Neuroimaging in Addiction presents an up-to-date, comprehensive review of the functional and structural imaging human studies that have greatly advanced our understanding of this complex disorder. Approaching addiction from a conceptual rather than a substance-specific perspective, this book integrates broad neuropsychological constructs that consider addiction as a neuroplastic process with genetic, developmental, and substance-induced contributions. The internationally recognized contributors to this volume are leaders in clinical imaging with expertise that spans the addiction spectrum.

Following a general introduction, an overview of neural circuitry and modern non-invasive imaging techniques provides the framework for subsequent chapters on reward salience, craving, stress, impulsivity and cognition. Additional topics include the use of neuroimaging for the assessment of acute drug effects, drug-induced neurotoxicity, non-substance addictive behaviors, and the application of imaging genetics to identify unique intermediate phenotypes. The book concludes with an exploration of the future promise for functional imaging as guide to the diagnosis and treatment of addictive disorders.

Scientists and clinicians will find the material in this volume invaluable in their work towards understanding the addicted brain, with the overall goal of improved prevention and treatment outcomes for patients.

Features a Foreword by Edythe London, Director of the Center for Addictive Behaviors, University of California at Los Angeles.
Neuroimaging in Addiction
Neuroimaging in Addiction

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To my lovely wife, Trish, and my wonderful children, Zack and Holly. Their love and support through the years have calmed my limbic hot spots.

Bryon Adinoff

To Marsha, Lindsay and Matthew: All that I am, all that I do, is better because of you.

Elliot Stein
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Foreword

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Addictive disorders are among the primary preventable causes of major health problems. They also present therapeutic challenges, and often are treatment-resistant and characterized by relapse. The quest for effective addiction treatments has evolved in parallel with major technical advances in the field of brain imaging, which have yielded convincing illustrations that addictions are “brain diseases.” With this in mind, it seems appropriate that a thorough understanding of how disturbances in brain circuitry promote and maintain addiction can help advance the development of effective addiction therapies.

Publication of Neuroimaging in Addiction is timely in view of substantial changes in technology and approaches since the appearance of a previous volume on the same subject, almost a decade ago [1]. Relevant advances include the development of new imaging techniques and their application to clinical problems. For example, although a patent was issued for the use of diffusion tensor imaging (DTI) in 1996 [2], it was years later, after the technique was deemed feasible for studies of the brain, that there was a proliferation of studies using DTI for assessment of white matter. Notably, most articles using DTI in studies of substance abuse have appeared in the literature only within the past three years. Similarly, while the technique of determining functional connectivity, using functional MRI in the resting state, was described in the late 1990s [3, 4], this approach has only been applied in addiction research in recent years [5]. Not only has the last decade seen the application of new imaging techniques, but there have also been substantial advancements in functional and structural image analysis procedures, which have greatly influenced the flexibility, scope, and sensitivity of neuroimaging studies [6].

With that in mind, the editors of this book, Bryon Adinoff and Elliot Stein, have assembled an outstanding group of international scholars who contributed to the present volume. The book provides a logical sequence of chapters, beginning with a presentation of current knowledge regarding the neural circuits and neurotransmitters affected by the acute and chronic administration of drugs of abuse, with a focus on findings gleaned primarily from animal studies. After a description of various imaging modalities and how they are used in studies of addiction, the next chapters deal with the acute effects of drugs of abuse, reward processing and craving, and the progression of changes that occur as addiction develops. The subsequent chapters discuss impulsive behavior and neuroimaging studies of disruptions in cognitive function, such as changes in decision-making, that contribute to the maintenance of addictions and that can interfere with behavioral treatments. Next, there is a chapter exploring the role of stress in the development of addiction and in relapse to substance abuse followed by a chapter that presents anatomical evidence for structural changes associated with addictive disorders.
In view of research developments over the past decade, including evidence that various addictions (alcohol, drugs, sugar, etc.) involve the same neurotransmitters and circuits, as well as commonalities in genetic markers of addiction vulnerability, the book generally considers addictions as a group of disorders that share neural substrates, without a primary focus on any one substance of abuse. This is exemplified by a chapter which has been devoted to neuroimaging studies of non-chemical addictions. Given the enormous contribution of uncontrolled eating to obesity, diabetes, and other highly prevalent and debilitating diseases, such as cardiovascular disease and stroke, major attention to non-substance addictions is warranted. Brain imaging studies point to commonalities in the neural correlates of these disorders, suggesting that approaches aimed at correcting neural function in common circuitry may be useful in treating the array of addictive disorders. Such approaches have the potential to reduce the burden of disease across a variety of syndromes that feature loss of self-control as a symptom.

With respect to addiction vulnerability, linkage analyses, candidate-gene analyses and genome-wide association studies have yielded findings that have implicated specific genes. Nonetheless, because of the profound influences of epigenetic and environmental factors, intermediate phenotypes at the level of neural systems can provide valuable correlates of behavioral measures. Furthermore, assessments of neural markers and responses can be used in studies of the mechanisms by which genotype can influence behavior. Considering these issues, a chapter in this volume focuses on the use of brain imaging studies to describe relevant intermediate phenotypes that are linked to addiction.

The volume closes with a chapter that integrates the previous chapters and provides examples and considerations of how brain imaging can be used to predict risk for addiction, diagnosis of addictive disorders, and personalization of treatment. Identification of individuals with neural phenotypes that confer risk for addiction can help target those who might maximally benefit from targeted preventive interventions. Such prophylaxes include educational programs, behavioral approaches, and even vaccines against drug addictions, which are currently under investigation. Although success in clinical trials can be predicted from self-reports of drug use and urine screening [7], which are less costly than neuroimaging, it is possible that identification of dysfunction at the circuit level may be useful in selecting an appropriate targeted treatment.

The birth of the field of brain imaging brought with it the hopes of diagnosing neuropsychiatric diseases that are difficult to discern from one another, and identifying the most relevant therapeutic targets. Although the use of brain imaging for diagnostic purposes has not been as successful as predicted 30 years ago, the increasingly progressive development of brain imaging technologies has provided us with the means to clarify the links between neural circuits and behavioral states that lead to and result from addictive disorders.

This volume brings us up to date on how imaging technologies are applied in understanding addiction and the therapeutic targets that it presents. Research in the next decade promises equally exciting advances in molecular brain imaging techniques and their application in drug abuse research. At the very least, positron emission tomography research is at the brink of providing new radiotracers that extend our ability to study the brain of drug-abusing individuals and to evaluate effects of treatments. For example, while currently available radiotracers can be used to assess striatal and extrastriatal D2-like dopamine receptor availability, ongoing development focuses on tracers for quantitative assay of dopamine dynamics in low-receptor areas of brain, such as the cerebral cortex. Furthermore, ongoing research is directed at overcoming the radiation dosimetry limitations of nuclear medicine approaches (PET and SPECT scanning), which restrict their
use in children and in multiple assessments of human subjects of any age. A promising area of technological development is the use of nonradioactive magnetonanoparticles, which are detectable by external imaging [8].

Another area of potential advancement in drug abuse research involves the use of real-time functional MRI feedback in facilitating behavioral change. In this regard, real-time functional MRI has been used to show that individuals can voluntarily control activation in a particular brain region, influencing the perception of pain [9]. It is conceivable that addiction-relevant behavioral states, such as craving, could be influenced as well.

Whereas these anticipated advances are the subject of future reviews, this highly informative volume describes the brain circuits and neurochemical pathways that contribute to addictive disorders with various technical approaches and how they have been used to elucidate the neural correlates of addictive behaviors and their links to genetics. It serves as an excellent reference volume to both researchers and students interested in the translational neurobiology of addictive disorders.

Edythe D. London, PhD

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Chapter 1

Introduction
Chapter 1

Introduction

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Derived from \textit{addictionem}, meaning “an awarding, a devoting,” the term addiction evolved in the 1600s to suggest a tendency of habits and pursuits. Used in the modern sense since the 1800s with reference to tobacco, opium, and spirits, addiction now describes a symptom complex of loss of control, compulsive use, and continued use despite adverse consequence. Although “dependence” was used by DSM III to describe the physical dependence upon drugs and alcohol (as evidenced by tolerance and withdrawal) and subsequently by DSM III-R and IV to include the three Cs (Control, Compulsive use, and Consequences), there is now relatively widespread agreement that “addiction” best denotes the symptom cluster that is the focus of this volume: \textit{Neuroimaging in Addiction} \cite{1}. As this book goes to press, the DSM-V work group on substance-related disorders has recommended that “addiction” replace “dependence” as the diagnostic label that defines these behaviors, concerns regarding its vagueness, associated stigma, overuse, and non-scientific formulation non-withstanding \cite{2}.

“Addiction,” however, has also been usurped in the public domain to describe any behavior that is performed in excess, including Internet use, sex, chocolate, shopping, pornography, gambling, tanning, or eating. Whether or not these behaviors are truly “addictive,” and whether these behaviors are consistent with a disease process, begs the question of how to definitively identify this disorder. The diagnosis of substance use disorders (in addition to other so-called “process” or “behavioral” addictions), unfortunately, shares a dilemma encountered throughout psychiatry – the diagnosis is based solely on descriptive, symptomatic checklist criteria. The use of biological measures, such as blood tests, physiological measures (e.g., blood pressure), electrocardiograms, or x-rays, to diagnosis disease states, which are standard protocol throughout the rest of medicine, continues to elude our field. The absence of accurate (or even partially accurate) biological markers to guide the diagnosis of neuropsychiatric disorders remains a critical limiting factor in discerning a neurobiologically-based disease from a non-pathological behavioral state and may, in part, be responsible for the poor outcome prognoses for many of our patients suffering from addiction. We believe that neuroimaging techniques offer the best hope to realize this Holy Grail of psychiatry.
When the editors began their training, brain imaging was in its early stages of development and implementation as a diagnostic tool. Researchers and clinicians were suddenly provided the opportunity to safely, and with relatively minimal patient discomfort, investigate the human brain in situ. The promises inspired by structural and functional brain imaging were profound. The 1990s were pronounced “The Decade of the Brain” and it was assumed that these tools would herald the neurobiologically based diagnosis and targeted treatment of psychiatric disorders by the turn of the twenty-first century. This, of course, did not happen. What did happen, however, were stunning technical advancements in assessing brain activity that allowed an unparalleled investigation of neural processes, exponentially increasing our understanding of how the brain perceives, integrates, and responds to sensory and affective stimuli. Steady progress has also been evident in unveiling the neurobiological differences in individuals with psychiatric disorders, albeit not (as of yet) with the diagnostic sensitivity and specificity required for clinical use. These advances, perhaps most impressive in the addictive disorders, has motivated the publication of Neuroimaging in Addiction.

The accomplishments in understanding the neural processes involved in addiction are due, at least in part, to superb animal models that closely mimic the repetitive and compulsive drug-taking behaviors observed in addicted humans. Neuroimaging techniques have provided the interface necessary to translate these anatomical, cellular and circuitry models into the human addicted brain. A major accomplishment of these closely aligned approaches is the elucidation of biologic processes that are shared across several substances of abuse. The growing confluence of these two approaches signaled to the editors that the timing was propitious to summarize the neuroimaging findings to-date and has guided two key concepts encapsulated in Neuroimaging in Addiction.

First, the chapters have been organized by key constructs shared across the various substances of abuse, starting with a description of shared disruptions in neurocircuitry and extending to experiential, cognitive and behavioral processes such as reward salience, craving, stress, and impulsivity. This approach, rather than a categorical approach based upon a specific drug of abuse, supports the common DSM-IV behavioral criteria used to describe all addictive disorders. Second, the title of the book refers to Addiction in the singular, denoting a common disease process that is differentially manifested (i.e., a shared etiology and neurocircuitry that is variably expressed with different drug choices) rather than a spectrum disorder (i.e., each substance addiction encapsulates its own etiologic and biologic profile with shared symptoms across each substance). This distinction has critical implications for our understanding, as well as treatment, of addiction.

Guided by this framework, the contributors to Neuroimaging in Addiction detail the state-of-the-art in their respective fields. Although the original intent of the editors was to specifically highlight the advances of neuroimaging in addiction, each chapter has also evolved into a superb overview of the construct or topic approached and thus simultaneously provides the reader with an excellent textbook on addiction neurobiology. This extensive overview emphasizes the remarkable progress that has occurred in our field over the past ten years.

Yet, as noted earlier, these great leaps forward have not been paralleled with similar progress in the diagnosis or treatment of addiction. Making accurate diagnoses on an individual subject/patient basis remains elusive, as does our ability to assess treatment efficacy. Nevertheless, dramatic advances in imaging technology, coupled with those in other fields (e.g., genomics, drug discovery), promise such breakthroughs in the not-too-distant future. New technologies have and will continue to offer new insights in
the structure and function of both the healthy brain and its pathophysiology. Justified excitement in the neuroimaging field can be seen in the recent advances in the ability to perform white matter tract tracing in situ, combine the excellent temporal resolution of EEG with the superb spatial resolution of fMRI in combined recording studies, and measure the important neurotransmitters glutamate and GABA via MR spectroscopy. New PET ligands are starting to emerge from the lab, promising the ability to make molecular measurements of compounds based on scientific hypotheses, not simply because a ligand was available. And new hardware continues to be developed, whether it be ever higher field MRI scanners (a human 11.7 T scanner is currently in development) or the exciting recent PET camera insert into a standard 3T MRI, allowing for the first time simultaneous measurements. Finally, especially in the field of MRI, new analysis methods are continually being developed to better extract information from the rich MRI signal. These developments include the rapidly evolving field of resting state functional connectivity, and its analysis using network and multivariate analyzes, although only the former has yet to be applied to the addiction field.

Elucidating subject-specific differences in brain functioning will enable the identification of neural correlates of behavioral complexes, unique intermediate phenotypes, and/or substance-specific disruptions as well as targeted treatment approaches and objective assessments of treatment efficacy. Clarification of the distinct and overlapping neural networks defining addictive and other psychiatric disorders, including schizophrenia, bipolar, post-traumatic stress, and antisocial social personality disorders, will allow increasingly focused treatment approaches. Finally, it is likely that identifying neural signatures of addiction will markedly diminish the stigma associated with addictive disorders. Such biological markers should lessen the fear and shame that accompanies this disease, and in turn, remove self-imposed, social, and medical obstacles in seeking and obtaining treatment. It is our hope that scientists, clinicians, and students will find the material in this volume useful as we continue our journey to understand the addicted brain with the goal of improved prevention and treatment outcomes for our patients.

References

Chapter 2

An Integrated Framework for Human Neuroimaging Studies of Addiction from a Preclinical Perspective
Chapter 2

An Integrated Framework for Human Neuroimaging Studies of Addiction from a Preclinical Perspective

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2.1 Introduction

Preclinical research into the neural substrates of drug dependence focused attention onto the dopamine-dependent functions of the nucleus accumbens of the ventral striatum in rewarded behavior (see recent review [1]). More recent analyzes have shown the importance of considering the neural context of the ventral striatum in subserving such behavior [2], including limbic-cortical and prefrontal interactions with the striatum. It is this framework of preclinical research that has guided the yet more complex issues of the neural substrates of addiction, particularly in humans, to a variety of drugs of abuse, including stimulants and opiates.

2.2 A Conceptual Framework for Understanding Drug Addiction Based on Preclinical Observations

Understanding the neural basis of drug addiction has required an integrated approach from both studies in cognitive and affective neuroscience on human volunteers and clinical patients, and also from behavioral neuroscientists and psychopharmacologists conducting well-controlled animal experiments. However, it was discoveries derived from experiments with animals that provided the first clues about how the brain might mediate reinforcement processes relevant to addiction, and it is this literature that underpins many of today’s sophisticated investigations of the neural substrates of human addiction. Perhaps the seminal discovery was that by Roberts et al. [3], who showed that depleting dopamine from the mesolimbic dopamine system appeared to block the self-administration of intravenous cocaine in rats in a way that could not easily be accounted for as a motor deficit (given the implication of dopamine in Parkinson’s disease). Previous work by several groups beginning with Crow [4] had implicated mesolimbic dopamine...
in a “brain reward system” from studies on intracranial self-stimulation via implanted electrodes in the medial forebrain bundle.

2.2.1 The Pivotal Role of the Nucleus Accumbens

One of the terminal regions of the mesolimbic dopamine system is a structure in the basal forebrain, associated with both the basal ganglia and the limbic system, the nucleus accumbens. Much interest was already focused on the role of the nucleus accumbens in reward processes when Hoebel et al. [5] showed that rats would self-administer d-amphetamine directly into this region unilaterally in very small volumes – with little evidence of other “hot-spots.” Phillips et al. [6] confirmed this finding with evidence from bilateral self-administered infusions that were up-regulated by simultaneously adding dopamine D1 or D2 receptor antagonists to the infusate – suggesting that the rats were “regulating” their preferred level of dopamine receptor stimulation, as rates of self-administration increased, again contrary to what would be expected of a purely motor function for these neurons.

Two other classic studies have confirmed an important focus on dopamine-dependent functions of the nucleus accumbens, while broadening its involvement to include non-stimulant drugs such as heroin and alcohol. DiChiara and Imperato [7], using in vivo microdialysis, have shown that many drug withdrawal states, whether from stimulants such as cocaine, nicotine, alcohol or heroin, all increase levels of dopamine sampled in the nucleus accumbens. This does not, of course, suggest that such an effect is sufficient or even necessary for drug reinforcement, as many other receptor-types and brain regions may be implicated for example in alcohol reinforcement, but the commonality is significant. However, Koob and LeMoal [8] have also highlighted many other neurochemical and neuroendocrine changes occurring in drug withdrawal. A second landmark study was that of Bozarth and Wise [9], which appeared to dissociate the positive reinforcing effects of opiates from their physical withdrawal signs. The latter were attributed to brain-stem systems, but rats would self-administer morphine directly into the vicinity of the dopamine cell bodies in the ventral tegmental area (VTA) in the absence of any obvious precipitated signs of withdrawal – implicating a dopamine system in the positively reinforcing actions of opiates. However, it was shown subsequently that not only did morphine self-administration occur in the nucleus accumbens but also that it was, perhaps surprisingly, not blocked by dopamine depletion from that structure (see [8] for a review). Thus, the nucleus accumbens clearly had an important role in opioid reinforcement, but its contribution to opioid self-administration was independent of its dopamine input.

2.2.2 The Nucleus Accumbens as a Limbic-Motor Interface

(see Figure 2.1)

The nucleus accumbens, as mentioned above, is a potential “interface,” as described by Mogenson et al. [10], between the limbic system and the striatum (or between “motivation and action” as some have also suggested). Major inputs to the nucleus accumbens include from the prefrontal cortex, hippocampus and amygdala (Figure 2.1). The role of amygdala afferents to the nucleus accumbens in aspects of addiction was first suggested by parallel studies in rats and human drug abusers. It had already been shown that some
Figure 2.1 Neural circuitry associated with the neuopathology of drug addiction, involving brain systems such as the nucleus accumbens, of which both the shell and the core are implicated in producing the powerful reinforcing effects of addictive drugs such as cocaine. Interactions between the nucleus accumbens, the basolateral amygdala and the hippocampus are important for conditioned reinforcement and the processing of contextual information, which underlie the feelings of drug cravings in the face of drug-related stimuli. Executive control from the prefrontal cortex over the nucleus accumbens and the dorsomedial striatum are needed to guide behavior according to the individual's expectations, values and goals. In the case of habitual behaviors, however, which occur independently from a goal, control from the prefrontal cortex gradually shifts towards the dorsolateral striatum. It has been hypothesized that stimulus-response habit learning plays an important role in development of drug addiction, as it may underlie the transition from the hedonically driven recreational drug use to more habitual, and eventually compulsive patterns of drug-taking, as seen in drug-addicted individuals. Green/blue arrows indicate glutamatergic projections; orange arrows indicate dopaminergic projections; pink arrows indicate GABAergic projections; Acb, nucleus accumbens; BLA, basolateral amygdala; CeN, central nucleus of the amygdala; VTA, ventral tegmental area; SNC, substantia nigra pars compacta. GP, globus pallidus (D, dorsal; V, ventral). Reproduced with permission from Figure 2.1b of Everitt and Robbins [25].

of the propensity for stimulant drugs to potentiate effects of appetitive conditioned reinforcers was dependent upon an input to the nucleus accumbens from the basolateral amygdala (BLA) [11]. This result suggested that stimulus-reward associations could be mediated in part by the amygdala and that this information was conveyed to the nucleus accumbens where it could be “gain-amplified” by its dopamine input. In human imaging studies, it was later shown that the amygdala was one of several brain regions...
in the temporal lobe activated in stimulant-dependent individuals by cues associated with the abused drug [12, 13]. Correspondingly, in studies of “drug-seeking” behavior in which rats worked under a so-called “second order” schedule to obtain intra-venous (i.v.) cocaine, performance is maintained at least partly by the cues associated with the drug, which are presented contingently as conditioned reinforcers during instrumental performance [14]. However, excitotoxic damage to the amygdala [15] and also to the core region of the nucleus accumbens to which it projects [16] blocked the acquisition of this drug-seeking behavior. There is also neurochemical specificity in this interaction: dopamine receptor blockade, but not AMPA receptor blockade, in the BLA reduced established cue-controlled cocaine-seeking. However, the reverse was true in the nucleus accumbens core sub-region [17]. Moreover, a disconnection experiment of the BLA and accumbens core by blocking dopamine receptors in the BLA on one side and AMPA receptors in the accumbens core on the other, dramatically reduces cocaine-seeking, indicating that these two regions are probably serially connected in functional terms [18], that is they are part of a common amygdala-ventral striatal system (see Figure 2.1). Other studies have revealed the importance of this amygdalo-striatal system in relapse, as measured in the reinstatement-extinction paradigm [19]. It is, however, of note that the predictive validity of the reinstatement paradigm and its functional equivalence to humans have been called into question [20, 21]. Specifically, it has been criticized that the reinstatement model depends on extinction, which does not mimic most situations in humans that lead to drug abstinence, and therefore, may not be suitable to model relapse.

The role of the hippocampus has been less clear. Fundamental studies have of course accorded this structure a role in memory and learning, but perhaps the most plausible contribution to addiction is modulation of the shell sub-region of the nucleus accumbens via its projections there, and its possible mediation of motivational aspects of context (as distinct from discrete cue) conditioning. Theta-bust stimulation of the hippocampus (a form of experimental deep brain stimulation) reinstates extinguished cocaine-seeking in a way that indicated a dependence on glutamate transmission in the VTA [22] – and a possible mechanism for the effects of context re-exposure on relapse. In fact, inactivation of the dorsal hippocampus does attenuate context-induced reinstatement of drug-seeking in rats [23]. Many electrophysiological studies indicate that amygdala, hippocampal and prefrontal cortical inputs may influence drug-seeking behavior via their convergence on the nucleus accumbens, possibly competing for access to different response selection mechanisms gated by the ascending dopamine system and the cortico-striatal-pallido-thalamic circuitry (Figure 2.1: [24]).

2.2.3 The Dorsal Striatum and Habits

Burgeoning evidence supports the notion that as drug-seeking becomes compulsive, there is a shift in the control of behavior from the prefrontal cortex to the striatum, and from the ventral striatum (i.e., nucleus accumbens) to the dorsal striatum (i.e., caudate-putamen in the rat) (see Figure 2.1: [25]. Similar views have been expressed by other authors [8, 26]. Some of the early evidence depended on observations that chronic i.v. self-administration of cocaine in rhesus monkeys initially produced changes in the expression of D1 receptors that were initially limited to the ventral striatum but then spread throughout the caudate nucleus and putamen [27]. Additionally, Ito et al. [28, 29] found that the conditioned reinforcer in a second order schedule evoked