# PET and SPECT in Psychiatry

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*Editors*

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Springer

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# Foreword

In this ambitious undertaking, the editors have assembled the most comprehensive and updated compilation of material, describing the use of single-photon and positron emission tomography in the neurosciences. Three volumes address the use of SPECT and PET in psychiatry, in neurology and in neurobiological systems. A large international team of experts have come together to accomplish this task.
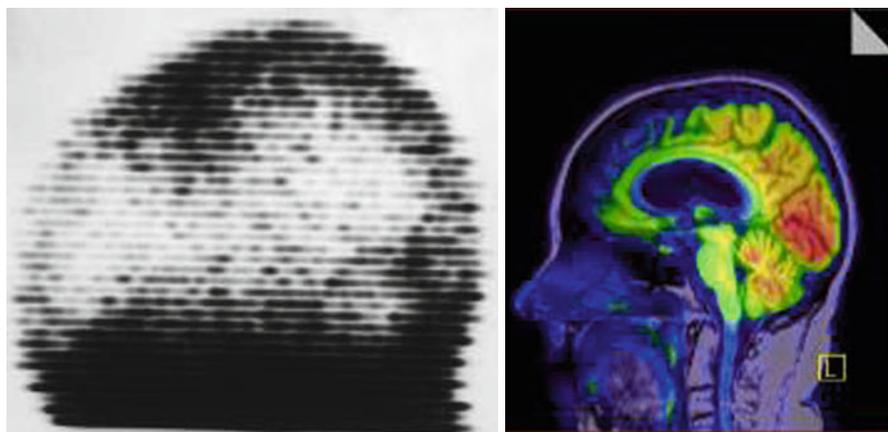


On the *left*, a 1969 blood–brain barrier scan in cerebral lymphoma and on the *right* a PETMR study in frontotemporal dementia. Institute of Nuclear Medicine 2012

The progress achieved in this area has been staggering. The two images below, obtained half a century apart, speak a thousand words.

In this context, this volume triad is needed and timely. Novel instrumentation and probes, and significant advances in the understanding of the pathophysiology of the various pathological entities described in these texts, have led to clear clinical benefit. This is apparent in the movement disorders, in the identification of non-lesional MR focal epilepsies, and now in a rapidly emerging field, in the diagnosis of fibrillar amyloid plaque deposition, in mild cognitive-impaired individuals. The next few years will see a rapid expansion of this already fast progressing field.

The editors are to be congratulated in bringing together and to print this significant volume of expertise and experience.

Peter J. Ell, FMedSci, DR HC
Emeritus University College London,
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# Preface

The neuroscientist of today disposes of a powerful instrumentarium for functional imaging that has never made more impressive advances than before, helping to better understand the mechanisms of diseases and to develop and design drug treatment options with a superior efficacy and safety profile. Among this instrumentarium, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have become forerunners in the functional imaging arena, much more than functional magnetic resonance imaging, and for this reason, this book is dedicated to PET and SPECT.

Although there have been some textbooks on PET or SPECT in the neurosciences, e.g. De Deyn et al. 1997, or Otte et al. 2004, the number of these books is limited, and – to the best of our knowledge – there is no recent comprehensive publication on PET and SPECT in the neurosciences, especially a compilation by a large number of international experts, as it is undertaken in the project at hand.

When the idea to edit a book on PET and SPECT in neurosciences came up, it was soon realized that all the new data would never fit into one single volume. Hence it was decided to write a trilogy. *PET and SPECT in Psychiatry* is the first volume of this trilogy: volume 2 (*PET and SPECT in Neurology*) and volume 3 (*PET and SPECT in Neurobiological Systems*) will complete the series.

In all volumes, we have tried to assemble the combined expertise of renowned authors whose dedication to the investigation of psychiatric and neurological disorders or of neurobiological systems through nuclear medicine technology has achieved international recognition. Prior to writing the trilogy, Rudi Dierckx organized an International Symposium on PET and SPECT in Neurology and Psychiatry in Groningen, the Netherlands (April 23–25, 2012). At this symposium, many of the authors included in this trilogy were invited to present a state-of-the-art review of their specific field of research. The editors, who are nuclear medicine specialists, radiochemists and biologists with a strong exposure to neurosciences, have also invited experts from the psychiatry, neurology and molecular neurobiology fields to enhance the editorial board as guest editors for each volume of the trilogy. For volumes 1, 2 and 3, these were respectively Johan A. (Hans) den Boer, Professor in Biological Psychiatry; Klaus L. (Nico) Leenders, Professor in Neurology; and Paul Luiten, Professor in Neurobiology. Furthermore, we tried to increase the quality of our books by introducing an external peer-review system with experts in the field in

addition to review by the editors. The external peer reviewers are listed in the corresponding *Appendix*.

We are very happy that our book is produced by one of the premier publishers in the field. This guarantees a high quality of reproduction and allows for the inclusion of many colour figures, which is essential in the field of functional neuroimaging.

We are intrigued by the enthusiastic response from contributors from all over the world who made this endeavour successful. We also would like to thank all external peer reviewers who have done an excellent work for ensuring the quality of this compilation. Finally, we would like to thank Dr. Ute Heilmann and Dr. Sylvana Freyberg from Springer-Verlag for their continuous help and support during the development of this book.

We sincerely hope that this book will become a key tool not only for all physicians in nuclear medicine, psychiatry, neurology or geriatrics, but also for all professionals working to understand or treat brain disorders. In addition, the trilogy may be interesting and important for industry, as PET and SPECT imaging of the brain is becoming more and more important in today's ageing population.

May this book serve as a guide towards the present use of PET and SPECT in brain disorders and as a catalyst for future research. There is much to be explored, and the engine has been started already.

| | |
|---|---|
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| Offenburg, Germany | Andreas Otte |
| Groningen, The Netherlands | Erik F.J. de Vries |
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# Part I
# Basics

# Neuroimaging in Psychiatric Drug Development and Radioligand Development for New Targets

**1**

Akihiro Takano, Christer Halldin, and Lars Farde

## Contents

**Abstract**

Positron emission tomography (PET) is an imaging modality used to measure physiological and biochemical markers in brain. Neuroreceptors, transporters, or enzymes are visualized and quantified with appropriate PET radioligands. In the development of drugs for treatment of psychiatric disorders, there are three major applications of PET. First, PET microdosing is used for pharmacokinetic evaluation. By injection of minute amount of radiolabeld drug, information about brain exposure can be obtained already at the early phase of drug development. Another application is receptor occupancy studies. Here, the competition between a drug and a PET radioligand binding is examined at the target sites. The competitive effect is useful to have when selecting the doses tested in further clinical trials. The third application is to use imaging biomarkers for diagnosis or efficacy. To widen the use of PET, the development of the PET radioligands for new targets is vital. Several criteria and characteristics such as binding affinity, selectivity and lipophilicity are important when selecting new PET radioligand candidates for targets in brain.

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## 1.1    Introduction

Drug development requires considerable investments of time and money. Since the technique of binding assay was introduced in the late 1950s (Yalow and Berson 1959), numerous compounds have been selected based on in vitro affinity data, evaluated in preclinical models and subsequently tested for efficacy in psychiatric diseases such as schizophrenia and mood disorder. However, as the pathophysiology of psychiatric diseases has not been fully understood, the industrial drug projects have had an evident element of "trial and error." Lack of or insufficient efficacy is thus a major reason for attrition and adds to failure for safety reasons (Arrowsmith 2011a, b). In some drug projects, the failure may be related to difficulties with dose finding. In other words, the doses used in preclinical and clinical trials were too low or too high. The fundamental question is thus whether the drug failed due to suboptimal brain exposure and target engagement of the drug or whether the target was invalid.

Positron emission tomography (PET) is an imaging modality by which it is possible to measure physiological and biochemical markers in the brain by using appropriate radioligands. Most PET radioligands are labeled with radionuclides having a short half-life such as C-11 (half-life, 20.4 min) or F-18 (109.8 min). Following the successful introduction of PET for neuroreceptor imaging in the 1980s (Farde et al. 1986), the technique has been widely used to visualize and quantify drug target sites, mainly neuroreceptors, enzymes, and transporters in the human brain in vivo.

In this chapter, we will focus on the major applications of PET in drug discovery and development. The need for development of novel radioligands for new targets will be given particular attention.

## 1.2    PET Application for Drug Development

### 1.2.1    PET Microdosing for Pharmacokinetic Evaluation

After radiolabeling of the drug itself with short-lived radionuclides, such as C-11 or F-18, the distribution of the drug can be examined in the living body. This approach has been referred to as "microdosing" (Lappin and Garner 2003). A "microdose" is defined as a dosage level less than 1/100 of the dose estimated to induce a pharmacological effect. In addition, a maximum dose has been set to 100 µg (EMEA 2003). Due to effective radiosynthesis and high specific radioactivity, the dose administered in a PET study is usually less than 1 µg.

There are several other approaches for microdosing, such as accelerator mass spectrometry (AMS) and LC/MS/MS. AMS is an ultrasensitive methodology that can be used to quantify C-14 in biological samples such as blood, urine, or tissue biopsies. LC/MS/MS is a technique that can measure very low

concentrations of unlabeled compounds in plasma, urine, or CSF. When compared with AMS and LC/MS/MS, PET has the advantage of extending the microdose concept from body fluids to organs in the whole body. In other words, AMS and LC/MS/MS technologies provide pharmacokinetic information based on the plasma levels of the compounds. PET extends traditional pharmacokinetics by providing information about drug concentration in the target organ or region. However, a limitation is that the short half-life of the PET radionuclides limits the time of data acquisition to about 2 h for C-11-labeled drugs and 12 h for F-18-labeled drugs.

Some failures in CNS drug development have been attributed to poor brain exposure of the drug (Taylor 2002). The PET-microdosing approach may thus be of particular importance in the development of CNS drugs since it has the potential to confirm sufficient brain exposure in early phase of drug development. The information is of particular value before investments are made into expensive phase II and III trials.

At least 1 % of injected radioactivity in the brain has been the finding for most of the drugs viewed as having acceptable brain exposure. However, no strict guidelines have yet been established for decision making. To efficiently translate small animal's results into human condition, microdosing PET study of nonhuman primate (NHP) is a useful intermediate since it can serve as a good predictor of brain exposure of the candidate drugs (Schou et al. 2013).

Although the drugs used in the field of psychiatry are mainly targeted to the CNS, whole body PET measurements can provide useful information in relation to potential side effects. A limitation of PET is that the radiolabeled drug will be metabolized in the living body. Measurement of radioactivity by PET machine can thus not differentiate the parent radiolabeled drug from radiolabeled metabolites. To overcome this problem, radiolabeling and administration of the metabolite only may provide additional information (Seneca et al. 2009).

Although the requirements for preclinical safety data for microdosing study have been reduced by regulatory authorities (Verbruggen et al. 2008), the radioligand production has to follow good manufacturing practice (GMP) (US FDA Code of Federal Regulations Title 21). This requirement has increased the costs of PET-microdosing studies in the human subjects.

## 1.2.2  PET Receptor Occupancy to Demonstrate Target Engagement and in Relation to Pharmacodynamics

A number of PET radioligands have been developed for several key targets related to neurotransmission (Table 1.1 and Fig. 1.1) (Halldin et al. 2001). Using these tools, it is possible to map and quantify the in vivo distribution of the target neuroreceptors or transporters. Details on quantification of the radioligand binding are described elsewhere in this textbook (Chapter 2).

**Table 1.1** Representative PET radioligands for neurotransmitter systems

| Neurotransmitter system | | PET radioligand |
|---|---|---|
| Dopamine | D1 | [11C]SCH23390 |
| | | [11C]NNC112 |
| | D2 | [11C]raclopride |
| | | [11C]FLB457 |
| | Transporter | [11C]PE2I |
| | | [18F]FEPE2I |
| 5HT | 1A | [11C]WAY10065 |
| | 1B | [11C]AZ10419369 |
| | 2A | [11C]MDL100907 |
| | Transporter | [11C]MADAM |
| | | [11C]DASB |
| GABA-benzodiazepine | | [11C]Flumazenil |
| | | [18F]Flumazenil |
| | | [11C]Ro15-4513 |
| Norepinephrine | Transporter | [18F]FMeNER-D2 |
| Cannabinoid | CB1 | [11C]MePPEP |
| | | [18F]FMPEP-d2 |

The change of radioligand binding between baseline and after drug administration is used to calculate the drug occupancy at the target neuroreceptor, transporter, or enzyme (Figs. 1.2 and 1.3).

PET determination of receptor occupancy has been most extensively applied for antipsychotic drug binding to the dopamine D2 receptor (Farde et al. 1988). The relationship between in vivo dopamine D2 receptor occupancy and antipsychotic drug effect was early established. More than 65–70 % of dopamine D2 receptor occupancy is required to obtain antipsychotic efficacy, but at more than 80 % of occupancy, there is a high risk for extrapyramidal symptoms (Farde et al. 1986; Kapur et al. 2000). The atypical antipsychotic clozapine is an exception since this drug has antipsychotic effect at lower dopamine D2 occupancy (Farde et al. 1992; Nordström et al. 1995).

The PET occupancy approach has now become widely applied to drug development and extended to several other targets including the serotonin and noradrenaline neurotransmission systems and enzymes such as monoamine oxidase B (Meyer et al. 2004; Hirvonen et al. 2009; Sekine et al. 2010). The target occupancy by a new candidate drug is usually estimated for different doses, so that the curvilinear relationship between dose/plasma level and occupancy can be established (Fig. 1.4). This key information will help efficient dose setting in phase II and III studies by avoiding doses that are too low or too high. For new targets, the relationship between target occupancy and clinical efficacy or side effects may be insufficiently understood. In such cases, the relationship between occupancy and pharmacodynamics can only be established after phase II and III studies when clinical data becomes available.

A recent successful example of the occupancy approach is [11C]AZ10419369, a PET radioligand for the serotonin 5HT1B receptor subtype (Figs. 1.2, 1.3 and 1.4). This radioligand was developed in a collaboration between Karolinska Institutet and AstraZeneca and has been used for the occupancy measurement by AZD3783,
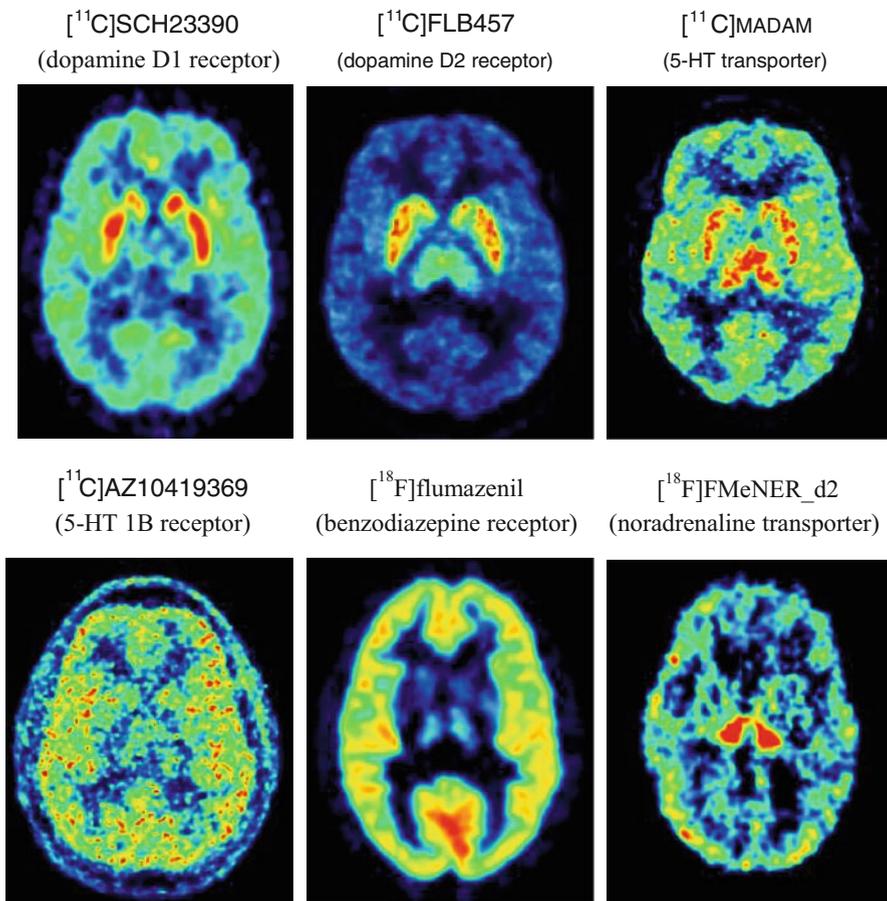
**Fig. 1.1** Horizontal brain sections through the striatal level showing the regional distribution of the binding of commonly used PET radioligands. Images represent radioactivity summed after radioligand injection (9–51 min for [$^{11}$C]SCH23390, 0–87 min for [$^{11}$C]FLB457, 7–93 min for [$^{11}$C]MADAM, 3–63 min for [$^{11}$C]AZ10419369, 9–93 min for [$^{18}$F]flumazenil, 90–210 min for [$^{18}$F]FMeNER_d2)
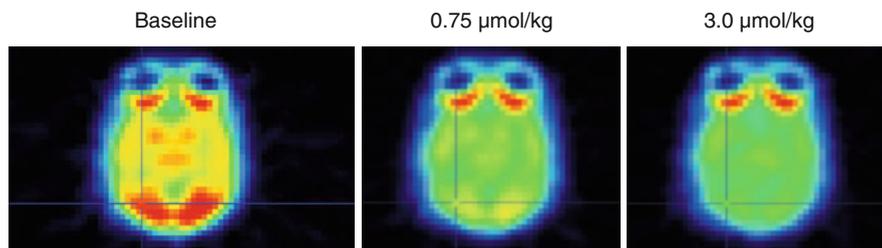


**Fig. 1.2** Horizontal PET images showing [$^{11}$C]AZ10419369 binding to the 5HT1b-receptor at baseline and after AZD3483 i.v. administration in a cynomolgus monkey
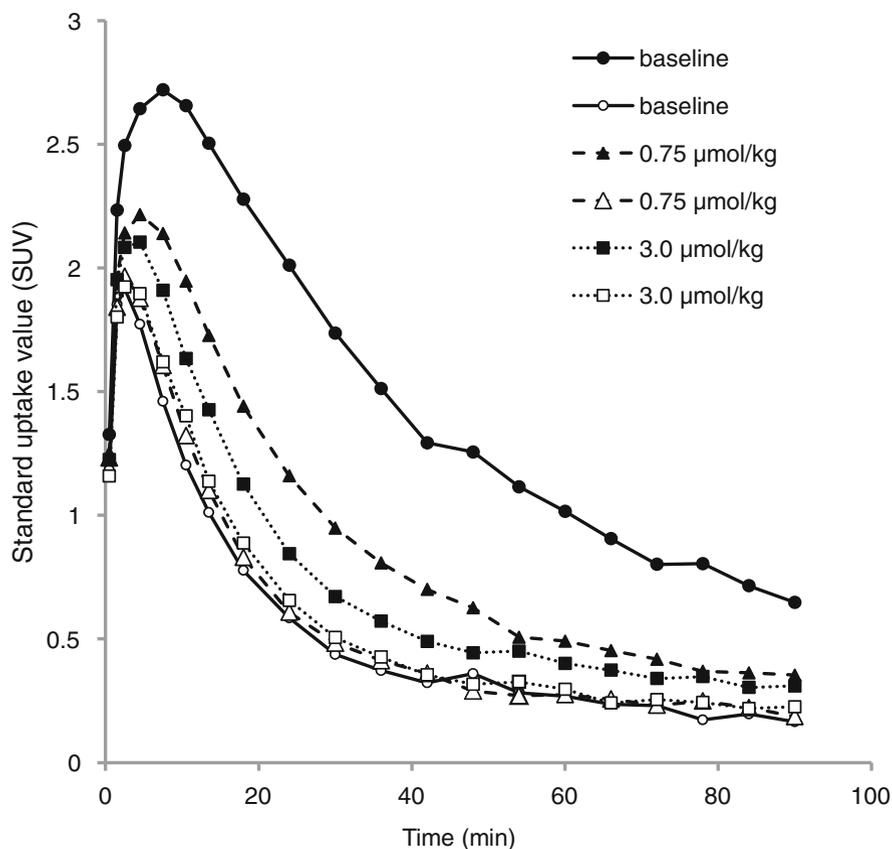
**Fig. 1.3** Time activity curves for the regional [¹¹C]AZ10419369 binding in a cynomolgus monkey illustrated in Fig. 1.2. *Filled marks* represent occipital cortex. *Open marks* represent the cerebellum

a candidate drug for treatment of depression (Pierson et al. 2008; Varnäs et al. 2011). The occupancy estimations were first performed in NHP and later in human subjects. The relationship between the dose and 5HT1B occupancy by AZD3783 was similar between nonhuman primates and human subjects (Varnäs et al. 2011). Despite the value demonstrated for nonhuman primate studies of AZD3783 to predict binding in the human brain, some caution must be exercised whenever making such predictions for new drug targets.

In an optimal occupancy study, a wide range of doses are investigated, ideally covering the interval from 0 to 100 %. However, in reality, due to the risk of side effects, the selection of the doses administered to human subjects is likely to be limited to lower doses. Due to a limited range of data, it may thus be difficult to confirm whether a maximal occupancy can be reached and whether the binding affinity estimates (Kiplasma values (Karlsson et al. 1995)) are reliable.

**Fig. 1.4** The curvilinear relationship between plasma concentration of the 5HT1b receptor antagonist AZD3783 and target receptor occupancy in cynomolgus monkeys (Modification of figure in Varnäs et al. 2011)
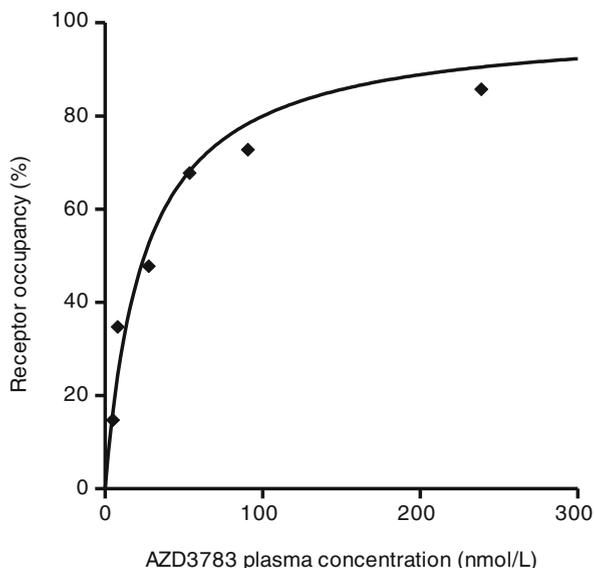
For some drugs, a pharmacologically active metabolite having affinity for the target may contribute to occupancy at the target sites (Takano et al. 2011). In NHP, the occupancy of the metabolite can be estimated by injection of the metabolite only. PET in NHP may thus provide additional useful information prior to the human PET study.

### 1.2.3   Pathophysiology Biomarkers for Diagnosis or Efficacy Studies

For most psychiatric disorders, there are not generally accepted biomarkers in spite of considerable efforts to reveal the pathophysiologies. The recent progress in neuroimaging of psychiatric disorders will be discussed in detail in other sections of this textbook.

A general approach applied in drug development is to use PET to measure physiological parameters such as cerebral blood flow or brain glucose metabolism using $[^{15}O]H_2O$ or $[^{18}F]FDG$. Change in cerebral blood flow or brain glucose metabolism at drug treatment can thereby be detected, which indirectly serves to confirm a drug effect in the brain. The combined study of occupancy at a biochemical marker and a physiological biomarker has a promising potential to further confirm target engagement but has so far been utilized in a few studies only (Halldin et al. 2001).

In a back-translational approach, animal models for psychiatric disorders can be investigated using micro-PET (Higuchi et al. 2010; Klunk et al. 2004). As the animal does not have to be sacrificed after each PET measurement, longitudinal evaluation of chronic administration of the candidate drugs can be performed. Such