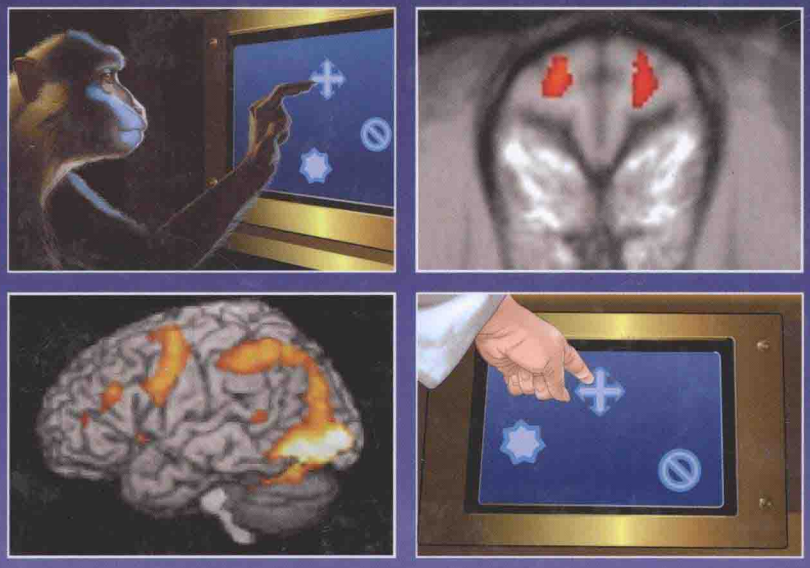
Translational Neuroimaging

Tools for CNS Drug Discovery, Development and Treatment



Edited by

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Academic Press is an Imprint of Elsevier

Academic Press is an imprint of Elsevier
32 Jamestown Road, London NW1 7BY, UK
225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-386945-6

For information on all Academic Press publications
visit our website at elsevierdirect.com

Typeset by TNQ Books and Journals Pvt Ltd.
www.tnq.co.in

Printed and bound in United States of America

12 13 14 15 16 10 9 8 7 6 5 4 3 2 1

Dedication

This book is dedicated to my friend and wife, Silvia Gatti-McArthur, who has been my constant support and companion throughout this enquiry into the translational relevance of methods, models, and biomarkers for CNS drug discovery and development. It was she who first encouraged me to take my enquiry beyond my area of expertise and to focus on translational neuroimaging. Thanks to her I have spent many an hour learning and debating its pros and cons. Thank you and T. for putting up with me and pointing me in the right direction.

Preface

Brain Imaging
Translational Tools for CNS Drug Discovery, Development, and Treatment

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1.0. INTRODUCTION

There has been an evolving crisis in the discovery and development of new drugs for the treatment of neuropsychiatric or central nervous system (CNS) disorders. Although therapeutic advancements in the treatment of some neurological disorders, for example multiple sclerosis, have been made,[1,2] no major drug for the treatment of psychiatric disorders with a truly novel mechanism of action has been registered since the middle decades of the 20th century.[3–6] This is despite the great and significant inroads that have been made in our understanding of the molecular and genetic

basis of these disorders and technological advancements available to study the brain and its biology, as well as an ever-increasing number of potential therapeutic drug targets.[7,8] Major initiatives have been proposed and implemented to address this issue[9] but, even so, costly Phase III failures are forcing major drug companies to abandon further CNS research.[10,11] There is an urgent need to realign preclinical drug discovery and development with clinical studies, particularly at the experimental medicine interface, to improve the chances of novel drug candidates being registered as effective treatments for neuropsychiatric disorders.

Translational research is one of the initiatives proposed to improve the registration rate of CNS therapeutic drugs.[12–14] There are many definitions of translational research.[15,16] In terms of CNS drug discovery and development, we have pragmatically defined it as the reciprocal partnership between preclinical and clinical research to further new molecular entities or compounds identified through the application of basic scientific discoveries, optimized into potential drug candidates, and eventually developed into clinically effective medications.[17]

Brain imaging has evolved into one of the main translational tools for the study of CNS function and its various psychiatric and neurological pathologies, and for the discovery and development of novel drugs that can be used for the treatment of CNS disorders'.[18–20] Neuroimaging fulfills many roles in the CNS drug discovery, development, registration, and treatment process, which include techniques by which the neurobiology of neuropsychiatric disorders can be studied and understood—especially in terms of systems biology and monitoring the interactions of novel molecules with neurobiological structures and systems. The fundamental role of neuroimaging has been the identification and validation of biological markers that can detect and differentiate neuropsychiatric disorders, monitor the rate of deterioration and impairment as the disorder progresses, and determine how this deterioration can be modified through therapeutic intervention.[21–29]

1.1. Biomarker Identification and Validation

Many putative biomarkers of neuropsychiatric disorders have been identified and proposed.[30] However, it is not sufficient simply to observe that a given biological phenomenon is associated with a particular neuropsychiatric disorder, or indeed that the phenomenon occurs *reliably* with the disorder, to qualify it as a biomarker.[21,26,31] Biomarkers, like animal models of the neuropsychiatric disorders, must undergo rigorous tests of validity[32–34] before being accepted as such.

Model development in animals and humans, including the identification and validation of biomarkers, is crucial for translational CNS drug discovery and development. Though no one animal model can fully recapitulate a neuropsychiatric disorder, the aspects of the disorder being modeled help us not only to understand the neurobiology of CNS disorders but also to identify and validate molecular targets that can be manipulated pharmacologically and through which the responses to these manipulations can be monitored.[35–38] Cross-species and homologous comparisons of these responses are fundamental for translational models.

Traditionally, animal models of CNS disorders have relied upon experimental manipulations that produce behavioral anomalies similar to the abnormal behaviors of humans, i.e. models endowed with great face validity. This modeling approach by analogy has been successfully exploited to produce more

specific drugs with arguably less harmful side effects than the first drugs discovered serendipitously during the middle decades of the last century. However, they have not been so successful in predicting the eventual clinical efficacy of compounds based upon new molecular targets and mechanisms of action. The predictive validity of traditional models has thus been questioned[39] and defended.[35,40]

The identification (and validation) of reliable biological markers of status, progression, and amelioration of CNS disorders that are homologous in animal and humans would contribute greatly to the construct and predictive validity of models, acquire regulatory body recognition and approval, and improve the probability of an innovative investigational compound with a novel mechanism of action achieving registration. The construct validity of animal and human models of neuropsychiatric disorders is based upon our knowledge and understanding of their biological underpinnings.[32,37] Notwithstanding the limitations of small animal neuroimaging discussed throughout this volume, this technique is being used extensively to characterize drug action in the brain and to provide construct validity not only to numerous animal models of abnormal behavior but also to putative biomarkers of the progression of behavioral disorders and their pharmacological amelioration.

Human and small animal neuroimaging is limited by methodological and standardization problems.[23,25,41,42] Nevertheless these techniques are capable of tracking the course of a disorder in humans and model systems, as well as tracking the effects of a potential therapeutic intervention with a known mechanism of action.[29] For example, changes in glucose metabolism, amyloid deposition, and altered brain structure can be reliably identified, tracked, and used to define stages of the disorder and differentiate Alzheimer disease (AD)[23,25] from other dementing disorders. The value of these biomarkers cannot be underestimated, particularly to help select subjects with a high probability of developing AD for clinical trials. Amyloid positron emission tomography (PET) can even track the changes in amyloid deposition induced by drugs targeting amyloid. However, an AD biomarker capable of substituting for a clinically meaningful endpoint, such as extended survival with improved cognition and function, and predicting the outcome of the therapeutic intervention[28] is still to be achieved.

Translational Neuroimaging: Tools for CNS Drug Discovery, Development, and Treatment is part of a series examining the translational value of animal models and other tools to further neuropsychiatric drug discovery and development.[43–45] In order to do so, contributors have been carefully selected from the foremost academic and industrial clinical and preclinical researchers involved in the process of drug discovery and development, as well as the treatment of neuropsychiatric patients. Translational neuroscience is a team effort, from the original synthesis of a compound, its testing and optimization, and clinical testing to its ultimate registration and prescription. In this spirit, therefore, the authors have been asked to collaborate as coauthors to examine the translational value of neuroimaging not only from their individual perspectives, but to then present a consensual view of their topic of enquiry.

Translational Neuroimaging: Tools for CNS Drug Discovery, Development, and Treatment is structured into two sections. The first section introduces the fundamental concepts of neuroimaging, the various neuroimaging modalities being used, how neuroimaging is used to study CNS disorders in general, and specifically how neuroimaging is being used for CNS drug discovery and development. It

focuses on the translational value of neuroimaging by discussing its unique contribution to neuroscience, but also the methodological issues that limit its use in humans and animals. Three introductory chapters are presented in the first section of the book.

2.0. FUNDAMENTALS OF NEUROIMAGING

In Chapter 1, Wise[46] presents a general overview of neuroimaging modalities and the physiological, metabolic, and functional measurements that are possible. Similar overviews also form part of the introductory material presented by the authors of several other chapters. Neuroimaging is characterized by an array of various modalities from X-rays, electroencephalography (EEG), PET, magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS), for example, each accompanied by their acronyms. This array can be so bewildering to the nonspecialist that a roadmap is considered appropriate. Each neuroimaging modality has its strengths and weaknesses. No one modality is sufficient to give a complete view of the brain or the effects of drugs on the brain and, indeed, various neuroimaging modalities can and are used in combination to give a more complete view. Neuroimaging provides a window into the brain, its structure, activation, and metabolic patterns under *default* or resting conditions, as well as in response to challenges such as disease, drugs, environment, or genetics. With appropriate radiolabeled tracers, PET can be used to quantify physiological processes and to *map* the brain, measure cerebral metabolism and blood flow, aid in differential diagnosis, and study receptor systems. PET is used, for example, to determine the engagement of a novel molecule with receptors, which is an essential step for CNS drug discovery and development. One drawback of neuroimaging techniques such as X-rays or PET imaging is the need to subject the body to various forms of radiation: thus, these techniques are limited by exposure levels.

There are a number of noninvasive techniques, of which EEG or magnetoencephalography (MEG) are well known and have been in practice for decades. EEG recordings in response to evoked potentials have long being used in the study of CNS disorders such as schizophrenia, depression, and AD. Magnetic resonance techniques such as MRI make use of physiological responses to magnetic fields without having to rely on radiolabeled isotopes. Changes in the structure of the brain in response to disease, as well as changes in function, can be studied with MR techniques. MRS, on the other hand, can be combined with imaging to detect and quantify changes in metabolites such as N-acetylaspartate, creatine, and choline by tapping into naturally occurring isotopes, which are indicative of neuronal health. Functional MRI (fMRI) is used to study changes in neural activity from changes in cerebral blood flow, volume, and oxygenation. Protocols include blood oxygenation level dependent (BOLD) contrast, which provides good temporal and spatial resolution, especially when examining the brain's response to specific tasks or demands. Arterial spin labeling (ASL) is another protocol used in functional neuroimaging. Functional neuroimaging can be performed under *resting* or *default* conditions, where the brain is assumed not to be responding to overt external stimulation, or in response to an externally applied task or condition such as the administration of a drug (as in pharmacological MRI; phMRI). fMRI techniques have become essential for the study of brain in terms of integrated systems of functional connectivity and how these systems are altered under states of

disease or disorder. phMRI, on the other hand, has been important for the development and use of drugs as pharmacological tools to probe brain function and as a method to characterize the distribution and interaction of novel drugs with brain systems in studies of mechanism of action and proof of concept.

In Chapter 2, Brown[41] presents a detailed explanation of the principles and the physics behind MRI modalities, and considers the strengths and weaknesses of each. The main advantage of MRI modalities is the ability to conduct repeated imaging without the need for contrast agents and multimodal imaging, where multiple readouts are possible from the same subject in a single session. An additional advantage of MRS, for example, is that it enables the assessment of metabolic changes in response to disease or drug exposure. Weaknesses of magnetic resonance modalities include a lack of standardization, which can affect the reliability and reproducibility of the method and intrinsic signal strength or spatial resolution and limit the types of observable nuclei, neurotransmitters, and metabolites, as well as leading to the ambiguous interpretation of some metabolites. Brown discusses the differences between BOLD fMRI and ASL. Both are noninvasive multimodal neuroimaging techniques that provide information about distributed brain function, and protocols exist for deriving BOLD and ASL signals from the same session. Weaknesses of using a BOLD protocol include derived rather than physiological readouts, blood-vein contrast differences, signal drop out due to magnetic field gradients, and image distortion. ASL protocols, on the other hand, are capable of deriving cerebral blood flow readouts in physiological units, minimize the blood-vein contrast limitation of BOLD, and are not as prone to signal dropout. However, ASL protocols have modest temporal resolution and poor signal-to-noise and contrast-to-noise ratios, which contrast with the better spatial and temporal resolution of BOLD protocols.

Small animal imaging is a valuable translational tool not only to study and characterize basic neurobiology in animals but also to help develop and validate models of CNS disorders, and ultimately progress a novel compound from discovery through to early clinical development. However, small animal imaging is restricted by a number of limitations, some of which are shared with human neuroimaging, particularly motion artifacts. In Chapter 3, Ferris and his colleagues[42] address these limitations by modifying the design of the apparatus, improving signal resolution, introducing image analysis software, and habituating animals to the procedure before performing an imaging experiment. For example, anesthesia is generally used to place an animal in a restrainer before being scanned and keep it from moving throughout the experiment. This is a major limitation of small animal neuroimaging because the introduction of an anesthetic is a confounding factor in these experiments, not least because of resulting changes in cerebral blood flow and drug–drug interactions on brain systems of interest.[41,47] Ferris and colleagues have overcome this limitation by habituating animals to the restraint and scanning procedure and independently monitoring the effects using physiological and neuroendocrinological markers of stress. This procedure is repeated over a period of weeks until there is a return to baseline responses.

In the development of animal models for CNS disorders, abnormal behaviors are induced by various manipulations such as acute or chronic drug administration, lesions, and genetic or environmental manipulations. The effects of these manipulations are then assessed using different

endpoints such as behavior, biochemistry, or neuroimaging, which help provide the construct validity of the model.[32] Throughout this book, there are numerous examples of how the construct validity of animal and human models of CNS disorders is assessed. Ferris and colleagues describe the development of a model of anxiety through predatory fear, whose effects are assessed in the conscious animal by neuroimaging. Following the habituation procedure described above, the animal is replaced in the scanning apparatus and subjected to the novel taste of sucrose in the presence of a predator. This presence of a predator elicits a biological fear response conditioned to the taste of sucrose such that physiological responses will be elicited in the absence of the predator during subsequent scanning. This procedure has revealed an integrated neural pathway in the circuit of Papez, on which the effects of therapeutic drug treatment on the behavioral and neuroactivation patterns can be assessed.

3.0. TRANSLATIONAL NEUROIMAGING

The second section of the book is subdivided into specific neuropsychiatric therapeutic areas, which are primarily psychiatric: autism spectrum disorders (ASDs), major depressive disorders, schizophrenia, and substance abuse disorders. These therapeutic areas were chosen on the basis of the extensive use of neuroimaging in their diagnosis and in monitoring the progression of the disorders and the effect of therapeutic intervention. These areas were also chosen to show how neuroimaging contributes to the discovery of novel compounds being developed to treat these disorders. Each therapeutic area in the second section is further subdivided into two chapters. The first focuses on the clinical aspects of neuroimaging techniques, that is, their use as diagnostic criteria and for monitoring disease progression. The second concentrates on the use of neuroimaging as a tool for drug development and validation of human and animal models of the CNS disorder being considered. Throughout the second section of *Translational Neuroimaging: Tools for CNS Drug Discovery, Development and Treatment* the following themes are explored: construct validity of animal and human experimental medicine models through neuroimaging, endophenotypes, imaging biomarkers, imaging genetics, and systems biology.

3.1. Alzheimer Disease

Although this volume concentrates on psychiatric rather than neurological disorders, it should not be inferred that neuroimaging has not had a major impact on basic neurological disorder research, drug discovery and development, and treatment.[48] Psychiatric disorders are defined primarily by clinical behavioral manifestations[49] as opposed to the physical, usually neurodegenerative, phenomena that characterize neurological disorders.[50] AD, however, is a neurological disorder that is characterized both behaviorally and physically. Two chapters examine the role of neuroimaging in the study of this disorder and on differential diagnosis and monitoring the effects of therapeutic interventions.

In Chapter 5, Schmidt and his colleagues[25] present a detailed discussion on PET imaging and its use as a diagnostic tool, a tool to identify and validate biomarkers of AD, and in clinical trials of novel therapeutic agents for its treatment. Neuropsychiatric clinical trials can be particularly problematic, not only because of the lack of neuroimaging standardization leading to poor reproducibility, as discussed by Brown in this volume,[41] but

also owing to the globalization and multiplicity of clinical trial centers, all of which can impact upon the reliability of the measures.[51,52]

Therapeutic effectiveness in psychiatric clinical trials,[51,53] as well as in clinical trials of prospective drugs for some neurological disorders with a strong behavioral component such as AD,[52] is assessed through the use of psychometric rating scales, scales of quality of daily living, and self- or carer assessments. These scales, though validated and used extensively over the years, are beset by many problems, including susceptibility to placebo responses,[54] lack of standardization of training of raters,[55] and cultural differences, especially in multicenter studies done in many countries.[51] Functional endpoints, including neuroimaging, can be measured with great accuracy and precision in both animals and humans and are used throughout the late discovery and early development stage of a potential drug candidate;[35] however, they do not necessarily correlate with subjective rating scale measures of clinical efficacy. The identification, development, and validation of neuropsychiatric biomarkers and their integration into clinical trials is being encouraged by regulatory bodies.[28,56–61]

Some sources of variability in PET imaging identified by Schmidt and his colleagues include: differences in data acquisition protocols; different scanner models; motion artifacts; comparison of several images taken over time and averaged across subjects; spatial mapping of a subject's PET or MRI image to a reference brain space; different software for normalizing images; and the analysis of image data. A number of government–academic–industrial initiatives and consortia have been established over the past decade in order to help standardize the use of neuroimaging in the study and treatment of AD, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), Australian Imaging Biomarkers and Lifestyle (AIBL) initiative, and the European Collaboration for the Discovery of Novel Biomarkers for Alzheimer's Disease (AddNeuroMed).

AD is a disorder whose final diagnosis has typically been dependent upon postmortem pathological evidence of neurodegeneration, neuritic plaques, and neurofibrillary tangles,[62] while diagnosis of probable AD has been made on the basis of progressive dementia and other cognitive deterioration in the absence of other neurologic, psychiatric, or systemic disorders.[63] These criteria have been reviewed over the years in order to define and monitor the progression of AD dementia from benign forgetfulness to mild cognitive impairment (MCI) and finally to Alzheimer dementia.[64] The recognition of a prodromal state of AD (amnestic MCI) has stimulated the search for biomarkers that can diagnose and monitor the progression of AD and differentiate AD from other forms of dementia. These biomarkers help to identify subjects who can be used in proactive clinical trials of AD therapeutic agents that may help treat patients before frank dementia occurs.

The amyloid hypothesis of AD [65] has been one of the dominant drivers of research into the causes of AD and its potential treatment. A number of radiolabeled amyloid tracers have been developed, such as ^{11}C-PiB, which have been used at multiple sites and for serial testing. ^{18}F-AV-45 has also been approved by the US Food and Drug Administration as an amyloid tracer. These tracers are being used to monitor the progression of dementia in the elderly from MCI to probable AD. Between 89% and 98% of probable AD subjects are PiB positive and a significant proportion of elderly subjects who go on to develop this disorder are also PiB positive. Notwithstanding the importance of the amyloid hypothesis to guide AD therapeutics,

this disorder is also associated with reduced cerebral glucose metabolism. Changes in brain glucose metabolism have been imaged using tracers such as ^{18}F-fluorodeoxyglucose. Studies using this tracer indicate that a pattern of cerebral hypometabolism related to progressive Alzheimer dementia can be differentiated from other types of dementia such as frontotemporal dementia.

In Chapter 4, Novak and Einstein[23] focus on the use of structural MRI (sMRI) as a tool to establish biomarkers for the study of AD. Similar to the discussion of PET by Schmidt and colleagues, they discuss the limitations and methodological problems arising from the use of MRI. The importance of MRI and its use in therapeutic clinical trials, as well as the position of regulatory authorities on the use of neuroimaging in clinical development, are also discussed. sMRI has been used to identify and follow the course of the key neuropathological changes in AD, that is, neuritic amyloid plaques, diffuse β-amyloid protein deposits, and neurofibrillary tangles, neurodegeneration, and gliosis. sMRI has also been used to relate neuroanatomical changes to neurocognitive tests and tests of functional ability. For example, it has been observed that cognitive impairments and loss of brain volume on MRI are more closely related to neurofibrillary tangles and neuron loss on post-mortem examination than to amyloid burden, particularly for medial temporal structures such as the entorhinal cortex and hippocampus. On the other hand, increased amyloid deposition occurs early in AD, perhaps initiating the pathological cascade of atrophy and cognitive deterioration. Regional patterns of atrophy described by sMRI have been used for differential diagnosis of AD from other dementing pathologies, such as frontotemporal dementia, to differentiate the pathological changes due to AD from those observed in healthy elderly subjects, and to map the modulatory effects of genetic polymorphisms such as the Apolipoprotein E ε4 (APOE ε4) allele on the rates of neurodegeneration and cognitive deterioration.

Both Schmidt and colleagues and Novak and Einstein review the use of neuroimaging during clinical trials of clinically active and potential therapeutic agents for the treatment of AD. The effects of clinically active and registered drugs such as donepezil (Aricept), memantine (Namenda), galantamine (Razadyne) have been examined by PET neuroimaging in clinical studies.[25] Aricept, Namenda, and Razadyne tend to maintain improved glucose metabolism in frontal and temporal cortices and these changes can be related to maintenance in cognitive scores. Aricept and Exelon (rivastigmine) have been studied in MCI subjects.[23] While Aricept failed to alter hippocampal or entorhinal volumes, it did lower the rate of brain atrophy and the effects correlated with cognitive scores. Exelon also induced a slower rate of ventricular volume change during the first two years of the study.

Neuroimaging has also been used to examine the effects of experimental drugs in AD patients and MCI subjects. Phenserine, intravenous immune globulin, intranasal insulin, and rosiglitazone all preserved or increased glucose metabolism associated with generally positive though varying effects on cognitive ability.[25] Novak and Einstein report on the use of MRI on clinical studies using vitamins in MCI and AD subjects.[66] Vitamin E had no effect, but the combination of vitamins B_6 and B_{12}, and folic acid reduced homocysteine values, reduced whole brain atrophy, and had positive effects on cognitive ability. The effects of the muscarinic M_1 receptor functional agonist, milameline, were also assessed by MRI. Though the trial was stopped for apparent lack of clinical efficacy,[67] changes in temporal horn volume that correlated significantly with cognitive

changes were observed.[23] Since, 2000, there has been a concerted effort to develop anti-amyloid treatment for AD through the use of antibodies [68,69] such as bapineuzumab and gantenerumab. Amyloid PET scanning has described reduced amyloid burden, as measured by ^{11}C-PiB-PET.[25] MRI assessment of the effects of bapineuzumab failed to show significant changes in brain or ventricular volume, but a reduction in volume loss, associated with clinical efficacy was seen in a subgroup of subjects who were APOE ε4 noncarriers. Nonetheless, reduced brain volume was noted in some AD patients treated with AN-1792, compared to placebo.[23]

3.2. Schizophrenia

3.2.1. Preclinical and Experimental Neuroimaging

Aspects of schizophrenia have been traditionally modeled pharmacologically using drugs like amphetamine that produce psychotic-like behavior in humans and animals.[70,71] It was later observed that NMDA (N-methyl-D-aspartate) receptor antagonists like phencyclidine and ketamine also produce psychotomimetic symptoms both in humans[72] and animals.[73] This work and others implicated two major neurotransmitters with schizophrenia and psychosis, and have given rise to the dopaminergic[74] and glutamatergic[75] hypotheses of this disorder. Steckler and Salvadore[76] discuss the use of neuroimaging following acute or repeated administration of these drugs, the effects of which are generally mirrored in animal and human experimental studies. The effects of amphetamine are related to the magnitude of dopamine release and can be blocked by dopamine receptor blockers. The effects of ketamine, however, are not generally altered by dopamine receptor blockers, but rather by drugs that enhance glutamatergic activity. Ketamine is being used in human experimental medicine as a model biological vulnerability to psychosis that is related to changes in prefrontal cortical activity and subsequent perceptual illusions and delusional ideations. The induction of positive symptoms by ketamine is related to increased glutamate in the anterior cingulate cortex (ACC). These results are also reflected in animal studies, providing cross-species consistency, and are of translational value.

Other models of schizophrenia in animals include genetic[77] and neurodevelopmental[78] models. Neuroimaging plays a major role in describing the effects of genetic variations on brain function and structure, and on the establishment of intermediate phenotypes or endophenotypes to study psychiatric disorders.[79] Imaging genetics is a rapidly expanding field that combines investigations of risk genes identified through genome-wide association studies, for example. This work could provide novel drug targets to be validated and taken beyond the limitations of traditional animal and human experimental models. Steckler and Salvadore focus on polymorphisms in the *ZNF804A* and *DISC1* genes to illustrate the methods and applications of imaging genetics and the translational potential of this approach. Genetic animal models reviewed by Steckler and Salvadore in Chapter 7 include transgenic mice expressing a dominant-negative form of the *DISC1* (*disrupted-in-schizophrenia 1*) gene; mice lacking the stable tubule-only polypeptide (STOP); *NCAM-180* knockout mice; mice lacking the *complexin-2* (*Cplx2*) gene; mice overexpressing the G-protein coupled receptor SREB2/GPR85; and transgenic *chakragati* (*ckr*) mice. These murine models display enlarged ventricles reminiscent of those reported in schizophrenic patients.

Schizophrenia can be regarded as a neurodevelopmental disorder modified by

environmental factors.[80] The time course of ventricle enlargement has been observed in young *DISC1* mutant mice and in *Cplx2* knockout mice subjected to a perinatal head trauma. The results of the latter study indicate the value of neuroimaging when carrying out genetic × environment studies in animal models. Among the neurodevelopmental animal models of schizophrenia are prenatal infection models of the dam using human influenza virus or agents that cause inflammation. These procedures have shown postnatal brain atrophy and anisotropy in the brains of the offspring, demonstrated by neuroimaging. Further, these prenatal insults are related to abnormal behaviors related to schizophrenia. Lateral structural enlargement appears to be a common sign of rodent models of schizophrenia, including prenatal lesion induction with the mitotoxin methylazoxymethanol acetate. Of note, however, is the specificity of these genetic models, which are also considered as models of autism.[16] This is consistent with the emerging view that many psychiatric disorders are part of spectra rather than categories.[81]

3.2.2. *Clinical Translational Neuroimaging*

Contrary to the neurodegenerative hypothesis of schizophrenia,[82] in Chapter 6 Tost et al.[26] propose that schizophrenia is a genetically predisposed state of maladaptive structural organization of neural circuits that promotes the emergence of clinical symptoms in adulthood. They do so through their examination of the role of neuroimaging in schizophrenia from a systems biology perspective that integrates regulatory neural prefrontal-limbic circuits, including the prefrontal cortex, hippocampus, and striatum. fMRI has contributed to this mapping of the neural systems underlying aspects related to schizophrenia such as impairments in working memory [dorsolateral prefrontal cortex (DLPFC), rostral ACC (rACC), and inferior parietal areas], reward and salience (midbrain and ventral striatum), and regulation of emotions (amygdala and higher-order areas of the prefrontal or cingulate lobe). Imaging genetics is an important tool in this mapping. The *ZNF804A* genotype and interstitial deletions in chromosome 22q11 are linked to genetic risks in schizophrenia and are implicated in abnormal prefrontal-hippocampal connectivity.[i]

Consistent reductions in gray matter volume, particularly frontal-temporal cortices, are found by sMRI in healthy but at-high-risk subjects, as well as in first-episode schizophrenics. Similarly, DTI studies indicate impaired axonal integrity, which has also been observed in healthy, but at-risk, relatives. These observations are important, suggesting potential endophenotypes or markers for the prodromal stage of schizophrenia.[83]

Dopaminergic ligands are used extensively in receptor occupancy studies.[84] In Chapter 7, Steckler and Salvadore[76] report a few inconsistent effects of clinically active antipsychotics such as haloperidol (Haldol), clozapine (Clozaril), risperidone (Risperdal), sulpiride (Dolmatil), or amisulpiride (Solian) in healthy subjects and rats. Haldol showed limited effects on cerebral blood flow, BOLD response, and metabolism in healthy human subjects. However, according to the review of Tost et al., describing clinically active antipsychotics in schizophrenic patients,[26] Haldol reduces global gray volume in schizophrenics, an effect associated with long-term antipsychotic

[i]See also Kumar et al. in Chapter 12 in this volume for further discussion on the abnormal prefrontal-hippocampal connectivity underlying a major psychiatric disorder.