Chapter from the book *Neuroimaging*
Downloaded from: http://www.intechopen.com/books/neuroimaging

Interested in publishing with InTechOpen?
Contact us at book.department@intechopen.com
Challenges for PET Neuroimaging of Depressive Disorders

Donald F. Smith\textsuperscript{a,c} and Philip W. Miller\textsuperscript{b,c}

\textsuperscript{a} Center for Psychiatric Research, Psychiatric Hospital of Aarhus University, 8240 Risskov, Denmark
\textsuperscript{b} Department of Chemistry, Imperial College London, South Kensington, London, SW7 2AZ, England
\textsuperscript{c} PET Center, Aarhus University Hospital, 8000 C Aarhus, Denmark

1. Introduction

This chapter deals with two major challenges facing PET neuroimaging of depressive disorders: determining the neurobiology of depressive disorders and inventing suitable positron-emitting radioligands for exploring molecular aspects of brain function. Over the years, PET neuroimaging of depressive disorder has focused almost exclusively on monoaminergic neurotransmission, but judging from recent reports, those studies have failed to demonstrate reliable links between either serotonergic or dopaminergic mechanisms and depressive disorders. Today, disturbances in numerous other neurobiological processes are thought to cause depressive disorder, but we lack PET radioligands to test most modern hypotheses in the living human brain. Thus, the future success of PET neuroimaging of depressive disorders depends on advances in neuroscience concerning molecular neurobiology and on advances in radiochemistry for the synthesis of novel positron-emitting molecules to test hypotheses on the neurobiology of depressive disorders. Success in PET neuroimaging of depressive disorders is expected to provide insight toward better prevention and treatment of these disabling conditions.

2. Depressive disorders

Depression is a severe, disabling, and sometime fatal illness. Symptoms of depression include a mental state of hopelessness, sleep disturbance, altered appetite, lack of energy, concentration difficulties, low self-esteem, self-destructive behavior, painful bodily sensations, and suicidal ideation. Needless to say, depressive disorders require prompt attention and appropriate care. A major current issue in psychiatry is the lack effective treatments to relieve the symptoms of depression in many sufferers (Berlim et al. 2008; Rush et al. 2003a; Rush et al. 2009). Hopefully, further studies of neurobiological mechanisms in depressive disorders will eventually lead to more effective antidepressant treatments. That hope has motivated many studies of molecular mechanisms in depression using positron emission tomography (PET).
3. Principles of PET neuroimaging

PET neuroimaging is a challenging technology. It requires rapid synthesis of highly-purified positron-emitting radioligands of high specific activity, intravenous injection of radioactive compound often with arterial blood sampling in partially immobilized subjects, 3-dimensional registration of photon emissions from the target organ over time, and computerized computations of kinetic parameters. The kinetic parameter used most often to describe the outcome of PET neuroimaging, namely the binding potential, is a complex entity composed of three factors: the number of receptors that are available for binding by the PET radioligand, the affinity of the available receptors toward the PET radioligand, and the concentration of molecules other than the PET radioligand that bind to those receptors (Dunlop and Nemeroff 2007; Laruelle 2000; Lammertsma 2002). The binding potential is an estimate that reflects a series of molecular events, and its value depends on the kinetic model selected for the data analysis. The contribution of individual factors to the binding potential cannot be determined by the single-scan design used in most PET studies of depression. Thus, the complexity of both depression and PET sets limits on the interpretation of findings.

Most PET studies of depressive disorders have been based on the monoamine hypothesis (Schildkraut et al. 1968; Schildkraut and Kety 1967), despite the clear-cut need for exploring other strategies (Hindmarch 2002; Berton and Nestler 2006; Pittenger and Duman 2008; Paschos et al. 2009; Covington, III et al. 2010; Wegener and Volke 2010). Here, we first review recent molecular PET reports on depressive disorders in humans. Next, we discuss challenges for PET in studying in humans the molecular basis of depressive disorders. Then, we outline the need for suitable positron-emitting radioligands for testing modern hypotheses on the causes and consequences of depressive disorders. Clearly, there are a number of major challenges facing those who care to know the molecular basis of these disabling and sometimes fatal diseases.

4. Recent PET studies of serotonin in depressive disorders

Serotonergic neurotransmission has received most attention in studies of depression (Nemeroff and Owens 2009; Owens and Nemeroff 1994). We find, however, that PET studies have not provided consistent findings of a causal link between serotonergic dysfunction and the severity of depressive disorders. Ten PET studies published in recent years have used $^{11}$C]McNeil 5652 or $^{11}$C]DASB to assess the serotonin transporter in depressed subjects and healthy controls. Four of those studies, plus a data re-analysis, noted less binding by the serotonin transporter in brain regions of depressed subjects (Miller et al. 2008; Oquendo et al. 2007; Parsey et al. 2006a; Reimold et al. 2008; Miller et al. 2009b), four studies found more binding by the serotonin transporter in depressed subjects (Reivich et al. 2004; Cannon et al. 2006b; Cannon et al. 2007; Boileau et al. 2008), and two studies found no difference between depressed subjects and healthy controls in binding by serotonin transporters in brain regions (Meyer et al. 2004; Bhagwagar et al. 2007).

Discrepancies are also apparent in the outcome of recent PET studies carried out with $^{11}$C]WAY-100635 or $^{18}$F]FCWAY to assess serotonin type 1A receptors in depressed subjects and healthy controls. Here, five studies noted less binding by serotonin type 1A receptors in brain regions of depressed subjects (Bhagwagar et al. 2004; Meltzer et al. 2004; Hirvonen et al. 2008; Drevets et al. 2007; Theodore et al. 2007), one study reported no
difference between depressed subjects and healthy controls in binding by serotonin type 1A receptors (Mickey et al. 2008), while more binding by serotonin type 1A receptors was found in three studies of depressed subjects or remitted, depressed subjects compared with healthy controls, with no correlation between receptor binding and depression severity (Parsey et al. 2006b; Miller et al. 2009a; Sullivan et al. 2009). In addition, neither antidepressant treatment including ECT nor induction of depression by depletion of tryptophan affected binding by serotonin type 1A receptors in brain regions (Moses-Kolko et al. 2007; Praschak-Rieder et al. 2004; Saijo et al. 2010). These findings clearly challenge the notion that alterations of serotonergic functions are causally linked with either depressive disorders or antidepressant efficacy.

Serotonin type 2 receptors have also been studied by PET in recent years in relation to depressive disorders. Two closely-related studies used [18F]altanserin for PET and noted less hippocampal binding in depressed subjects than in healthy controls (Mintun et al. 2004; Sheline et al. 2004). In contrast, two other PET studies used either [11C]MDL 100,907 or [18F]setoperone to assess serotonin type 2 receptors and noted more binding in depressive subjects than in healthy controls (Bhagwagar et al. 2006; Meyer et al. 2003). In our view, PET studies with the radioligands that are currently available for assessing serotonergic functions in the living human brain have failed to provide conclusive evidence for aberrant serotonergic mechanisms in depressive disorders. We have noted, however, that receptor occupancy of serotonin transporters can be assessed reliably by PET with [11C]DASB or [11C]McNeil 5652 (Voineskos et al. 2007; Miller et al. 2008). Perhaps studies of receptor occupancy before and during antidepressant therapies can provide a means of determining whether treatment-resistance stems from inadequate receptor blockade.

Monoamine oxidase has also received attention in PET studies of depressive disorders. One study used [11C]harmine, a reversible inhibitor of type A MAO, for PET scanning in order to see whether the activity of that enzyme differs between depressed patients and healthy subjects (Meyer et al. 2006a). More binding of [11C]harmine was noted in brain regions of depressed patients than in healthy controls, but no correlation was found between clinical variables and PET findings in the patients. A lack of correspondence between clinical condition of patients and degree of binding of [11C]harmine in brain regions was also observed in a recent follow-up PET study of type A MAO in depressive disorders; an elevated distribution volume of the PET radioligand persisted in patients despite symptom-reduction during antidepressant drug treatment (Meyer et al. 2009a).

5. Recent PET studies of dopamine in depressive disorders

Dopaminergic neurotransmission is thought to play a role in depression, perhaps via defects in central reward systems (Randrup and Braestrup 1977; Spanagel and Weiss 1999). Several PET radioligands have been used in recent years for probing dopaminergic mechanisms in depressed humans. [18F]Fluoro-L-dopa is used routinely for assessing dopamine synthesis by PET in Parkinson’s disease (Takikawa et al. 1994), and it showed reduced striatal uptake in depressed subjects with retarded movement (Bragulat et al. 2007). Certain dopamine receptors have also been examined by PET in recent years in depressed subjects. Dopamine D1 receptors were assessed by [11C]SCH 23,390 or [11C]NNC-112 in two PET studies of depression (Dougherty et al. 2006; Cannon et al. 2008), and both reports found less binding in striatal regions of depressed subjects than of healthy controls. Dopamine D2/3 receptors
have been assessed in five PET studies using either \[^{11}C\]raclopride or \[^{11}C\]FLB 457 in depressed subjects and healthy controls; one study noted more striatal binding by dopamine D\(_{2/3}\) receptors in depressed subjects (Meyer et al. 2006b), another study found less dopamine D\(_{2/3}\) receptor binding in depression (Montgomery et al. 2007), and three studies showed no difference between depressed and healthy subjects in dopamine D\(_{2/3}\) receptor binding in brain regions (Kuroda et al. 2006; Montgomery et al. 2007; Busto et al. 2009). The transport of dopamine as well as noradrenaline from the synaptic cleft into presynaptic terminals was assessed by PET using \[^{11}C\]RTI-32 in 20 Parkinson patients, some of which were depressed (Remy et al. 2005). Less transporter binding was noted in brain regions of depressed Parkinson patients than of non-depressed patients with Parkinson’s disease. In our view, a consistent picture of causal relationships between dopaminergic disturbances and depression has failed to appear from PET studies carried out with the positron-emitting radioligands that are currently available for use in humans, except perhaps for movement disorders of depressed subjects.

6. Recent PET neuroimaging of non-serotonergic and non-dopaminergic mechanisms in depressive disorders.

Relatively few PET studies of depressive disorders have been reported recently on molecular mechanisms unrelated to serotonergic and dopaminergic neurotransmission. In one study, \[^{11}C\]doxepin was used to see whether human depression depends on histaminergic mechanisms (Kano et al. 2004). The binding potential of the PET radioligand in some brain regions was lower in depressed patients than in healthy subjects and was correlated negatively to the patient’s self-rated depression severity. In another PET study, the role of cholinergic processes in major depressive disorder was studied using \[^{18}F\]FP-TZTP (Cannon et al. 2006a). The depressed patients had a diagnosis of either recurrent major depressive disorder or bipolar disorder. \[^{18}F\]FP-TZTP binding in cortical brain regions and white matter was lower in bipolar depressed patients than in healthy subjects and was correlated negatively to depression severity. A third PET study used 2-\[^{18}F\]FA-85380 to look at cholinergic function and self-rated symptoms of depression in patients with Parkinson disease (Meyer et al. 2009b). Although none of the Parkinson patients met standard criteria for major depressive disorder (Schrag et al. 2007; Bech 1984), negative correlations were noted between self-rated depression scores and binding of the PET radiotracer in several cortical regions. Another PET study of subjects with only mild self-rated symptoms of depression used \[^{18}F\]FDDNP to explore possible correlations with aggregates of amyloid and tau proteins in brain regions (Lavretsky et al. 2009). Subjects with mild cognitive impairment showed a positive correlation between self-rated depression scores and radioligand binding in medial temporal lobe.

7. Challenges for PET neuroimaging of depressive disorders

Molecular tools currently available for PET neuroimaging in humans assess primarily monoaminergic receptors on surface of brain cells. As a result, most PET neuroimaging studies of depressive disorder focus on some aspect of the monoamine hypothesis. In our view, such PET studies have neither proved nor refuted conclusively any aspect of the monoamine hypothesis for depression (Schildkraut and Kety 1967; Asberg et al. 1976; Meltzer...
and Lowy 1987). While that monoamine hypothesis has been fruitful in certain ways, advances in neurobiology and neuropsychopharmacology have introduced a variety of additional molecular mechanisms into research on depressive disorders (Figure 1). Today, depression is viewed as the result of multiple neurobiological processes including disturbances of gene expression, intracellular signaling, cytokines and neurotropic agents (Tanis and Duman 2007; Berton and Nestler 2006; Krishnan and Nestler 2008; Maes 2008; Pittenger and Duman 2008). In our view, the success of PET scanning in determining the role of diverse neurobiological processes in depression will depend heavily on the invention of appropriate molecular tools, in the form of positron-emitting radioligands, for testing directly, in the living human brain, ever-changing hypotheses on causal connections between neuromolecular processes and the symptoms and severity of depressive disorders. PET neuroimaging has been unable to pinpoint neurobiological defects in the brain of humans suffering from depressive disorders. This is perhaps not surprising, given the limited number of suitable positron-emitting radioligands that are currently available for PET studies of neurobiological processes in humans. Despite more than two decades of research, inconsistent findings have been obtained between molecular PET studies of depressive disorders, with few replication attempts. An important challenge facing PET neuroimaging of depressive disorders resides, therefore, in determining which aspects of depressive disorders to study next. We propose that particular attention be given to studying antidepressant non-response by PET, because that condition remains a major challenge for medical and social resources, with 25 – 50% of people suffering from major depressive disorder never recovering fully (Rush et al. 2003b; Rush et al. 2008; Fava 2003; Petersen et al. 2005; Berlim and Turecki 2007). Severe aberrations in molecular mechanisms at multiple cerebral sites may be involved in antidepressant non-response (Krishnan and Nestler 2008; Berton and Nestler 2006; Ressler and Mayberg 2007; Drevets et al. 2008). Success in determining by PET the neurobiological basis of antidepressant non-response can be expected to provide an improved understanding of depressive disorders and point to more effective ways of treating them.

The richness of human emotions, thoughts, and actions along with the complexity of molecular events in the human brain caution, however, against expectations of rapid progress in discovering by PET neuroimaging an improved diagnostic system or a panacea for depression (MacQueen 2009). This brings us to another challenge for PET neuroimaging of depressive disorders, namely that of integrating rapid advances in neuroscience into suitable positron-emitting radioligands and PET research designs. In view of the heterogeneous nature of depressive disorders (Berlim and Turecki 2007; Parker 2000; Pae et al. 2009; Thase 2009), multiple molecular pathways may cause symptoms of the disease. Some of the pathways that may be causally connected to depressive disorders include genes that encode presynaptic vesicular proteins, plasma membrane receptors, intracellular signaling molecules, proteins that regulate the actin cytoskeleton, and the transcriptional regulatory machinery (Covington, III et al. 2010). Additional molecular pathways thought to be either causative or curative of depression include neuroplasticity, neuuropeptides, and nitric oxide synthase (Pittenger and Duman 2008; Paschos et al. 2009; Wegener and Volke 2010). Clearly, responding promptly to ever-changing notions on molecular pathways of depressive disorders constitutes a major challenge for PET neuroimaging.

Another challenging issue for PET neuroimaging of depressive disorders concerns financial support of research. Compared with the costs of brain diseases in the US and Europe...
(Sobocki et al. 2006;Greenberg et al. 2003;Russell et al. 2004), national funding of molecular brain imaging is miniscule. In Europe, for example, the total annual cost of depression in 2004 was 120 billion Euro, for a population of 466 million with at least 21 million affected residents (Sobocki et al. 2006), making depression the most costly brain disorder. In contrast, recent annual funding for molecular brain imaging of depressive disorders can be estimated at only 0.001 – 0.003 billion Euro, which is 100,000 times less than the annual cost of the disease. Without substantial funding, molecular brain imaging by PET may continue to be severely handicapped in providing reliable findings on molecular causes, consequences, and cures of depressive disorders.

An additional challenge for PET neuroimaging of depressive disorders concerns the invention of appropriate research strategies for testing multiple hypotheses on molecular mechanisms in the living brain. At present, two opposing strategies characterize research in this field. One strategy advocates the use of positron-emitting radioligands with marked selectivity and high affinity for a single, specific neuronal macromolecule such as a monoamine receptor or enzyme. That approach has, in fact, been used in the majority of PET studies on molecular mechanisms in depression and may reflect the assumption that depressive disorders are caused by a dysfunction of a single molecular mechanism. The other strategy advocates the use of positron-emitting radioligands with affinities for several neuronal macromolecules. This approach may rest on the assumption that depressive disorders are caused by disturbances in any number of multiple molecular pathways. Recently, we followed the notion of multiple molecular pathways in a PET study of treatment-resistant depression (Smith et al. 2009). Using \[^{11}\text{C}]\text{mirtazapine}, a positron-emitting radioligand of an antidepressant drug affecting several receptor systems (Millan 2006;Millan 2009;Smith et al. 2007), we studied by PET a group of depressed subjects who had failed to benefit from at least two antidepressant treatments (Smith et al. 2009). All subjects had received no antidepressant medication for at least 2 months before the study. We found that binding potentials of \[^{11}\text{C}]\text{mirtazapine} in cerebral cortical regions were, in general, lower in depressed nonresponders than in healthy controls, while removal rates of \[^{11}\text{C}]\text{mirtazapine} were generally higher in diencephalic regions of depressed nonresponders than in healthy controls. In keeping with the notion that depressive disorders are heterogeneous (Berlim and Turecki 2007;Parker 2000;Pae et al. 2009;Thase 2009), we noted that the binding of \[^{11}\text{C}]\text{mirtazapine} in brain regions of some of the depressed, antidepressant-nonresponders was well-within the normal range, whereas reduced regional binding of \[^{11}\text{C}]\text{mirtazapine} was noted in other depressed subjects. A challenge for additional PET studies with \[^{11}\text{C}]\text{mirtazapine} is to see whether the procedure can provide a neuromolecular-screening devise that can distinguish between neurobiologically-distinct subgroups of depressed, antidepressant-nonresponders.

One of the most formidable challenges for PET neuroimaging of depressive disorders relates to the blood-brain-barrier (BBB). The BBB is a limiting factor for PET studies of neuromolecular processes in the living human brain because it both restricts the passage of endogenous and foreign substances into the brain and expels many substances rapidly from the brain (Beduneau et al. 2008;Gjedde et al. 2000;Haldal et al. 2001;Kreuter 2001;Laruelle et al. 2002;Misra et al. 2003;Tosi et al. 2008). Thus, failure to traverse the BBB in sufficient quantities and/or to remain in brain tissue for a sufficient duration in the course of a PET-scanning session has caused many candidate radioligands to be discarded. PET neuroscientists will need to devise ways of improving the passage of novel positron-
emitting radioligands across the BBB for binding to molecular targets within the central nervous system. One possibility that may deserve close attention in the time ahead concerns the use of nanoparticles in PET neuroimaging. Some nanoparticles have already been shown to markedly enhance the level of certain drugs in the central nervous system (Gelperina et al. 2009; Kreuter 2002; Vergoni et al. 2009), indicating a potential role of nanoparticles as carrier-molecules for ushering novel PET radioligands to their neurobiological targets.

8. Challenges for PET radiochemistry

The synthesis and development of radiopharmaceuticals for PET is a complicated and extremely challenging process. The main challenge of using the short-lived PET radioisotopes carbon-11 (t_{1/2} = 20.4 min), fluorine-18 (t_{1/2} = 110 min), nitrogen-13 (t_{1/2} = 9.97 min) or oxygen-15 (t_{1/2} = 2.04 min) for the synthesis of radiopharmaceuticals is that of time (Fowler and Wolf 1997). The short half-lives of these radioisotopes imposes severe time restrictions when preparing radiolabelled compounds for PET. Such short time periods limit the range of synthetic strategies that are available to obtain target radiolabelled compounds, confining them to chemical reactions and processes that are on the order of seconds and minutes rather than hours. Many PET radiolabelling procedures are therefore limited to only one or two distinct chemical steps with the introduction of the PET radioisotope as late in the radiosynthesis as possible. The radioisotopes ^{13}N and ^{15}O are of limited applicability for imaging receptor-related processes of the CNS because their short half-lives prohibit the synthesis of complex tracer molecules and are generally not commensurate with the time frames required for monitoring ligand-receptor based processes. ^{11}C and ^{18}F are therefore the most commonly used radioisotopes in PET for imaging neuroreceptor processes, having half-lives that are long enough to enable multistep synthesis of quite complex radioligands in addition to being appropriate for monitoring ligand-receptor processes. The choice of which radioisotope, ^{11}C or ^{18}F, to use depends on a number of decisive factors. Firstly, the structure of the target molecule. For example, does it have fluorine atom and would introducing an ^{18}F adversely affect its biological properties? Secondly, the ease of synthesis. Can the target molecule be synthesised using available chemical techniques and are the appropriate ^{18}F or ^{11}C precursors available for reaction? There may be an obvious advantage in using one radioisotope over the other in terms of radiochemical yield, specific activity or speed of labelling. Thirdly, the time frame of the biological process under investigation; ^{18}F may be a more appropriate isotope for the investigation of longer biological processes such as protein synthesis.

Carbon is present in all natural products and almost every artificially synthesised drug-like compound. The replacement of a naturally abundant ^{12}C atom with that of a positron-emitting ^{11}C isotope results in ^{11}C-labeled molecules that will have essentially identical chemical and biological properties of the parent compound. This is a hugely important feature since it removes any doubts about the effect of introducing an artificial exogenous radioisotope (e.g. ^{18}F) or tag (e.g. [Ga-DOTA] complex) into the parent molecule which may affect its biological behaviour. Although the short 20 min half-life of ^{11}C precludes long multistep syntheses, a wide range of chemical reactions have been developed for synthesising ^{11}C labelled compounds (Miller et al. 2008). In comparison, ^{18}F has a considerably longer half-life of 110 min which permits longer and more complex radiosynthetic strategies in addition to allowing the transportation of doses to scanning sites
several hours away. The key concern, alluded to above, of introducing an 18F radioisotope into a molecule is the unknown effects the fluorine atom may have on the biological properties of the newly labelled compound. Radiosynthesis with 18F may be classified into two areas: (i) direct fluorination, where the 18F isotope is introduced into the target molecule in one chemical step, and (ii) indirect fluorination which requires a multi-step synthesis for the preparation of so-called 18F prosthetic groups that are then further reacted to give the target molecule. Considerable effort has been devoted to the development of these small and reactive 18F prosthetic groups for the rapid labelling of a range of 18F molecules. In recent years the development of rapid ‘click chemistry’ methods continues to generate much interest in this area (Glaser and Robins 2009).

Some of the challenges within PET radiochemistry are evidently more obvious than others and relate to the technical challenges associated with the fast, efficient and safe handling of short-lived radioactive material. The production of a pharmaceutical-quality radiotracer sample ready for injection requires the synthesis, purification, and analysis to be complete, generally, within three half-lives of the radioisotope in order to provide enough radioactivity for a reliable scan. In the case of a 11C radiosynthesis, this would be within 60 min from the end of bombardment. The need for such fast reactions and processes has lead, not only to new chemical methodologies, but to technological advancements in the development of fully automated and programmable synthesis units for performing and processing radiosynthetic reactions. New technologies such as microwave cavities (Elander et al. 2000), microfluidic reactors (Miller 2009), and solid-phase synthesis methods (Marik et al. 2006) have been adapted to enhance the speed, reproducibility, and efficiency of radiolabelling reactions.

Other challenges are more subtle and include the unusual scale of PET labelling reactions where the cold precursor in the reaction is often in huge excess (>1000 fold) compared with the radiolabelled compound. This can lead to unpredictable reaction kinetics and the formation of unwanted by-products from competing side reactions. There is often a desire to improve radiochemical yields (RCY) and to obtain high specific activities from labelling reactions. Although high RCYs are not always essential, they do provide a very useful measure of the efficiency of the radiolabelling procedure. The requirement of high specific activity, on the other hand, is often essential for the study of neuroreceptors such as those associated with depressive disorders. Specific activities of a radiolabelled compound for a PET study of neuroreceptors are typically required to be in the order of 50–500 GBq μmol⁻¹.

The requirement of high specific activities is most apparent if the radioligand has a high affinity for a receptor. Radiotracers produced with low specific activity will result in poor PET images owing to the rapid saturation of the binding sites by the proportionately higher amount of non-radioactive ligand. The production of radiotracers with high specific activity is therefore highly desirable but can be challenging and depends on the radioisotope selected for the radiosynthesis, choice of synthetic precursor material and radiosynthetic labelling route. Take, for example, the selective 5-HT1A receptor antagonist WAY-100635 which can be radiolabelled using 11C in the carbonyl position to give [carbonyl-11C]WAY-100635 (figure 2). This is usually achieved via the two-step reaction of 11CO₂ with cyclohexylmagnesium chloride sequentially followed by addition of thionyl chloride to give the reactive [carbonyl-11C]cyclohexyl acid chloride. Reaction of [carbonyl-11C]cyclohexyl acid chloride with the WAY-100634 amine precursor generates the desired [carbonyl-11C]WAY-100635 (McCarron et al. 1996). One of the key challenges with the synthesis of [carbonyl-
11C]WAY-100635 is the exclusion of atmospheric 12CO2 which poses a significant risk of contaminating the reaction at the initial first step. Without due care, contamination from atmospheric 13C results in an undesirably low specific radioactivity, and consequently poor PET images. The labelling position of radioisotope on the ligand is also a key consideration, and can pose significant challenges. Two key questions should be asked regarding labelling position, (i) is it viable, synthetically, to radiolabel in the position that we desire? and (ii) will the labelling position be metabolically stable? An understanding of the metabolic fate of a radiotracer can be vitally important in the development of a radiotracer and in determining the best position to radiolabel. There is usually a choice of positions within the molecule for radioisotope labelling, with some positions being more challenging than others. However, labelling a molecule in several different positions can yield important metabolic information about the fate of the molecule in vivo and can be useful in determining which labelling position is best for imaging. Metabolism of the labelled compound in the body may result in undesired labelled metabolites which can give two undesired effects: (i) an enhanced unwanted background signal which results in poor quality PET image, and (ii) pharmacologically active metabolites that compete with the parent compound for the biological target and complicate the interpretation of PET data. The importance of the labelling position can be illustrated by past experiences with the 11C labelling of WAY-100635 radioligand. WAY-100635 can be labelled in either the O-methyl position on the phenyl ring via a [11C]methylation reaction or on the carbonyl position as previously mentioned above (figure 2). [O-methyl-11C]WAY-100635 was however found to have limitations for imaging 5-HT1A receptors in human owing to the formation of the more lipophilic descyclohexanecarbonyl ([O-methyl-11C]WAY-100634) metabolite in vivo. This metabolite was found to enter the brain much more readily than the parent [O-methyl-11C]WAY-100635 (Osman et al. 1996) and thus complicate quantification of the 5-HT1A receptors by competing with [O-methyl-11C]WAY-100635 for 5-HT1A binding sites and by contributing to the non-specific binding signal. In contrast, by selecting to label WAY-100635 in the carbonyl position (figure 2) significantly improved PET images with much superior delineation of 5-HT1A receptors in human brain were obtained (Pike et al. 1996). The reason for [carbonyl-11C]WAY-100635 giving better images is due to the metabolism of this compound and position of the radioisotope; with the 11C isotope on the carbonyl group adjacent to the cyclohexyl ring, in vivo metabolism cleaves the cyclohexyl and 11C carbonyl and generates the labelled metabolite [11C]cyclohexanecarboxylic acid which is hydrophilic and, therefore, does not readily enter the brain to confound the signal from the parent [carbonyl-11C]WAY-100635 molecule.

Appropriate pharmacodynamic properties, such as high affinities and selectivities for the target, are central to characterising the success of a PET radioligand (Passchier et al. 2002). The affinity of the probe for the binding site is a key factor that affects the degree of nonspecific binding. Nonspecific binding is a major challenge in the development of radioligands and is often cited for the high failure rate of new radioligands. Nonspecific binding occurs when the radioligand binds or interacts with a molecular target or tissue other than the site of interest. This could include interactions of the radioligand with membrane structures or with receptors which are not under investigation. A high proportion of nonspecific binding signal may result in a severe reduction in the PET signal contrast when investigating a specific receptor with a radioligand. The lipophilicity of the
tracer molecule is frequently quoted as an important factor in discussions of nonspecific binding. Highly lipophilic molecules are known to interact extensively with the fatty residues in membrane bilayers which can prevent penetration of the radioligand into brain tissue and therefore prevent it from reaching the intended molecular target. The challenges in terms of the design and selection of tracer molecules to image the CNS often involve tailoring the lipophilicity of a radioligand. Successful PET CNS radiotracers normally have lipophilicities (logP, logarithm of the octanol/water partition coefficient) within an optimal logP window of 1.5-3 in order to ensure the passage through the BBB. Although logP values are an important indicator in ligand design, they can lead to an oversimplification of ligand selection. A greater understanding of the causes of nonspecific binding at a molecular level may be key to achieving higher success rates for radioligand selection. A recent study has used computation methods to estimate the interaction energy between candidate molecules and phospholipids which can then be used as a predictor for nonspecific binding in vivo (Rosso et al. 2008). Results from this study interestingly show that the drug’s interaction with the lipid molecule is a better predictor for nonspecific binding than the experimentally measured logP value. Further recent work in this area suggests that alternative transport mechanisms of drug molecules through biological membranes, which result in the chemically activated degradation of the phospholipid membranes, may be related to nonspecific binding (Casey et al. 2008).

Concluding remark
We hope that the challenges described here will inspire scientists to carry out many more studies using PET neuroimaging in order to eventually discover new and better procedures for diagnosing and treating major depressive disorders.

9. Chemical names

| Chemical Name | Chemical Structure |
|---------------|--------------------|
| Altanserin    | 3-2,4-4-Fluorobenzoyl-1-piperidinylethyl-2,3-dihydro-2-thiooxo-41H-quinazolinone |
| DASB          | 3-Amino-4-[[2-[dimethylaminomethyl] phenyl]thio] benzonitrile |
| DOTA          | 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid |
| Doxepin       | 3-dibenzo[b,e]doxepin-116H-ylidene-N,N-dimethylpropan-1-amine |
| 2-FA-85380    | 2-fluoro-3-(2S)-2-azetidinyl(methoxy)-pyridine |
| FCWAY         | 3-[2-[4-2-Methoxyphenyl-1-piperazinyl]ethyl]-N-2-pyridinyl-trans-4-fluorocyclohexylcarboxamide |
| FDDNP         | 2-(1-[6-[(2-fluorine-18-fluoroethyl)(methyl)amino-2-naphthyl]ethylidene) malonitrilte |
| FESP          | 3-2-Fluoroethyl-8-[4-4-fluorophenyl-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one |
| FLB 457       | 5-Bromo-N-[25-1-ethyl-2-pyrrolidinyl]-methyl]-2,3-dimethoxybenzamide |
| Fluoro-L-dopa | 2-Fluoro-5-hydroxy-L-tyrosine |
| FP-TZTP       | 3-3-3-Fluoroproplthio-1,2,5-thiadiazol-4-yl-1,2,5,6-tetrahydro-1-methylpyridine |
10. Conflict of interest

The authors declare that, except for income received from their primary employer, no financial support has been received for their research activity, including the writing of this review.

11. Acknowledgments

We thank everybody at the Center for Psychiatric Research and the PET Center of Aarhus University for providing a positive atmosphere in which to work. DFS thanks the Danish Medical Research Council for research funding, and PWM is grateful to the EPSRC for the award of a Life Sciences Interface fellowship (EP/E039278/1).

12. References

Asberg M, Thoren P, Traskman L, Bertilsson L, Ringberger V. 1976. "Serotonin depression"—a biochemical subgroup within the affective disorders? Science 191:478-480.
Bech P. 1984. The instrumental use of rating scales for depression. Pharmacopsychiatry 17:22-28.
Beduneau A, Hindre F, Clavreul A, Leroux JC, Saulnier P, Benoit JP. 2008. Brain targeting using novel lipid nanovectors. J Control Release 126:44-49.
Berlim MT, Fleck MP, Turecki G. 2008. Current trends in the assessment and somatic treatment of resistant/refractory major depression: an overview. Ann Med 40:149-159.
Berlim MT, Turecki G. 2007. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. Eur Neuropsychopharmacol 17:696-707.
Berton O, Nestler EJ. 2006. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 7:137-151.

Bhagwagar Z, Hinz R, Taylor M, Fancy S, Cowen P, Grasby P. 2006. Increased 5-HT(2A) receptor binding in euthymic, medication-free patients recovered from depression: a positron emission study with [(11)C]MDL 100,907. Am J Psychiatry 163:1580-1587.

Bhagwagar Z, Murthy N, Selvaraj S, Hinz R, Taylor M, Fancy S, Grasby P, Cowen P. 2007. 5-HTT binding in recovered depressed patients and healthy volunteers: a positron emission tomography study with [11C]DASB. Am J Psychiatry 164:1858-1865.

Bhagwagar Z, Rabiner EA, Sargent PA, Grasby PM, Cowen PJ. 2004. Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography with [11C]WAY-100635. Mol Psychiatry 9:386-392.

Boileau I, Warsh JJ, Guttman M, Saint-Cyr JA, McCluskey T, Rusjan P, Houle S, Wilson AA, Meyer JH, Kish SJ. 2008. Elevated serotonin transporter binding in depressed patients with Parkinson's disease: a preliminary PET study with [11C]DASB. Mov Disord 23:1776-1780.

Bragulat V, Pailiere-Martinot ML, Artiges E, Frouin V, Poline JB, Martinot JL. 2007. Dopaminergic function in depressed patients with affective flattening or with impulsivity: [18F]fluoro-L-dopa positron emission tomography study with voxel-based analysis. Psychiatry Res 154:115-124.

Busto UE, Redden L, Mayberg H, Kapur S, Houle S, Zawertailo LA. 2009. Dopaminergic activity in depressed smokers: a positron emission tomography study. Synapse 63:681-689.

Cannon DM, Carson RE, Nugent AC, Eckelman WC, Kiesewetter DO, Williams J, Rollis D, Drevets M, Gandhi S, Solorio G, Drevets WC. 2006a. Reduced muscarinic type 2 receptor binding in subjects with bipolar disorder. Arch Gen Psychiatry 63:741-747.

Cannon DM, Ichise M, Fromm SJ, Nugent AC, Rollis D, Gandhi SK, Klaver JM, Charney DS, Manji HK, Drevets WC. 2006b. Serotonin transporter binding in bipolar disorder assessed using [11C]DASB and positron emission tomography. Biol Psychiatry 60:207-217.

Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, Manji HK, Drevets WC. 2007. Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [11C]DASB; comparison with bipolar disorder. Biol Psychiatry 62:870-877.

Cannon DM, Klaver JM, Peck SA, Rollis-Voak D, Erickson K, Drevets WC. 2008. Dopamine Type-1 Receptor Binding in Major Depressive Disorder Assessed Using Positron Emission Tomography and [(11)C]NNC-112. Neuropsychopharmacology 34:1277-1287.

Casey DR, Sebai SC, Shearman GC, Ces O, Law RV, Templer RH, Gee AD. 2008. Formulation affects the rate of membrane degradation catalyzed by cationic amphiphilic drugs. Ind Eng Chem Res 47:650-655.

Covington HE, III, Vialou V, Nestler EJ. 2010. From synapse to nucleus: Novel targets for treating depression. Neuropharmacology 58:683-693.

Dougherty DD, Bonab AA, Ottowitz WE, Livni E, Alpert NM, Rauch SL, Fava M, Fischman AJ. 2006. Decreased striatal D1 binding as measured using PET and [11C]SCH 23,390 in patients with major depression with anger attacks. Depress Anxiety 23:175-177.

Drevets WC, Savitz J, Trimble M. 2008. The subgenual anterior cingulate cortex in mood disorders. CNS Spectr 13:663-681.
Drevets WC, Thase ME, Moses-Kolko EL, Price J, Frank E, Kupfer DJ, Mathis C. 2007. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. Nucl Med Biol 34:865-877.

Dunlop BW, Nemeroff CB. 2007. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 64:327-337.

Elander N, Jones JR, Lu SY, Stone-Elander S. 2000. Microwave-enhanced radiochemistry. Chem Soc Rev 29:239-249.

Fava M. 2003. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 53:649-659.

Fowler JS, Wolf AP. 1997. Working against time: Rapid radiotracer synthesis and imaging the human brain. Accounts Chem Res 30:181-188.

Gelperina S, Maksimenko O, Khalansky A, Vanchugova L, Shipule E, Abbasova K, Berdiev R, Wohlfart S, Chepurnova N, Kreuter J. 2010. Drug delivery to the brain using surfactant-coated poly(lactide-co-glycolide) nanoparticles: Influence of the formulation parameters. Eur J Pharm Biopharm 74:157-163.

Gjedde A, Gee AD, Smith DF. 2000. Basic CNS Drug Transport and Binding Kinetics in Vivo. In: Begley DJ, Bradbury MW, Kreuter J, editors. The Blood-Brain Barrier and Drug Delivery to the CNS2. New York / Basel: Marcel Dekker, Inc.p 225-243.

Glaser M, Robins EG. 2009. 'Click labelling' in PET radiochemistry. J Label Compd Radiopharm 52:407-414.

Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK. 2003. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry 64:1465-1475.

Halldin C, Gulyas B, Langer O, Farde L. 2001. Brain radioligands--state of the art and new trends. Q J Nucl Med 45:139-152.

Hindmarch I. 2002. Beyond the monoamine hypothesis: mechanisms, molecules and methods. Eur Psychiatry 17 Suppl 3:294-299.

Hirvonen J, Karlsson H, Kajander J, Lepola A, Markkula J, Rasi-Hakala H, Nagren K, Salminen JK, Hietala J. 2008. Decreased brain serotonin 5-HT1A receptor availability in medication-naive patients with major depressive disorder: an in-vivo imaging study using PET and [carbonyl-11C]WAY-100635. Int J Neuropsychopharmacol 11:465-476.

Kano M, Fukudo S, Tashiro A, Utsumi A, Tamura D, Itoh M, Iwata R, Tashiro M, Mochizuki H, Funaki Y, Kato M, Hongo M, Yanai K. 2004. Decreased histamine H1 receptor binding in the brain of depressed patients. Eur J Neurosci 20:803-810.

Kreuter J. 2001. Nanoparticulate systems for brain delivery of drugs. Adv Drug Deliv Rev 47:65-81.

Kreuter J. 2002. Transport of drugs across the blood-brain barrier by nanoparticles. Curr Med Chem - Centr Nerv Syst Agents 2:241-249.

Krishnan V, Nestler EJ. 2008. The molecular neurobiology of depression. Nature 455:894-902.

Kuroda Y, Motohashi N, Ito H, Ito S, Takano A, Nishikawa T, Suhara T. 2006. Effects of repetitive transcranial magnetic stimulation on [11C]raclopride binding and cognitive function in patients with depression. J Affect Disord 95:35-42.

Lammertsma AA. 2002. Radioligand studies: imaging and quantitative analysis. Eur Neuropsychopharmacol 12:513-516.

Laruelle M. 2000. Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. J Cereb Blood Flow Metab 20:423-451.
Laruelle M, Slifstein M, Huang Y. 2002. Positron emission tomography: imaging and quantification of neurotransporter availability. Methods 27:287-299.

Lavretsky H, Siddarth P, Kepe V, Ercoli LM, Miller KJ, Burggren AC, Bookheimer SY, Huang SC, Barrio JR, Small GW. 2009. Depression and anxiety symptoms are associated with cerebral FDDNP-PET binding in middle-aged and older nondemented adults. Am J Geriatr Psychiatry 17:493-502.

MacQueen GM. 2009. Magnetic resonance imaging and prediction of outcome in patients with major depressive disorder. J Psychiatry Neurosci 34:343-349.

Maes M. 2008. The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. Neuro Endocrinol Lett 29:287-291.

Marik J, Hausner SH, Fix LA, Gagnon MKJ, Sutcliffe JL. 2006. Solid-phase synthesis of 2-[F-18]fluoropropanyl peptides. Bioconjugate Chem. 17:1017-1021.

McCarron JA, Turton DR, Pike VW, Poole KG. 1996. Remotely-controlled production of the 5-HT1A receptor radioligand, [carbonyl-C-11]WAY-100635, via C-11-carboxylation of an immobilized Grignard reagent. J Label Compd Radiopharm 38:941-953.

Meltzer CC, Price JC, Mathis CA, Butters MA, Ziolko SK, Moses-Kolko E, Mazumdar S, Mulans BH, Houck PR, Lopresti BJ, Weissfeld LA, Reynolds CF. 2004. Serotonin 1A receptor binding and treatment response in late-life depression. Neuropsychopharmacology 29:2258-2265.

Meltzer HY, Lowy MT. 1987. The serotonin hypothesis of depression. In: Meltzer HY, editor. Psychopharmacology: The Third Generation of Progress. New York: Raven Press. p 513-526.

Meyer JH, Ginovart N, Boovariwala A, Sagrati S, Hussey D, Garcia A, Young T, Praschak-Rieder N, Wilson AA, Houle S. 2006a. Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. Arch Gen Psychiatry 63:1209-1216.

Meyer JH, Houle S, Sagrati S, Carella A, Hussey DF, Ginovart N, Goulding V, Kennedy J, Wilson AA. 2004. Brain serotonin transporter binding potential measured with carbon 11-labeled DASB positron emission tomography: effects of major depressive episodes and severity of dysfunctional attitudes. Arch Gen Psychiatry 61:1271-1279.

Meyer JH, McMann S, Kennedy SH, Korman L, Brown GM, DaSilva JN, Wilson AA, Blak T, Eynan-Harvey R, Goulding VS, Houle S, Links P. 2003. Dysfunctional attitudes and 5-HT2 receptors during depression and self-harm. Am J Psychiatry 160:90-99.

Meyer JH, McNeely HE, Sagrati S, Boovariwala A, Martin K, Verhoeff NP, Wilson AA, Houle S. 2006b. Elevated putamen D(2) receptor binding potential in major depression with motor retardation: an [11C]raclopride positron emission tomography study. Am J Psychiatry 163:1594-1602.

Meyer JH, Wilson AA, Sagrati S, Miller L, Rusjan P, Bloomfield PM, Clark M, Sacher J, Voineskos AN, Houle S. 2009a. Brain monoamine oxidase A binding in major depressive disorder: relationship to selective serotonin reuptake inhibitor treatment, recovery, and recurrence. Arch Gen Psychiatry 66:1304-1312.
Meyer JH, McNeely HE, Sagrati S, Boovariwala A, Martin K, Verhoeff NP, Wilson AA, Houle S. 2009b. Reduced alpha4beta2*-nicotinic acetylcholine receptor binding and its relationship to mild cognitive and depressive symptoms in Parkinson disease. Arch Gen Psychiatry 66:866-877.

Mickey BJ, Ducci F, Hodgkinson CA, Langenecker SA, Goldman D, Zubieta JK. 2008. Monoamine oxidase A genotype predicts human serotonin 1A receptor availability in vivo. J Neurosci 28:11354-11359.

Millan MJ. 2006. Multi-target strategies for the improved treatment of depressive states: Conceptual foundations and neuronal substrates, drug discovery and therapeutic application. Pharmacol Ther 110:135-370.

Millan MJ. 2009. Dual- and triple-acting agents for treating core and co-morbid symptoms of major depression: novel concepts, new drugs. Neurotherapeutics 6:53-77.

Miller JM, Brennan KG, Ogden TR, Oquendo MA, Sullivan GM, Mann JJ, Parsey RV. 2009a. Elevated serotonin 1A binding in remitted major depressive disorder: evidence for a trait biological abnormality. Neuropsychopharmacology 34:2275-2284.

Miller JM, Kinnally EL, Ogden RT, Oquendo MA, Mann JJ, Parsey RV. 2009b. Reported childhood abuse is associated with low serotonin transporter binding in vivo in major depressive disorder. Synapse 63:565-573.

Miller JM, Oquendo MA, Ogden RT, Mann JJ, Parsey RV. 2008. Serotonin transporter binding as a possible predictor of one-year remission in major depressive disorder. J Psychiatr Res 42:1137-1142.

Miller PW. 2009. Radiolabelling with short-lived PET (positron emission tomography) isotopes using microfluidic reactors. J Chem Technol Biotechnol 84:309-315.

Miller PW, Long NJ, Vilar R, Gee AD. 2008. Synthesis of C-11, F-18, O-15, and N-13 Radiolabels for Positron Emission Tomography. Angew Chem Int Edit 47:8998-9033.

Mintun MA, Sheline YI, Moerlein SM, Vlassenko AG, Huang Y, Snyder AZ. 2004. Decreased hippocampal 5-HT2A receptor binding in major depressive disorder: in vivo measurement with [18F]altanserin positron emission tomography. Biol Psychiatry 55:217-224.

Misra A, Ganesh S, Shahiwala A, Shah SP. 2003. Drug delivery to the central nervous system: a review. J Pharm Pharm Sci 6:252-273.

Montgomery AJ, Stokes P, Kitamura Y, Grasby PM. 2007. Extrastriatal D2 and striatal D2 receptors in depressive illness: pilot PET studies using [11C]FLB 457 and [11C]raclopride. J Affect Disord 101:113-122.

Moses-Kolko EL, Price JC, Thase ME, Meltzer CC, Kupfer DJ, Mathis CA, Bogers WD, Berman SR, Houck PR, Schneider TN, Drevets WC. 2007. Measurement of 5-HT1A receptor binding in depressed adults before and after antidepressant drug treatment using positron emission tomography and [11C]WAY-100635. Synapse 61:523-530.

Nemeroff CB, Owens MJ. 2009. The role of serotonin in the pathophysiology of depression: as important as ever. Clin Chem 55:1578-1579.

Oquendo MA, Hastings RS, Huang YY, Simpson N, Ogden RT, Hu XZ, Goldman D, Arango V, van Heertum RL, Mann JJ, Parsey RV. 2007. Brain serotonin transporter binding in depressed patients with bipolar disorder using positron emission tomography. Arch Gen Psychiatry 64:201-208.
Osman S, Lundkvist C, Pike VW, Halldin C, McCarron JA, Swahn CG, Ginovart N, Luthra SK, Bench CJ, Grasby PM, Wikstrom H, Barf T, Cliffe IA, Fletcher A, Farde L. 1996. Characterization of the radioactive metabolites of the 5-HT1A receptor radioligand, [O-methyl-C-11]WAY-100635, in monkey and human plasma by HPLC: Comparison of the behaviour of an identified radioactive metabolite with parent radioligand in monkey using PET. Nucl Med Biol 23:627-634.

Owens MJ, Nemeroff CB. 1994. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin Chem 40:288-295.

Pae CU, Tharwani H, Marks DM, Masand PS, Patkar AA. 2009. Atypical depression: a comprehensive review. CNS Drugs 23:1023-1037.

Parker G. 2000. Classifying depression: should paradigms be regained? Am J Psychiatry 157:1195-1203.

Parsey RV, Hastings RS, Oquendo MA, Huang YY, Simpson N, Arcement J, Huang Y, Ogden RT, van Heertum RL, Arango V, Mann JJ. 2006a. Lower serotonin transporter binding potential in the human brain during major depressive episodes. Am J Psychiatry 163:52-58.

Parsey RV, Oquendo MA, Ogden RT, Olvet DM, Simpson N, Huang YY, van Heertum RL, Arango V, Mann JJ. 2006b. Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study. Biol Psychiatry 59:106-113.

Paschos KA, Velezsa S, Chatzaki E. 2009. Neuropeptide and sigma receptors as novel therapeutic targets for the pharmacotherapy of depression. CNS Drugs 23:755-772.

Passchier J, Gee A, Willemsen A, Vaalburg W, van Wa arde A. 2002. Measuring drug-related targets for the pharmacotherapy of depression. CNS Drugs 23:755-772.

Petersen T, Papakostas GI, Posternak MA, Kant A, Guyker WM, Iosifescu DV, Yeung AS, Nierenberg AA, Fava M. 2005. Empirical testing of two models for staging antidepressant treatment resistance. J Clin Psychopharmacol 25:336-341.

Pike VW, McCarron JA, Lammertsma AA, Osman S, Hume SP, Sargent PA, Bench CJ, Cliffe IA, Fletcher A, Grasby PM. 1996. Exquisite delineation of 5-HT1A receptors in human brain with PET and [carbonyl-C-11]WAY-100635. Eur J Pharmacol 301:R5-R7.

Pittenger C, Duman RS. 2008. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 33:88-109.

Praschak-Rieder N, Hussey D, Wilson AA, Carella A, Lee M, Dunn E, Willeit M, Bagby RM, Houle S, Meyer JH. 2004. Tryptophan depletion and serotonin loss in selective serotonin reuptake inhibitor-treated depression: an [(18)F] MPPF positron emission tomography study. Biol Psychiatry 56:587-591.

Randrup A, Braestrup C. 1977. Uptake inhibition of biogenic amines by newer antidepressant drugs: relevance to the dopamine hypothesis of depression. Psychopharmacology (Berl) 53:309-314.

Reimold M, Batra A, Knobel A, Smolka MN, Zimmer A, Mann K, Solbach C, Reischl G, Schwarzler F, Gruender G, Machulla HJ, Bares R, Heinz A. 2008. Anxiety is associated with reduced central serotonin transporter availability in unmedicated patients with unipolar major depression: a [11C]DASB PET study. Mol Psychiatry 13:606-613.

Reivich M, Amsterdam JD, Brunswick DJ, Shiu CY. 2004. PET brain imaging with [11C]{+}McN5652 shows increased serotonin transporter availability in major depression. J Affect Disord 82:321-327.
Remy P, Doder M, Lees A, Turjanski N, Brooks D. 2005. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain 128:1314-1322.

Ressler KJ, Mayberg HS. 2007. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci 10:1116-1124.

Rosso L, Gee AD, Gould IR. 2008. Ab initio computational study of positron emission tomography ligands interacting with lipid molecule for the prediction of nonspecific binding. J Comput Chem 29:2397-2405.

Rush AJ, Thase ME, Dube S. 2003a. Research issues in the study of difficult-to-treat depression. Biol Psychiatry 53:743-753.

Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, Nierenberg AA. 2009. STAR*D: Revising Conventional Wisdom. CNS Drugs 23:627-647.

Rush AJ, Wisniewski SR, Warden D, Luther JF, Davis LL, Fava M, Nierenberg AA, Trivedi MH. 2008. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. Arch Gen Psychiatry 65:870-880.

Russell JM, Hawkins K, Ozminkowski RJ, Orsini L, Crown WH, Kennedy S, Finkelstein S, Berndt E, Rush AJ. 2004. The cost consequences of treatment-resistant depression. J Clin Psychiatry 65:341-347.

Saijo T, Takano A, Suhara T, Arakawa R, Okumura M, Ichimiyas T, Ito H, Okubo Y. 2010. Effect of electroconvulsive therapy on 5-HT1A receptor binding in patients with depression: a PET study with [11C]WAY 100635. Int J Neuropsychopharmacol 13:785-791.

Schildkraut JJ, Davis JM, Klerman GL. 1968. Biochemistry of Depressions. Psychopharmacology: A Review of Progress, 1957-1967. Bethesda, Maryland: National Institute of Mental Health. P. 625-648.

Schildkraut JJ, Kety SS. 1967. Biogenic amines and emotion. Science 156:21-30.

Schrag A, Barone P, Brown RG, Leentjens AF, McDonald WM, Starkstein S, Weintraub D, Poewe W, Rascol O, Sampaio C, Stebbins GT, Goetz CG. 2007. Depression rating scales in Parkinson's disease: critique and recommendations. Mov Disord 22:1077-1092.

Sheline YI, Mintun MA, Barch DM, Wilkins C, Snyder AZ, Moerlein SM. 2004. Decreased hippocampal 5-HT(2A) receptor binding in older depressed patients using [18F]altanserin positron emission tomography. Neuropsychopharmacology 29:2235-2241.

Smith DF, Stork BS, Wegener G, Ashkanian M, Jakobsen S, Bender D, Audrain H, Vase KH, Hansen SB, Videbech P, Rosenberg R. 2009. [11C]Mirtazapine binding in depressed antidepressant nonresponder studied by PET neuroimaging. Psychopharmacology (Berl) 206:133-140.

Smith DF, Stork BS, Wegener G, Jakobsen S, Bender D, Audrain H, Jensen SB, Hansen SB, Rodell A, Rosenberg R. 2007. Receptor occupancy of mirtazapine determined by PET in healthy volunteers. Psychopharmacology (Berl) 195:131-138.

Sobocki P, Jonsson B, Angst J, Rehnberg C. 2006. Cost of depression in Europe. J Ment Health Policy Econ 9:87-98.

Spanagel R, Weiss F. 1999. The dopamine hypothesis of reward: past and current status. Trends Neurosci 22:521-527.

Sullivan GM, Ogden RT, Oquendo MA, Kumar JS, Simpson N, Huang YY, Mann JJ, Parsey RV. 2009. Positron emission tomography quantification of serotonin-1A receptor binding in medication-free bipolar depression. Biol Psychiatry 66:223-230.
Takikawa S, Dhawan V, Chaly T, Robeson W, Dahl R, Zanji I, Mandel F, Spetsieris P, Eidelberg D. 1994. Input functions for 6-[fluorine-18]fluorodopa quantitation in parkinsonism: comparative studies and clinical correlations. J Nucl Med 35:955-963.

Tanis KQ, Duman RS. 2007. Intracellular signaling pathways pave roads to recovery for mood disorders. Ann Med 39:531-544.

Thase ME. 2009. Atypical depression: useful concept, but it’s time to revise the DSM-IV criteria. Neuropsychopharmacology 34:2633-2641.

Theodore WH, Hasler G, Giovacchini G, Kelley K, Reeves-Tyer P, Herscovitch P, Drevets W. 2007. Reduced hippocampal 5HT1A PET receptor binding and depression in temporal lobe epilepsy. Epilepsia 48:1526-1530.

Tosi G, Costantino L, Ruozzi B, Forni F, Vandelli MA. 2008. Polymeric nanoparticles for the drug delivery to the central nervous system. Expert Opin Drug Deliv 5:155-174.

Vergoni AV, Tosi G, Tacchi R, Vandelli MA, Bertolini A, Costantino L. 2009. Nanoparticles as drug delivery agents specific for CNS: in vivo biodistribution. Nanomedicine 5:369-377.

Voinoskos AN, Wilson AA, Boovariwala A, Sagrati S, Houle S, Rusjan P, Sokolov S, Spencer EP, Ginovart N, Meyer JH. 2007. Serotonin transporter occupancy of high-dose selective serotonin reuptake inhibitors during major depressive disorder measured with [11C]DASB positron emission tomography. Psychopharmacology (Berl) 193:539-545.

Wegener G, Volke V. 2010. Nitric oxide synthase inhibitors as antidepressants. Pharmaceuticals 3:273-299.

Figure legends

**Figure 1.** Major molecular pathways involved in neuroplasticity and affected by stress, depression, and antidepressant treatment. Some major molecular pathways involved in both short- and long-term neuroplastic changes are shown. Certain intermediates and other details are left out for clarity. Many of these pathways are influenced in opposite ways by stress and depression. For example, both chronic stress in animals and depression in humans have been associated with reductions in the transcription factor CREB, and antidepressants enhance CREB activity in the hippocampus. Abbreviations: NMDA, N-methyl-D-aspartate glutamate receptor; AMPA, amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid glutamate receptor; VGCC, voltage-gated calcium channel; 5-HT, 5-hydroxytryptamine (serotonin); NE, norepinephrine; DA, dopamine; BDNF, brain-derived neurotropic factor; Trk-B, BDNF receptor; AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; AMP, adenosine monophosphate; PDE, phosphodiesterase, CaMK, calcium-calmodulin-dependent kinase; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; PKA, protein kinase A; Rsk, ribosomal S6 protein kinase; CREB, cAMP response element-binding protein. Reprinted by permission from Macmillan Publishers Ltd: Neuropsychopharmacology, Pittinger, C. and Duman, R.S., 33: 88-109, copyright 2008.

**Figure 2.** The selective 5-HT1A receptor antagonist WAY-100635 which can be labelled on the methyl position to give [O-methyl-11C]WAY-100635 or the carbonyl position to give [carbonyl-11C]WAY-100635. Labelling positions are indicated with (*).
Figure 1

Major molecular pathways involved in neuroplasticity and affected by stress, depression, and antidepressant treatment. Some major molecular pathways involved in both short- and long-term neuroplastic changes are shown. Certain intermediates and other details are left out for clarity. Many of these pathways are influenced in opposite ways by stress and depression. For example, both chronic stress in animals and depression in humans have been associated with reductions in the transcription factor CREB, and antidepressants enhance CREB activity in the hippocampus. Abbreviations: NMDA, N-methyl-D-aspartate glutamate receptor; AMPA, amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid glutamate receptor; VGCC, voltage-gated calcium channel; 5-HT, 5-hydroxytryptamine (serotonin); NE, norepinephrine; DA, dopamine; BDNF, brain-derived neurotropic factor; Trk-B, BDNF receptor; AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; AMP, adenosine monophosphate; PDE, phosphodiesterase, CaMK, calcium-calmodulin-dependent kinase; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; PKA, protein kinase A; Rsk, ribosomal S6 protein kinase; CREB, cAMP response element-binding protein. Reprinted by permission from Macmillan Publishers Ltd: Neuropsychopharmacology, Pittinger, C. and Duman, R.S., 33:88-109, copyright 2008.
Figure 2
Neuroimaging has become a crucial technique for Neurosciences. Different structural, functional and neurochemical methods, developed in recent decades, have allowed a systematic investigation on the role of neural substrates involved in functions performed by the central nervous system, whether normal or pathological. This book includes contributions from the general area of the neuroimaging to the understanding of normal functions and abnormalities of the central nervous system.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Donald Smith and Philip W. Miller (2010). Challenges for PET Neuroimaging of Depressive Disorders, Neuroimaging, Cristina Marta Del-Ben (Ed.), ISBN: 978-953-307-127-5, InTech, Available from: http://www.intechopen.com/books/neuroimaging/challenges-for-pet-neuroimaging-of-depressive-disorders