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## **Recent applications of positron emission tomographic (PET) imaging in psychiatric drug discovery**

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### **Abstract**

#### **Introduction**

Psychiatry is one of the medical disciplines that suffers most from a lack of innovation in its therapeutic arsenal. Many failures in drug candidate trials can be explained by pharmacological properties that have been poorly assessed upstream, in terms of brain passage, brain target binding and clinical outcomes. Positron emission tomography can provide pharmacokinetic and pharmacodynamic data to help select candidate-molecules for further clinical trials.

#### **Areas covered**

The aim of this review is to explain and discuss the various methods using positron-emitting radiolabeled molecules to trace the cerebral distribution of the drug-candidate or indirectly measure binding to its therapeutic target. More than an exhaustive review of PET studies in psychopharmacology, this article highlights the contributions this technology can make in drug discovery applied to psychiatry.

#### **Expert opinion**

PET neuroimaging is the only technological approach that can, in vivo in humans, measure cerebral delivery of a drug candidate, percentage and duration of target binding, and even the pharmacological effects. PET studies in a small number of subjects in the early stages of the development of a psychotropic drug can therefore provide the pharmacokinetic/pharmacodynamic data required for subsequent clinical evaluation. While PET technology is demanding in terms of radiochemical, radiopharmacological and nuclear medicine expertise, its integration into the development process of new drugs for psychiatry has great added value.

### **Keywords**

Drug discovery; Drug occupancy; Neuroimaging; Positron Emission Tomography; Neuropsychopharmacology; PET microdosing; Psychiatry; Radiopharmaceutical.

## 1. Introduction

### 1.1. The challenges of drug discovery in psychiatry

The search for new brain drugs for psychiatry is confronted by a paradoxical situation. On the one hand, there is a growing global need for new psychiatric medications. On the other hand, there has been a retreat from research into new therapeutics following numerous difficulties and failures. Mental disorders are one of the major health burdens in terms of years of life lost. They are the leading cause of years lived with disability [1,2]. Mental disorders account for five of the ten leading causes of disability and premature death. People with severe mental disorders die prematurely, up to two decades earlier, often as a result of preventable somatic deterioration. Financially, mental health disorders are expected to cost \$6.5 billion by 2030, making mental illness the most expensive disease category [2]. It is clear that there is a need for more comprehensive care, given that mental disorders can affect one in five people at some point in their lives.

At the same time, psychiatry has not seen any significant therapeutic advances for decades [3]. The vast majority of drugs available to psychiatrists were developed long ago, and are based on pharmacological concepts that have evolved little since then. For example, antipsychotics and antidepressants are largely based on the monoamine theory, including the dopaminergic and serotonergic systems [4,5]. Anxiolytics and hypnotics act mainly on the gabaergic system. And while normothymics, such as lithium, have more complex and less well-identified intracellular targets, they are still discoveries from over 40 years ago. This is not in itself a handicap, as old drugs can be good drugs, with proven risk-benefit ratio. However, many molecules are not very effective, or are even ineffective in a significant percentage of patients, and they often have adverse effects such as neurological and metabolic issues [6]. Psychedelic molecules such as LSD and psilocybin are among the most recent to be revisited, with potential indications in depression and anxiety, and nearly 60 companies have been formed to explore their potential and bring derivatives to market [7].

Renewing the medicines used in psychiatry is therefore a challenge and a real opportunity for pharmaceutical companies. However, the search for new drugs is very complex, with high failure rates, particularly for psychiatric indications [8]. The difficulties stem primarily from the conceptual limitations of biological psychiatry: poorly understood pathophysiology, poorly predictive animal models, a virtual absence of validated biomarkers, and a frequent placebo effect [3]. Failure can also result from basic pharmacokinetic and pharmacological factors such as bioavailability and target binding. Drugs for the brain have a fundamental limitation: they have to get into the brain, the organ best protected from exogenous molecules by the blood-brain barrier.

Taken together, these factors explain the attrition rate for CNS drugs, which, at over 90%, is the highest of all drug classes [9,10]. Detailed analysis of clinical development programs in psychiatry shows that a third of failures are related to inadequate clinical efficacy and a half to safety problems. Among these failures, ex-post analyses regularly point the finger at poor dose selection and pharmacokinetic data that were insufficiently known in advance and therefore not considered in protocol design. As a result of these repeated failures, major industry groups have gradually withdrawn from psychiatric research. The 2010s were the *anni horribiles*, with the beginnings of closure of psychopharmacology research programs for GlaxoSmithKline, AstraZeneca, Novartis, MSD, Sanofi and Pfizer [11]. Taking risks with no return on investment justified these strategic decisions, reinforced by repeated failures to develop an Alzheimer's disease molecule. The years that followed were marked by the continuation of research in psychopharmacology, but almost exclusively within small biopharma/biotech structures, exploring new pharmacological concepts and targets in the hope that any lead they found would be acquired by a big pharma company and taken into clinical development. These years have also been marked by a

real introspection in the discipline of neuropsychopharmacology, both academically and industrially. The question now is: how can we make drug discovery in psychiatry more efficient and fill the pipeline with drug candidates?

As an initial response, a collaborative study between academia and industry highlighted three issues that need to be addressed prior to any clinical trial in psychiatry, in order to significantly increase the chances of success [12]. The first point concerns exposure at the target site of action. The basic principle is that drug exposure at the target site is necessary to elicit a pharmacological effect of the desired duration. The second point concerns binding to the pharmacological target. The basic principle is that target occupancy is a prerequisite for pharmacologic expression and target modulation. The third point concerns pharmacologic expression. The basic principle is that functional modulation of the target is a prerequisite for the expression of pharmacological activity to test the mechanism. These are not the only reasons for past failures. But being able to control them in advance of phase II and III clinical trials would enable us to avoid a significant number of false leads, avoid unnecessary enrolment of research-ready patients and ultimately increase the chances of success at a reasonable financial cost.

In this context, much hope has been pinned on in-vivo neuroimaging [13]. In particular, positron emission tomography (PET), a nuclear medicine technique that uses radiopharmaceuticals labeled with short half-life radionuclides: fluorine-18 or carbon-11, suitable for small molecules. PET provides access to molecular and functional information [14]. It is based on radiopharmaceuticals injected in sub-microgram “tracer” doses, which bind to the target (receptors, transporters, etc.) with very high specificity. This in-vivo binding can be visualized and quantified using adapted PET scanners, the spatial resolution of which may be limited to a few millimeters but which reveal a highly specific chemical signature. In other words, PET allows us to see brain chemistry in animal models or humans, with a unique translational approach.

Here we describe how PET brain scans can be used throughout the drug discovery process for new therapeutic molecules in psychiatry. While most of the methods described can be applied to animal models using the same radiopharmaceuticals and dedicated PET scanners, this review will only cover applications in humans, both healthy volunteers and research patients. We have also chosen to include Alzheimer's disease and related disorders, which have psychiatric comorbidities. PET applications in psychiatric drug discovery will be reviewed according to the translational pharmacological approach: the target, then the bioavailability of the drug candidate and its occupancy rate, and the resulting pharmacological effects.

## **2. PET and visualization and quantification of drug targets in the brain**

The first challenge of PET imaging was to visualize brain targets, such as receptors or transporters (Figure 1). The earliest publication of a PET image of a brain target in humans dates back to 1983, with the work of Garnett and collaborators in Hamilton, Canada, using L-DOPA radiolabeled with fluorine-18 [15]. At almost the same time, Henry Wagner's team at Johns Hopkins University in Baltimore, USA, published the first human PET image of D<sub>2</sub> receptors [16]. These pioneering PET explorations paved the way for other radiopharmaceutical developments, first in animal models (rodents and primates), before moving on to humans and taking on the status of radiopharmaceutical drugs [16]. The radiochemists who synthesized radiolabeled molecules with carbon-11 or fluorine-18 were initially inspired by existing psychotropic drugs, such as antipsychotics or SSRIs. Given the limited success of this work (a good psychotropic drug is not necessarily a good radiopharmaceutical), derivative

molecules were developed. At present, more than thirty proteins of interest located in the brain can be quantified using radiopharmaceuticals authorized for human use [17]. It is therefore possible to visualize, quantify and longitudinally follow almost all the pharmacological targets of current psychiatric drugs [18, 19]. The 2000s were the golden age of biological psychiatry and the search for the biological signatures of mental pathology. Psychiatrists had high expectations of PET technology, believing that significant specific changes in receptor density could be identified for each pathology. D<sub>2</sub> dopamine receptors and the dopamine transporter were extensively studied in schizophrenia and depression [20, 21]. Serotonin receptors, including 5-HT<sub>1A</sub>, were studied in depression [22,23]. However, this approach soon showed its limitations, with results that were occasionally significant but then not reproduced by other teams, particularly when different PET radiopharmaceuticals were used. For example, the increased density of 5-HT<sub>1A</sub> receptors seen in the raphe and hippocampus of depressed bipolar patients [24] raised great hopes for a pathophysiological clue or even a therapeutic strategy targeting this receptor family. Unfortunately, subsequent meta-analyses showed that receptor density was not a sensitive and specific biomarker of pathology. For example, 5-HT<sub>1A</sub> receptor density is altered in anxiety disorders, major depressive disorder, bipolar depression and schizophrenia, without brain region specificity [25].

However, while today's biological psychiatry no longer believes in pathology signature based on a single receptor, the search for new targets with PET radiopharmaceuticals remains of interest. Most PET radiopharmaceuticals are developed at the request of teams of pharmacologists working on new targets for psychiatry. The ideal is to have a companion PET radiotracer that accompanies the drug candidate through preclinical and then clinical development, contributing to the proof of concept of its therapeutic effect [26]. For example, the interest of the psychopharmacological community in esketamine, used for its antidepressant properties, has led various teams of radiochemists and radiopharmacologists to develop PET radiotracers for glutamatergic receptors of the NMDA family, targeting the GluN2B subunit in particular [27]. As another example, the search for a radiopharmaceutical targeting 5-HT<sub>6</sub> receptors [28, 29] was motivated by psychopharmacological leads in obesity, cognitive decline, Alzheimer's psychosis or as adjuvant treatment in schizophrenia [30-32], but without convincing clinical results so far [33].

### **3. PET and drug entry into the brain**

Intracerebral passage of a drug from the CNS is a prerequisite, but also one of the most limiting steps in CNS pharmacology today [34, 35]. In fact, over 95% of organic molecules with favorable binding properties are unusable in neuropsychiatry because they do not sufficiently cross the blood-brain barrier. This percentage is even higher for high molecular weight molecules, which constitute the emerging therapeutic field of biotherapies (monoclonal antibodies, antisense oligonucleotides, etc.), a field currently limited to neurology [36] but likely to reach psychiatry.

Animal models allow in-vivo measurement of the mechanisms of action of psychotropic molecules [37], but information on bioavailability remains limited in terms of predictability for translation to humans. The only non-invasive method that can follow the passage of a molecule of interest through the brain is PET microdosing. This approach is simple in principle, as it consists in making a candidate molecule radioactive by replacing a non-radioactive carbon-12 or fluorine-19 atom that is part of the chemical structure with the corresponding PET radioactive atom: i.e., carbon-11 or fluorine-18 [38, 39, 40]. Implementation is more complex in terms of chemical methods, which are not always applicable to all heterocyclic molecule structures and require expertise in radiochemistry. In the end, the

radioactive molecule will have the same pharmacological and pharmacokinetic properties as the original molecule of interest. The next step is to administer the candidate radioactive molecule intravenously to not more than 10 healthy volunteers and monitor cerebral distribution with a PET camera (Figure 2). This approach has been used many times in the preclinical development of psychotropic molecules (SSRI antidepressants, etc.), to rapidly select which of several candidates best penetrates the brain and is therefore to be preferred for further clinical trials in larger numbers of subjects. Several antidepressant candidates with structures similar to current SSRIs have been tested with a view to possible market positioning. A few doses of their radiolabeled carbon-11 form were sufficient to eliminate them from further clinical development due to low brain uptake in humans, despite encouraging preclinical data (personal data). PET microdosing data can also be informative when examined retrospectively for molecules used in psychiatry. For example, a PET microdosing study in non-human primates showed very different brain uptake for a dozen psychotropic molecules such as citalopram, clomipramine, clozapine, diazepam, doxepine, seligiline, sertraline, sulpiride, venlafaxine, ...all radiolabeled with carbon-11 [4][11]. The PET microdosing approach therefore has its place in the preclinical development of molecules for psychiatry [42]. It should be noted, however, that, as this work is essentially carried out in the context of industrial R&D, the data obtained are included in the scientific dossiers submitted to the regulatory authorities but are only rarely published and evaluated academically. The term "microdose" is therefore recognized by the regulatory agencies and integrated as a regulatory concept in phase 0 of drug development [43, 44]. For example, the European Agency for the Evaluation of Medicinal Products (EMA) defines a microdose as a dose of a drug candidate that is less than 1% of the expected pharmacologically active dose, less than 100 µg per dose, intended for fewer than 10 healthy volunteers, and for an administration time of less than 7 days [45]. These microdoses allow pharmacokinetic studies to be carried out using microanalytical analyses (accelerator mass spectrometry, etc.) to determine the fate of the molecule in biological fluids. This regulatory framework, which has been adopted in a similar form by various regulatory agencies, ensures early administration in humans prior to advanced pharmacology safety studies [46]. The microdose concept has been adopted by the PET neuroimaging community, which found similarities with the tracer dose concept [40]. In fact, PET brain radiopharmaceuticals have a molar concentration that allows weight-based administration in the µg range, thus meeting microdose specifications. The main information provided by microdosing PET is therefore the cerebral passage of the drug candidate. Thus, a few brain PET scans can be used to rule out a molecule with inadequate brain passage on a go-no-go basis, economizing on subsequent clinical trials that are doomed to failure. This saves time, limits unnecessary exposure of research-ready subjects and saves money. However, the microdosing PET approach has its limitations and cannot guarantee full predictivity, particularly for quantitative pharmacokinetic measurements (retention and clearance times, etc.). In fact, extrapolation from a microdose to a pharmacological dose may be biased by differences in kinetic behavior related to mass or possible target saturation.

#### **4. PET and drug engagement with target**

Assessment of the pharmacological efficacy of a drug candidate in psychiatry is not limited to its ability to penetrate the brain. We also need to be sure of the drug's engagement with its target: i.e., its percentage occupancy during treatment. Drug occupancy and occupancy duration are therefore critical parameters that only PET imaging can provide in-vivo in humans [47]. This requires a radiopharmaceutical that binds to the same target as the drug candidate and can therefore compete with it. It is therefore important to have as many PET radiopharmaceuticals as possible that have been

validated for specific binding to one of the many targets used in psychopharmacology (mainly neurotransmitter receptors and transporters). The principle is that each subject is their own control. The first step is to obtain an initial PET image before administering the candidate drug. The drug is then administered to the subject, either as a single dose or repeatedly. The subject is then given the PET radiopharmaceutical again for a second PET scan. The two PET images, before and after drug administration, are compared and used to calculate the percentage of the target occupied by the drug (Figure 3). Several small groups of subjects can be set up using this protocol, with each group receiving a different dose of the drug being tested. Pooling results provides valuable information. We can determine the percentage of the target occupied by the drug, depending on the dose administered and, if the protocol allows, for how long. These data, obtained from a limited number of subjects, can be used to suggest future doses and dosing frequencies for subsequent clinical phases. This approach was first profiled during the development of neuroleptics, where the question of dose is directly related to antipsychotic efficacy, dosing frequency and the occurrence of extrapyramidal side-effects [48,49, 50, 51]. The main mechanism of action of antipsychotic drugs is inhibition of dopamine D<sub>2</sub> receptors; this achieves the expected antipsychotic effects, but blocking receptors in the caudate putamen causes severely disabling extrapyramidal neurological effects. The challenge is therefore to determine the optimal antipsychotic dose, above the threshold for psychiatric efficacy and below that at which adverse neurological effects occur [51]. In this context, [<sup>11</sup>C]raclopride is the most widely used radiopharmaceutical, because of its binding properties to D<sub>2</sub> receptors, particularly in the striatum. Other PET radiopharmaceuticals targeting D<sub>2</sub> receptors are also used, such as [<sup>11</sup>C]FLB45710 or [<sup>18</sup>F]-fallypride, which have a higher affinity for the receptor and enable visualization of extrastriatal sites. The Karolinska Institute in Stockholm conducted pioneering work in this area [52]. They were the first to show that antipsychotics, with the exception of clozapine, require an occupancy rate of more than 70% to have a behavioral effect, but not more than 80%, as otherwise the incidence of extrapyramidal symptoms increases. A number of studies clarified the relationship between antipsychotic efficacy and receptor occupancy, defining a therapeutic window of 65-70% occupancy. These studies preceded or accompanied the marketing of most “2<sup>nd</sup> generation” antipsychotics, such as paliperidone [53], blonanserin in its various galenic forms [54,55, 56] and aripiprazole [57, 58, 59]. PET technology was not available when they came on the market, and PET studies allowed optimal doses of 1st-generation antipsychotics, including the emblematic haloperidol, to be re-evaluated a-posteriori [60]. As antipsychotics have a broad receptor spectrum, other targets are also being explored using this approach. Second-generation antipsychotics are pharmacologically defined by their marked effect on serotonin 5-HT<sub>2A</sub> receptors. Fluorine-18-labeled altanserin binds specifically to this receptor. However, there is no evidence of a relationship between 5-HT<sub>2</sub> receptor occupancy and clinical efficacy and/or the occurrence of adverse effects, as is the case for D<sub>2</sub> receptors [61]. This explains the paucity of PET occupancy studies of these receptors in the context of antipsychotic drug discovery. However, this target has recently gained new interest with the revival of psychedelic molecules (LSD, psilocybin), indications for which in psychiatry are being re-examined. The current hypothesis is that psychedelic effects result from agonistic stimulation of these 5-HT<sub>2A</sub> receptors [62]. A relationship between psychedelic effects and the occupancy rate of 5-HT<sub>2A</sub> receptors was recently demonstrated in volunteers using a competition protocol between the radiopharmaceutical [<sup>11</sup>C]Cimbi-36, a 5-HT<sub>2A</sub> agonist radioligand, and increasing doses of psilocybin [63].

## 5. PET quantification of cerebral drug action

Intracerebral passage and adequate target binding are prerequisites for a pharmacological effect, but not sufficient to guarantee a therapeutic effect. Although PET imaging cannot replace clinical evaluation, it can indirectly measure the biological expression of a drug's pharmacological effects. Unlike neurology, where pathophysiology is often based on the presence of a brain lesion of defined location, psychiatry does not currently have a sufficiently solid mechanistic basis for PET biomarkers. However, there are some applications of PET imaging in monitoring cognitive status following pharmacological treatment. These mainly concern psychiatric manifestations of neurodegenerative pathologies, such as Alzheimer's disease, which are of interest to both neurologists and psychiatrists. The challenge is to visualize and quantify the pathological protein aggregates that are the signature of Alzheimer's disease: i.e., beta-amyloids and hyperphosphorylated tau proteins. These aggregated proteins can be visualized using PET radiopharmaceuticals, one of which, [<sup>11</sup>C]PIB, was the precursor for beta-amyloid imaging, marking the entry of pathological aggregated proteins into the radiopharmaceutical field in 2003 [64]. Currently, more than a dozen fluorine-18-labeled radiopharmaceuticals have been validated in humans, for both beta-amyloid and tau proteins [65,66].

The primary use of these radiopharmaceuticals is to assist enrolling subjects with the corresponding lesions. Cognitive decline and associated clinical symptoms are not specific to Alzheimer's disease and may be caused by other neurodegenerative pathologies. The problem is that their pathophysiological mechanisms are likely to be different, with other forms of aggregated proteins such as alpha-synuclein, TDP-43 protein and FUS protein being potential targets [67]. It is therefore crucial to include subjects with a significant amyloid burden in therapeutic trials testing anti-amyloid immunotherapy, to ensure a homogeneous group in terms of target [68]. An initial PET scan with an amyloid radiopharmaceutical is therefore used to select "positive" subjects. Various studies have shown that, on average, 18.7% of subjects are excluded thanks to this prior PET imaging [69].

The other contribution of aggregated protein radiopharmaceuticals is to aid in the evaluation of anti-Alzheimer's drug candidates by longitudinally monitoring their possible decline over the course of the treatment being tested [70]. The advantage of PET imaging is that it allows longitudinal monitoring of the subject under his or her own control, with a first PET scan prior to treatment initiation and a second for comparison after several months' treatment (Figure 4). This was the case for anti-amyloid immunotherapies recently proposed as anti-Alzheimer's treatments, such as aducanumab [71] and lecanemab [72], validated by the FDA in 2021 and 2023 respectively. Both aducanumab and lecanemab were shown to reduce amyloid burden as measured by PET and to slow cognitive decline [73, 74]. This was seen as encouraging in comparison with earlier attempts at immunotherapy, such as bapineuzumab or aducanumab, where PET imaging with [<sup>11</sup>C]-PIB or [<sup>18</sup>F]-florbetapir showed a reduction in amyloid burden, which unfortunately did not translate into clinically significant effects [75,76]. These various recent examples remind us that the molecular signature of beta-amyloid radiopharmaceuticals or aggregated tau is a confirmatory marker of pharmacological effect, but cannot be considered as a PET biomarker companion in the absence of strict correlation between aggregated protein load and the subject's cognitive status.

Given these limitations of PET imaging of aggregated proteins, the value of metabolic and functional PET imaging needs to be reconsidered, as being less specific but perhaps more robust. Fluorodeoxyglucose ([<sup>18</sup>F]-FDG) imaging is currently an accepted method for measuring global and regional cerebral metabolism as a reflection of neuronal activity. It is commonly used to help diagnose cognitive decline in patients with Alzheimer's disease [77,78] and is readily available in nuclear medicine departments. Although this method is not innovative, it could be adapted to monitor changes in [<sup>18</sup>F]-FDG binding patterns when evaluating anti-Alzheimer's treatment [79]. Only if the treatment halted or reversed the decline in [<sup>18</sup>F]-FDG accumulation in the brain regions most affected by



Alzheimer's disease (temporoparietal cortices) would there be evidence of a clinically significant effect. Metabolic [<sup>18</sup>F]-FDG PET imaging has been used for other anti-Alzheimer's therapeutics, such as nerve growth factor (NGF), for which delivery by gene therapy showed an increase in uptake pattern 6 months after ex-vivo administration of the NGF gene, but without significant clinical effect [80]. More recently, this approach was also used in a Phase-IIa clinical trial investigating the procognitive effects of benfotiamine in Alzheimer's patients [81]. Benfotiamine is a precursor of thiamine synthesis, with multiple enzymatic, metabolic, anti-inflammatory and antioxidant effects that have been suggested to be neuroprotective. The aim of this clinical trial was to test whether benfotiamine treatment could delay clinical decline in amyloid-positive patients with amnesic cognitive impairment. Cerebral glucose metabolism, as measured on [<sup>18</sup>F]-FDG PET imaging, was assessed as a secondary endpoint. The molecule did not show significant clinical efficacy, but PET imaging was available to corroborate that finding by showing no change in the cerebral metabolic pattern. Finally, although longitudinal follow-up with [<sup>18</sup>F]-FDG PET imaging has been reported for various antipsychotic [82-87] and antidepressant treatments [88-91], the results were too heterogeneous and variable between individuals for it to be a robust marker with added value for drug discovery of new molecules.

## 6. Conclusions

The vast majority of drugs available in psychiatry were developed several decades ago, and the psychopharmacological arsenal is struggling to renew itself, being still largely based on monoamine-targeting approaches. What is more, psychiatric drugs are the therapeutic class with the highest attrition rate: i.e., failures that limit new market launches. In addition to poor choice of therapeutic target, and thus ultimately no therapeutic effect, or the significant side-effects that can occur during clinical trials, failures are often related to inappropriate PK/PD properties, such as insufficient cerebral passage of the drug or insufficient binding to target. PET imaging provides tools and methods to track a candidate molecule, radiolabeled with a positron-emitting atom. PET also allows in-vivo measurement of target binding, a prerequisite for any pharmacological effect. Finally, in certain more limited cases, PET can be used to visualize neurodegenerative proteins with evolution accompanying pharmacological efficacy. While these molecular neuroimaging approaches do not claim to predict the clinical efficacy of a drug candidate in psychiatry, they are a prerequisite for validating the basic pharmacological properties essential for efficacy: i.e., binding the right target, with sufficient intensity and at the right time. At present, only PET technology can assess these criteria in humans, confirming or invalidating data previously obtained in animal models. The challenge now is to foster an exchange between psychopharmacologists and clinical psychiatrists who are developing new candidate molecules, and brain PET experts who can propose the right tools and methods to meet the pharmacological and clinical challenges.

## 7. Expert Opinion

PET imaging is a unique translational tool for identifying therapeutic targets in humans, checking cerebral passage of the drug candidate, binding to the target, retention time and, in some cases, therapeutic effect. However, it must be recognized that PET imaging could be better integrated into

the preclinical and clinical development stages of future psychiatric drugs. There are a number of reasons for this, and possible avenues for improvement.

### **7.1. Technical limitations**

Feedback from unsuccessful CNS drug development projects often points to inadequate knowledge of human pharmacokinetic and pharmacodynamic parameters. The drug candidate is not always sufficiently well characterized in humans in terms of brain passage, biodistribution, elimination kinetics and actual binding to the therapeutic target. These are fundamental questions that are too often neglected or based on animal data alone. Although preclinical data obtained in animal models of psychiatric pathology are extensive and may provide insight into pathophysiological mechanisms [92-95], they do not systematically predict results that will be obtained in humans, even when obtained in non-human primates. Interspecies differences in the distribution or density of efflux transporters across the blood-brain barrier may explain the low cerebral passage of molecules in humans, whereas this was not a problem in the animal model. In addition, hepatic metabolism may be different, explaining the difference in kinetics in humans. Finally, target affinity in-vivo may be different from conventional in-vitro binding findings. Preclinical research and PET imaging studies in animal models are thus important for establishing initial proof of concept, but need to be followed up as quickly as possible by human PET studies to confirm bioavailability for the drug candidate.

PET imaging, with its PET microdosing and drug occupancy approaches, can provide this type of information, with a small number of subjects. In humans, a few PET scans are sufficient to check that the drug is indeed entering the brain at a rate and within a timeframe consistent with the expected treatment dose. Other types of PET scans can provide information about how long the drug candidate binds to the target. This preliminary PET approach can quickly rule out a molecule that does not meet PK/PD requirements in humans, avoiding the need for large-scale clinical trials. This early go-no-go approach saves investigators time and money and avoids subjecting patients to clinical trials that are doomed to fail.

However, we must be aware of the limitations of PET imaging in pharmacology. While PET approaches can predict basic pharmacological data, they do not provide data on clinical pharmacological effects and therapeutic efficacy, which only clinical studies can provide. Moreover, currently available PET tools, such as radiopharmaceuticals, have their own radiopharmacological limitations and do not cover the full range of future therapeutic targets in psychiatry.

### **7.2. Current tools and tools to be developed**

PET imaging for psychiatric drug discovery relies on radioactive probes in the form of radiopharmaceuticals. The number of PET brain radiotracers that can be used in humans, and therefore have the pharmaceutical status of radiopharmaceuticals, is relatively small, compared to the number of potential therapeutic targets. Some cerebral targets can be visualized by several different PET radiopharmaceuticals ( $D_2$  receptors, 5-HT<sub>2A</sub> receptors, etc., to cite classic targets in neuropsychopharmacology). The choice of radiotracer for a study of drug occupancy or receptor density during treatment is not trivial, as results obtained with one radiopharmaceutical are not systematically transferable to another. This may be due to differences in target specificity, affinity, radioactive kinetics or radiometabolites. Ideally, therefore, comparative or multicenter studies using the same radiopharmaceuticals are to be preferred.

There are also a large number of therapeutic targets for which there are no dedicated radiopharmaceuticals, and we are calling for their development. For example, several serotonergic and

glutamatergic receptors do not yet have their own PET radiopharmaceutical, despite pharmacological work targeting them. It turns out that developing a new radiopharmaceutical for the brain is a long and risky process. It starts with selection and chemical synthesis of the precursor, validation of its radiolabeling process, and the inherent radiopharmaceutical controls [96, 97]. This is followed by all the stages of in-vitro and in-vivo radiopharmacological characterization in animal models and, finally, the first human administration, which is becoming increasingly demanding in terms of regulatory requirements [98-100].

The search for new PET radiopharmaceuticals to support research in psychopharmacology must also go beyond the classical targets of psychiatry: membrane receptors, in particular G protein-coupled receptors, and transporters [101-103]. In fact, psychopharmacology will increasingly turn to intracellular or even epigenetic targets, like in neurology (kinases, phosphodiesterases, etc.) [104, 107]. This will compound the difficulty of searching for new radiopharmaceuticals that need to be able to cross the blood-brain barrier as well as the membrane barrier for intracellular binding.

New concepts in radiopharmacology are also emerging, based on pharmacological properties that have been little exploited in PET neuroimaging. For example, agonist radiopharmaceuticals are being developed based on molecules with biased agonist properties, allowing study of the receptors targeted by the drug under development, but only the fraction of these receptors coupled to intracellular proteins: i.e., that are functional [108, 110]. This high-precision PET molecular imaging approach is still in its infancy, but will be able to support future pharmacological developments in psychiatry by targeting receptors specifically associated with pharmacological response [111, 112].

As we have seen, PET imaging is primarily molecular, which is a strength, but has limited spatial resolution, which is a weakness when studying the brain. PET scanners can therefore benefit from recent technological advances to achieve better specifications. For example, whole-body PET scanners have been developed, offering greater sensitivity [113]. PET scanners dedicated to the brain and adaptable to seated rather than supine subjects are also under study [114]. PET therefore benefits from the contributions of other imaging modalities, in particular MRI, which has been widely developed in neuroscience. MRI is unrivalled in terms of spatial resolution, sensitivity to different tissue types, and even functional imaging using the BOLD modality. Fusion of PET and MRI images is commonplace in neuroimaging, and this approach is greatly enhanced by the hybrid PET/MRI cameras now on the market [115]. In this way, hybrid PET/MRI approaches make it possible to study the properties of drug occupancy at a receptor in a given subject using the PET modality, followed by functional brain activation following the action of the molecule using MRI [116, 117].

Multimodal imaging applied to psychopharmacology can also legitimately expect to see advances in artificial intelligence [118]. These machine-learning approaches will allow PET receptology data to be linked to brain activation data, pharmacogenomic data and other data, through powerful correlation maps that provide information on functional connectivity [119-121]. At present, these tools are being developed mainly to help classify psychiatric pathologies, an essential prerequisite for the proper inclusion of subjects in future therapeutic trials.

### **7.3. Gathering expertise around PET imaging for drug discovery in psychiatry**

The contribution of PET neuroimaging to drug discovery in psychiatry depends on the quality of the interactions between the medical and scientific psychopharmacology community and scientists with expertise in neuroimaging. Psychiatrists and psychopharmacologists often have limited knowledge of the opportunities offered by PET neuroimaging. For the medical community, neuroimaging is little used

in routine psychiatric diagnosis and care, and is rather a tool reserved for research [122], whereas it is often associated with neurological healthcare. In the scientific community, pharmacochemists and pharmacologists involved in drug discovery programs are also unfamiliar with the benefits of isotopic molecular imaging. A real effort therefore needs to be made to educate the psychiatric community in PET molecular neuroimaging. On the one hand, psychopharmacologists need to explain in detail their expectations: i.e., the pharmacokinetic and pharmacodynamic information they wish to validate and confirm in humans on the basis of available preclinical data. On the other hand, PET neuroimaging experts need to clearly specify the scope and nature of the data that will be provided by PET imaging. The advantages are undeniable, with the unique possibility of in-vivo translational brain exploration at the molecular level. There are also limitations in terms of spatial resolution and experimental limitations related to radiopharmaceutical production or subject dosimetry. The challenge is to bring together these communities, which no longer meet so frequently. This is already happening through learned societies such as the European college of neuropsychopharmacology (ECNP) or the American college of neuropsychopharmacology (ACNP), which links PET neuroimaging with psychopharmacology.

We also need to facilitate interaction and collaboration between the R&D teams of pharmaceutical and biopharmaceutical companies and the academic neuroimaging community. A few years ago, some large pharmaceutical companies had their own PET imaging platforms (including cyclotron and radiochemistry departments) and clinical pharmacologists therefore had expert contacts in-house. They were fully involved in the development of drug candidates with the concomitant development of the radiolabeled molecule for microdosing PET or even the companion PET biomarker [123, 124]. The technological requirements and the cost of equipment and personnel for these platforms led to the gradual relocation and outsourcing of these PET biomarker departments. Preclinical and clinical PET technology platforms, including their cyclotrons and radiochemistry and radiopharmacy departments, are now often associated to academic institutions such as university hospitals. As a result, in-house PET neuroimaging expertise has largely disappeared from pharmaceutical companies. It is time to revive the association of academic and industrial pharmaceutical teams in PET imaging platforms. Early investment in the development of drug candidates will be more secure if go-no-go decisions are made before embarking on large-scale clinical trials, which are doomed to failure in the absence of basic pharmacological data obtained in vivo in humans.

Finally, the contribution of PET imaging to drug discovery in psychiatry will require the renewal and strengthening of the scientific and medical brain imaging community. This community is highly multidisciplinary, with radiochemists, pharmacologists, radiopharmacists, nuclear physicians and scientists specializing in compartmental modeling. In particular, it will be necessary to strengthen certain fields of study, such as radiochemistry and radiopharmacology, where the pool of talent is currently too limited at international level [125-127].

## Article highlights box

- In psychiatric drug development, the highest failure and discontinuation rate is in the pre-marketing clinical phases.
- One of the main reasons for these failures is the lack of PK/PD data in humans prior to clinical trials.
- PET provides methods for monitoring the fate of a drug candidate in terms of cerebral passage, target binding and the evolution of any targeted protein.
- More systematic use of PET neuroimaging can consolidate and confirm PK/PD data in humans, a prerequisite for extending clinical trials.
- The medical and scientific neuropsychopharmacology community is not sufficiently aware of the benefits of PET neuroimaging in the early stages of human disease.

### Figure legends

**Figure 1.** Positron emission tomography (PET) to visualize and quantify brain targets. Left: Molecular modelling of the binding of a fluorine-18 radiopharmaceutical to a specific serotonin receptor. Right: PET image of the serotonin receptor distribution.

**Figure 2.** Positron emission tomography (PET) to measure brain uptake of a drug candidate. Left: Drug candidate radiolabeled with a fluorine-18 replacing a non-radioactive fluorine-19. Right: PET image of the radiolabeled drug distribution showing its brain penetration.

**Figure 3.** Positron emission tomography (PET) to measure target engagement of a drug candidate. Left: PET image of the distribution of a D<sub>2</sub> receptor radiopharmaceutical before administration of the drug candidate (here an antipsychotic). Right: PET image of the same subject with the same radiopharmaceutical after administration of the antipsychotic drug, which competes with the radiotracer and allows its occupancy to be measured.

**Figure 4.** Positron emission tomography (PET) to measure the effect of a drug candidate on aggregated proteins. Left: PET image of an Alzheimer's patient before treatment. Right: PET image of the same patient several months after treatment with an anti-amyloid antibody.

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### Declaration of interest

The author has no competing interests to declare.

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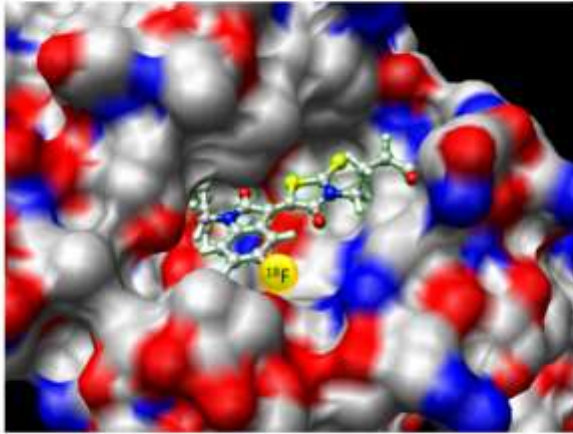
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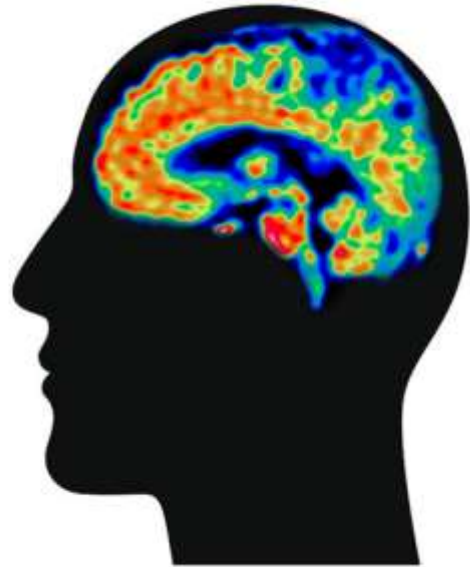
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## PET target quantification

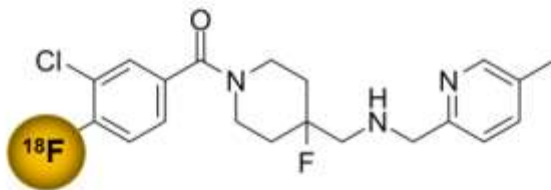


Radiopharmaceutical binding

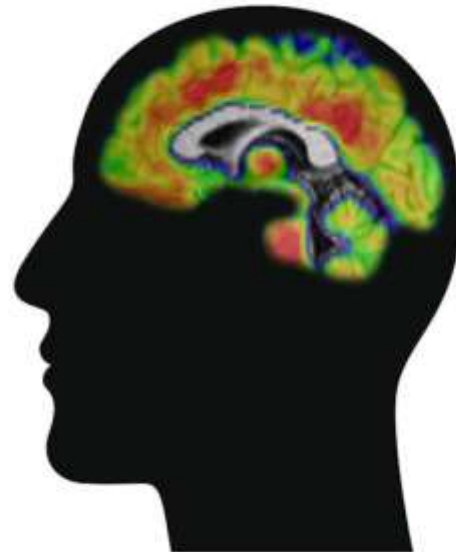


Brain receptor distribution

## Drug candidate microdosing

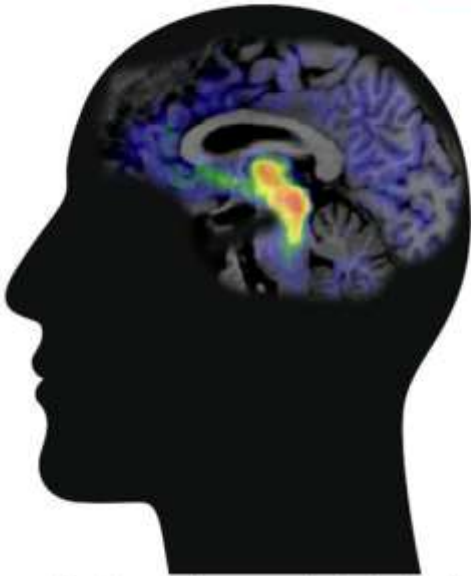


Radiolabeled drug



Brain distribution of radiolabeled drug

**Drug target occupancy**



Before drug administration



After drug administration

**Effect on the target**



Aggregated proteins before treatment



After treatment