensional image reflecting the spatial distribution of radionuclides can be reconstructed [16]. Depending on the radionuclide tracer used, different aspects of brain function can be measured and localized, such as oxygen consumption (using $^{15}O_2$), glucose utilization (using ^{18}F-deoxyglucose), and blood flow (using $H_2^{15}O$). Indeed, one of the great strengths of PET imaging is the large variety of radioactive tracers available which can quantitatively measure a large array of brain functions [17].

PET scans, however, suffer from several significant limitations. The spatial resolution of PET imaging is relatively poor due to the fact that emitted positrons travel an average of 2–3 mm from their source before colliding with an electron (the event which generates the gamma rays used for localization), thus limiting spatial

resolution to typically 6–8 mm^3 voxels [16]. *Voxels* are three-dimensional pixels which comprise the basic "building blocks" of three-dimensional images; smaller voxels result in higher resolution images. In addition, the expense of PET scan machines and the need to have particle accelerators nearby to generate radionuclides with short half-lives limit the number of PET studies possible. Finally, while PET scans are noninvasive, they do involve the injection of radioactive materials, raising safety concerns for participants.

Functional Magnetic Resonance Imaging (fMRI)

The development of functional MRI largely circumvented the limitations of PET scanning, thus becoming the functional imaging modality of choice in the modern era. Machines capable of acquiring fMRI scans are widely available, as they are captured using the same machines that perform structural MRIs. Further, MRI scans do not involve the use of radioactive tracers, use magnetic fields which are considered safe, and routinely achieve spatial resolutions down to less than 1 mm^3 [18]. Depending on the strength of the main magnetic coil (stronger magnets produce higher resolution images), resolutions as fine as 0.1 mm may be theoretically achieved [19]. Structural MRIs are based on the principle that many nuclei, such as hydrogen ions, possess magnetic properties (*angular momentum*) which vary depending on their surrounding chemical environment. These magnetic properties can be probed by the application of strong magnetic fields and radiofrequency pulses, forming the basis of identification of chemical compounds by *nuclear magnetic resonance* (NMR) spectroscopy. In 1973, Paul Lauterbur and Peter Mansfield hit upon the idea of applying graded magnetic fields to localize NMR signals in space, forming the basis of *magnetic resonance imaging* [14]. The resulting MRI images could differentiate different types of biological matter (for example, cerebrospinal fluid, white matter, and gray matter) based on their differing magnetic properties [18].

Early attempts to measure brain activity with MRI focused on techniques to measure cerebral blood flow, taking advantage of the fact (established in earlier PET studies [20]) that regional blood flow and regional brain activity are highly correlated. The exact mechanism of this *cerebral autoregulation* is still unclear, but from a functional perspective, it appears to be based on the fact that neurons are entirely dependent on glucose as an energy source. Since the brain contains very limited glucose reserves, increased neural activity must be supported by an increased rate of delivery of glucose, which is accomplished by increased blood flow [21].

Initially, researchers injected magnetic contrast agents such as gadolinium into the bloodstream, which, by virtue of its sequestration in the intravascular space, could be imaged to measure localized cerebral blood volumes [22]. Using this technique, Belliveau and colleagues were able to map out human visual cortex using MRI by visualizing areas of increased blood flow in response to a flickering stimulus known to strongly drive activity in visual cortical neurons [23]. It was Ogawa and colleagues, however, who revolutionized functional MRI (fMRI) with the discovery of blood oxygenation level-dependent (BOLD) contrast [24]. In essence,

Ogawa and colleagues rediscovered Linus Pauling's original 1936 finding [25] that hemoglobin (the principal oxygen-carrying molecule in red blood cells) has slightly differing magnetic qualities when bound or unbound to oxygen. Ogawa serendipitously found that these differences could be visualized by MRI, enabling the creation of real-time maps of blood oxygenation levels in the brain without the need for contrast agents. Relative blood oxygenation levels (the basis of the BOLD signal) could then be used to infer regional brain activity (regions of the brain that "work hard" recruit more blood flow, raising regional blood oxygen levels). Soon after Ogawa's discovery, a slew of studies demonstrated the use of the BOLD signal to detect regional increase of neural activity, and the fMRI was born [26–29].

Distributed Processing and Functional Specialization

The advent of functional brain imaging laid to rest a long-running debate about the nature of brain computing, characterized at one extreme by *localists* such as Franz Joseph Gall, and on the other by *holists* such as Pierre Flourens. Gall first proposed in the early 1800s his theory that the mind arose from operations of the brain, with each mental faculty localizing in a 1:1 manner to a specific brain area. He identified at least 27 distinct regions which were purported to correspond to a wide range of behaviors and mental states such as generosity, secretiveness, and religiosity [30]. Gall's ideas led to the development of the (now) much-maligned field of *phrenology* (an extension of the then popular science theory of *physiognomy*) which postulated that a person's "character" could be determined by bumps and ridges on the skull, the idea being that mental faculties that were exercised would lead to growth of corresponding brain areas which could be detected by protrusions into overlying skull bone. Unfortunately, although many of Gall's ideas were prescient, they were not based on empirical data such as brain lesion studies, and in retrospect were naive and overly simplistic.

On the other hand, advocates of the *holistic* view of the brain, such as the physiologist Pierre Flourens, believed that brain computing was accomplished in a totally distributed manner, so that any part of the brain could perform any function, akin to the generic computer servers that comprise cloud computing. Flourens' theories (based on his work in the 1820s making focal lesions in animals) were carried into the twentieth century by advocates such as Karl Lashley, who noted in his experiments that rats who were given brain lesions and then had to learn to navigate a maze, appeared to have learning deficits that corresponded to the size of the lesion and not to the specific area of the lesion. Lashley concluded, in his theory of *mass action,* that it was the total mass of the brain that was important to accomplish mental functions, not specific brain areas [30].

Over time, however, converging evidence emerged favoring localist theories of brain function [30]. Broca and Wernicke's work on stroke patients in the mid-nineteenth century localized specific language deficits to specific areas of cortex (now referred to as *Broca's area* and *Wernicke's area*). Hughling Jackson's work on patients with focal epilepsy strongly suggested that motor and sensory functions were based on different areas of cortex. Painstaking work at the microscopic level

by the anatomist Korbinian Brodmann elucidated at least 52 distinct brain areas (*Brodmann's areas*) distinguished by differences in cell morphology and spatial arrangement (*cytoarchitectonics*), supporting the idea that distinct cortical areas were specialized for distinct functions [31].

Meanwhile, electrophysiologists Gustav Fritsch and Eduard Hitzig demonstrated in 1870 that electrical stimulation in discrete areas of precentral gyrus in dogs caused characteristic limb movements—in effect, they discovered primary motor cortex and its topographical organization. Later, topographical maps of motor and somatosensory cortex were directly demonstrated in humans by neurosurgeons such as Wilder Penfield in the 1950s, who electrically stimulated discrete areas of cortex as part of functional mapping preceding epilepsy surgery [32]. Electrophysiological work by Hubel and Wiesel in the 1950s–1970s pushed mapping to the extreme, elucidating the exquisite retinotopic organization of cat visual cortex and its spatial segregation into ocular-dominance and orientation-selective columns [33].

The advent of functional brain imaging techniques revolutionized our understanding of how the human brain accomplishes tasks. Unlike lesion studies or electrophysiological stimulation studies, simultaneous activity patterns across the entire brain could be seen for the first time. Further, because functional brain imaging is noninvasive, extensive studies in humans became possible. The consensus model of brain function that has emerged from thousands of functional imaging studies is *distributed processing* [34], which integrates ideas from both localist and holistic paradigms. The distributed processing model of brain function acknowledges that brain areas are specialized for basic functions (*functional specialization* [35]) but extends localist models by positing that the brain accomplishes any given task by dynamically recruiting a set of localized/specialized cortical modules, which act in a coordinated, circuit-based fashion to produce the desired result. This is akin to how different apps on smartphones differentially activate computer chips, each specialized for various functions (GPS, graphics, sound, memory, etc.), which work as an ensemble to accomplish the tasks required by the app.

The distributed processing model explains both why lesions to specific areas can cause specific deficits, and why sometimes they do not—for example, some complex tasks such as speech generation rely heavily on specific cortical modules (e.g., Broca's area) which are critical to the task, while other tasks such as maze-learning are accomplished by a flexible network of modules with some redundancy, so that destruction of any one cortical module does not destroy the overall ability [36].

Key Neuroinnovation: Elucidation of the Human Connectome

Recent advances in neuroimaging techniques have allowed researchers to image connections between brain areas at a large scale, resulting in the elucidation of the *human connectome*, essentially a blueprint for the wiring diagram of the human brain, revealing the anatomical basis allowing for coordinated activities of distributed networks. This was a significant milestone in neuroscience, and the basis of a new approach in conceptualizing and treating brain disorders as "circuitopathies" [37].

Early attempts at elucidating brain connectivity were slow and laborious, involving the injection of radioactive, fluorescent, or viral tracers into specific brain areas in laboratory animals, waiting days to weeks for the tracer to diffuse down axonal pathways, then sacrificing the animal and visualizing pathways of tracer diffusion in brain slices, which could then be laboriously reconstructed to form a 3D image of a specific axonal pathway (for example, [38]). In a technical tour de force, investigators at the Allen Institute pushed this technique to the limit, generating a reasonably detailed whole-brain connectivity map of the mouse brain by injecting fluorescent viral tracers into hundreds of non-overlapping anatomical brain locations and reconstructing the resulting labeled fiber pathways in 3D [39].

Obviously, such tracer studies would not be possible in living human subjects. It is only recently that noninvasive neuroimaging techniques became refined enough to visualize brain connectivity in the intact human brain. One of these, *diffusion tensor imaging* (DTI), relies on the fact that while MRIs do not have the resolution to directly visualize axonal pathways, they do have the ability to track diffusion patterns of water molecules. Because water molecules in neurons are more likely to diffuse up and down the axon, rather than across it (a property referred to as *anisotropic diffusion*), tracking the diffusion of water molecules indirectly visualizes anatomical fiber tracts [2]. The other technique, *resting-state fMRI* (rs-fMRI), relies on statistical analysis of fMRI brain scans of subjects while at rest (in contrast to *task-based* fMRI, in which brain scans are recorded while subjects are engaged in a particular task of interest). Brain areas naturally fluctuate in activity over time, and by analyzing which brain areas fluctuate together (either correlated or anticorrelated), inferences can be drawn regarding functional connectivity [2].

Together, these two approaches, which map brain connectivity in complementary ways (DTI visualizing anatomical connectivity, rs-fMRI revealing functional connectivity), have formed the methodological basis of a large-scale, publicly funded (in part by the BRAIN initiative), multicenter collaborative effort known as the Human Connectome Project (HCP, http://www.humanconnectomeproject.org/), whose goal is to create highly accurate, high-resolution connectivity maps of the human brain based on thousands of high-quality brain scans [40]. At this point, the HCP has amassed data on over 1100 human subjects to form a brain connectivity map with unprecedented accuracy and resolution. The consortium has made all this data freely available to the research community, along with tools to help researchers navigate the data. This invaluable resource, a high-resolution map of brain connectivity, has played a vital role in advancing circuit-based understanding of psychiatric illnesses [36], opening up the potential for circuit-based approaches to treatment [37].

From Neuroinnovation to Neurotherapeutics for Depression

The increasing availability of neuroimaging tools in the 1980s and 1990s led to converging observations that informed initial models of the neural bases of major depression; these models then provided a road map, identifying potential targets of