Chapter 6

PET Imaging of the Serotoninergic 5-HT1A System

Amélie Lothe, Sandrine Bouvard and Philippe Ryvlin

Additional information is available at the end of the chapter

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1. Introduction

Serotonin (5-hydroxytryptophan, 5-HT) is a modulating neurotransmitter of the central nervous system involved in a large spectrum of emotional and cognitive processes and physiological activities [1, 2], including sleep, locomotion, eating, memory, endocrine modulation, and sexual behaviour. The serotoninergic system is modulated in humans by both genetic and environmental factors. Furthermore, the central serotoninergic system is altered in multiple diseases such as depression [3, 4], migraine [5, 6], epilepsy [7-9], Alzheimer's disease [10, 11], eating disorders [12], anxiety [13], schizophrenia [14] and autism [15, 16]. Various radioligands are currently available for *in vivo* brain imaging of the serotoninergic system in humans, including antagonists for the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_4 receptors, and for the serotonin transporter (SERT) [17].

5-HT exerts its multiplicity of actions though seven classes of 5-HT receptors (17 subtypes identified to date), involving different signal transduction pathways [18, 19, 2]. The 5-HT_{1A} receptors were the first to be cloned in humans and are probably the best-characterized subtype of 5-HT receptors [20]. These receptors are G protein coupled receptors (GPCRs); 5-HT binding to 5-HT_{1A} receptors causes neuronal hyperpolarization through the G-protein-coupled opening of K+ channels [21, 22]. The 5-HT_{1A} receptors are mostly expressed in neurons, either as heteroreceptors when located in target regions of 5-HT neurons with a particularly high concentration in limbic areas, such as cingulate cortex and hippocampus, or as autoreceptors on the soma and dendrites of 5-HT neurons in raphe nuclei, where they exert negative feedback on the serotoninergic neuron firing rate and 5-HT release [23, 24]. Thus, serotoninergic neurotransmission is strongly modulated by 5-HT_{1A} receptors.

Several PET tracers have been developed for imaging 5-HT_{1A} receptors [25]. The most commonly used radioligands are [^{11}C]WAY-100635 (N- [2-[4-(2-methoxyphenyl)-1-piperazin-

yl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide) and [^{18}F]MPPF (4-(2′-methoxyphenyl)-1-[2′-(N-2-pirydynyl)-p-fluorobenzamido]-ethyl-piperazine) (see figure 1).

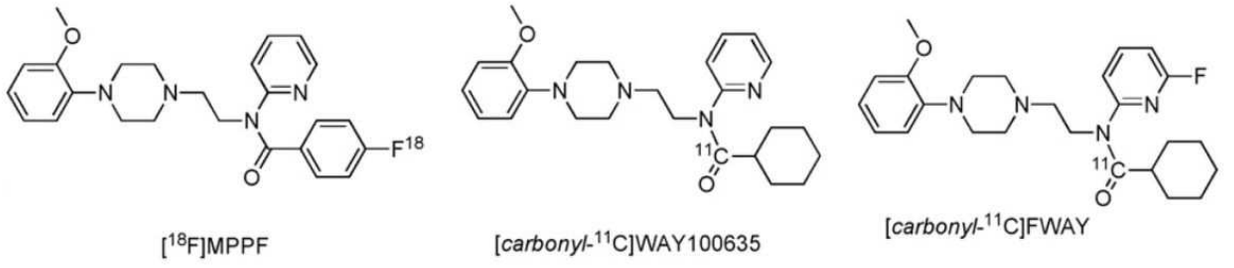

Figure 1. Chemical structure of antagonist PET tracers of 5-HT$_{1A}$ receptors

In this chapter, we will start by reviewing the different binding properties of [^{18}F]MPPF versus [^{11}C]WAY-100635. We will then discuss in more detail PET data obtained with [^{18}F]MPPF in comparison with those obtained with [^{11}C]WAY-100635 in various pathological conditions, including major depressive disorder, depressive comorbidity in temporal lobe epilepsy, and schizophrenia.

2. Binding properties of [^{18}F]MPPF versus [^{11}C]WAY-100635

[^{18}F]MPPF and [^{11}C]WAY-100635 are both selective and potent antagonists at 5-HT$_{1A}$ autoreceptors and heteroreceptors, but differ in their binding properties at 5-HT$_{1A}$ receptors.

Firstly, [^{18}F]MPPF is characterized by a lower affinity for 5-HT$_{1A}$ receptors (Ki=3.3 nM in rat hippocampal membrane homogenates) than [^{11}C]WAY-100635 (Ki=0.8 nM) [26] and [^{18}F]FCWAY (Ki=0.25 nM) [27].

The high affinity of [^{11}C]WAY-100635 for 5-HT$_{1A}$ receptors would make it relatively insensitive to changes in endogenous 5-HT concentration. Indeed, the binding of [^{11}C]WAY-100635 remained unchanged after injection of fenfluramine or after depletion of 5-HT by treatment with p-chlorophenylalanine (p-CPA) or with reserpine in rodents [28, 29]. In this regard, a decreased [^{11}C]WAY-100635 binding will be interpreted as reflecting a reduction in the density of 5-HT$_{1A}$ receptors.

Conversely, the affinity of [^{18}F]MPPF is closer to that of endogenous 5-HT for 5-HT$_{1A}$ receptors (Ki=4.2 nM in rat frontal cortex homogenates) [30]. Thus, [^{18}F]MPPF appears to be sensitive to the extra-cellular concentration of endogenous 5-HT [31, 32, 33]. Several studies using β-sensitive microprobes and microdialysis in the brain of rats demonstrated decreases in [^{18}F]MPPF binding after pharmacologically or electrical stimulation induced increases in the concentration of extracellular 5-HT [31, 32], while the binding of [^{18}F]MPPF is increased in the hippocampus following a reduction in the extracellular 5-HT concentration in rats treated with p-EPA, an inhibitor of tryptophan hydroxylase [33]. These findings

were confirmed with simulated [^{18}F]MPPF PET data [34]. Moreover, an original PET study using [^{18}F]MPPF and alpha-[^{11}C]Methyl-L-Tryptophan (AMT), a precursor of 5-HT, reported a significant negative correlation between 5-HT synthesis and 5-HT_{1A} binding potential (BP) bilaterally in hippocampus and anterior insula and in the left anterior cingulate gyrus in healthy subjects [35].

Accordingly, in contrast to [^{11}C]WAY-100635, a decreased [^{18}F]MPPF binding could either reflect lower 5-HT_{1A} receptor density or a higher extracellular concentration of 5-HT that could be associated with various changes in the number of 5-HT_{1A} receptors.

Secondly, [^{18}F]MPPF binds to externalized 5-HT_{1A} receptors only, while [^{11}C]WAY-100635 also binds to internalized receptors [36]. As a result of this property, [^{18}F]MPPF may allow indirect assessment of the internalization of 5-HT_{1A} autoreceptors [37].

Using β-sensitive microprobes in rats, a significant decrease of [^{18}F]MPPF binding was observed in the dorsal raphe nucleus (autoreceptors), but not in the hippocampus (heteroreceptors), after acute treatment with 8-OH-DPAT, a 5-HT_{1A} receptor agonist, or with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) [37, 38]. This reduction is associated with the internalization of 5-HT_{1A} autoreceptors of dorsal raphe nucleus observed in parallel using quantitative electron microscopic immunocytochemistry [38]. Similarly, a [^{18}F]MPPF PET study conducted in cats reported a decreased BP in the dorsal raphe nucleus after acute fluoxetine administration [39]. Finally, an interesting [^{18}F]MPPF PET study has examined this property by investigating healthy subjects five hours after the randomized, double-blind administration of a single oral dose of fluoxetine [40]. As expected, [^{18}F]MPPF binding in raphe nuclei is decreased in response to fluoxetine in each healthy subject [40].

Thirdly, the 5-HT_{1A} binding of both ligand was found to be differentially influenced by several factors, including genetic factors, age and gender.

Several genetic factors, including the triallelic 5-HT transporter gene-linked polymorphic region (5-HTTLPR) and 5-HT_{1A} promoter polymorphism, have a significant impact on [^{18}F]MPPF and [^{11}C]WAY-100635 binding [41-47].

Two [^{11}C]WAY-100635 PET studies showed a significant impact of the 5-HTTLPR polymorphism on the 5-HT_{1A} receptor binding, but in different directions [41-42]. One of the two studies reported lower [^{11}C]WAY-100635 BP in various limbic and neocortical brain regions in healthy subjects (predominantly men) with S/S or S/L genotypes compared to those with L/L genotype [41], whereas the other series found greater BP in the cingulate gyri in healthy women with S/S and S/L genotypes compared to those with L/L genotype [42]. Similarly, we observed a greater [^{18}F]MPPF non displaceable BP_{ND} ($BP_{ND} = f_{ND}.B_{avail}/K_D$ where f_{ND} is the fraction of radioligands free and non specifically bound, B_{avail} is the total number of available receptors for binding and $1/K_D$ is the affinity of the radioligand) [48] in homozygote women carriers of the S allele of 5-HTTLPR compared with carriers of at least one L_A allele over large brain regions including temporal and parietal lobes as well as the insula, cingulate gyri and left orbitofrontal cortex [43]. In contrast, a recent PET study failed to show a significant effect of the 5-HTTLPR polymorphism on the [^{11}C]WAY-100635 BP in a large population of 54 healthy volunteers, but that included men predominantly [47].

The association of C(-1019)G 5-HT_{1A} promoter polymorphism and 5-HT_{1A} receptor binding has also been evaluated in humans in three [^{11}C]WAY-100635 PET studies and one [^{18}F]MPPF study [41, 44-46]. One of these [^{11}C]WAY-100635 studies reported no association between C(-1019)G 5-HT_{1A} promoter polymorphism and 5-HT_{1A} receptor BP in a homogenous group of healthy subjects [41]. We also failed to detect a significant relationship between C(-1019)G 5-HT_{1A} promoter polymorphism and [^{18}F]MPPF binding in healthy subjects. However our data suggest that women homozygote for the G allele have greater [^{18}F]MPPF BP_{ND} compared to other individuals primarily over the frontal and temporal neocortex. The other two [^{11}C]WAY-100635 PET studies, performed in a mixed population of depressed and healthy individuals, demonstrated greater BP in limbic regions and the raphe nuclei, in carriers with at least one G allele compared to the C/C genotype [45, 46].

5-HT_{1A} receptor binding measured by either [^{18}F]MPPF and [^{11}C]WAY-100635 significantly declines with age [49-52]. However, this effect was especially observed on [^{18}F]MPPF binding in women [50] and, conversely, on [^{11}C]WAY-100635 binding in men [52]. Note that one [^{11}C]WAY-100635 PET study failed to show any significant correlation between age and 5-HT_{1A} receptor binding [53].

With regard to the gender factor, greater [^{18}F]MPPF BP_{ND} values independent of age were demonstrated in women compared to men, in limbic and paralimbic regions, predominantly in the right hemisphere [50]. Furthermore, after controlling for age and 5-HTTLPR polymorphism, a higher [^{18}F]MPPF BP_{ND} to 5-HT_{1A} receptors was also observed in women than in men over a very restricted set of brain regions, including the left temporal pole and parahippocampal gyrus [43]. Thus, we might speculate that the larger gender difference could partly reflect unbalanced 5-HTTLPR polymorphism between men and women.

A few PET studies have also examined the effects of gender on [^{11}C]WAY-100635 binding to 5-HT_{1A} receptors, reporting contradictory findings. Two previous studies found no effect of gender on [^{11}C]WAY-100635 binding [51, 54], whereas other series reported higher binding in women compared to men [47, 53, 55].

Overall, [^{18}F]MPPF and [^{11}C]WAY-100635 are likely to yield different and complementary PET findings in different pathological conditions.

3. Major depressive disorder

Depression is a common mental disorder, affecting about 121 million people worldwide. By the year 2020, depression is projected to become the second most important cause of disease burden, as measured by Disability-Adjusted Life Years (DALYs) (World Health Organization). The average lifetime prevalence of Major Depressive Disorder (MDD) is 14.6% in high-income countries [56], with the typically reported rates of 5% to 12% for men and 10% to 26% for women.

According to the Diagnostic Statistical Manual of Mental Disorders [57], Fourth edition, Text revision (DSM-IV-R), a Major Depressive Episode is characterized by a depressed mood and/

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or a markedly diminished interest or pleasure in all or almost all activities most of the day during the same 2-week period. In addition, three or more of the following symptoms must be present: gain or loss of weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, diminished ability to concentrate, and recurrent thoughts of death or suicidal ideation.

MDD is associated with diminished role functioning, poor health-related quality of life, medical comorbidity, such as cardiovascular disease [58], and increased risk of mortality [59].

Since roughly the 1970s, 5-HT has been involved in the pathophysiology of MDD [60, 61]. Numerous studies reported a reduction of 5-HT plasma concentrations and 5-HT metabolite levels in the cerebro-spinal fluid of patients with MDD [62, 63]. In addition, pharmacological agents that reduce brain 5-HT levels (e.g. reserpine) can induce depressive symptoms in healthy subjects as well as in recovered depressed patients [4, 64-66]. More recently, PET studies using alpha-[^{11}C]Methyl-L-Tryptophan (AMT) showed a reduction of this tracer uptake in the anterior cingulate gyrus and left mesial temporal cortex in MDD patients, supporting the possibility of reduced extracellular 5-HT concentration in depression [67, 68].

The involvement of 5-HT$_{1A}$ receptors in depression is well recognized; however the nature of their modifications is still controversial (see for review [69, 70]). A large number of PET studies have investigated 5-HT$_{1A}$ receptors in patients with MDD using [^{11}C]WAY-100635 [3, 69, 71-81].

Most previous [^{11}C]WAY-100635 PET studies showed a reduction of 5-HT$_{1A}$ receptor BP$_{ND}$ in various limbic and neocortical brain regions, as well as in the raphe nuclei, of untreated, treated, remitted MDD patients as well as in drug-naïve primary-care patients with MDD [3, 71, 73, 74-76, 79]. Interestingly, a [^{18}F]MPPF PET study performed in a monkey model of depression also reported a reduced BP in limbic regions and raphe nuclei [82]. It is in agreement with the majority of post-mortem data demonstrating decreased 5-HT$_{1A}$ receptor density in depressed suicide victims in different brain regions including the raphe nuclei, the hippocampus, and the frontal cortex [83-89]. The reduction of 5-HT$_{1A}$ receptor binding could be partly the consequence of a possible hypersecretion of endogenous corticosteroids (see for review [69, 90]).

However, other PET studies using [^{11}C]WAY-100635 reported an increased ratio of specifically bound ligand over free ligand (BP$_F$) in the same regions in MDD patients never or not recently exposed to antidepressants, compared with controls [77-79]. Similarly, an increased 5-HT$_{1A}$ BP$_F$ has been shown in patients with MDD during sustained remission and not having taken antidepressant medications for at least six months, compared with healthy controls [81]. These authors suggest that higher 5-HT$_{1A}$ autoreceptor binding in the raphe nuclei could lead to greater inhibition of 5-HT neuron firing rate and decreased 5-HT release in the target regions of 5-HT neurons, possibly leading to compensatory up-regulation of 5-HT$_{1A}$ receptors in the same regions [78].

These discordant PET findings might partly reflect differences in the modeling methods used to calculate BP (BP$_{ND}$ versus BP$_F$) [48], the choice of the reference region (e.g. inclusion of cerebellar vermis and gray matter in the reference region or use of white matter) [91], MDD severity, treatment status, and genetic polymorphism status (e.g. for the C-1019G 5-HT$_{1A}$

receptor and 5-HTTLPR polymorphisms) of the patients selected [79] (see for review [70]). Thus, regarding the choice of the reference region, scans from the same patient population, analysed with SRTM and a cerebellar reference region, could either demonstrate reduced 5-HT_{1A} BP_{ND} when using cerebellar gray matter, or increased or unchanged BP_{ND} when using cerebellar white matter [79, 81]. Indeed, the grey matter of cerebellum contains limited but significant amount of 5-HT_{1A} receptors, while its white matter does not and thus represents a more appropriate reference. Furthermore, as already mentioned, [^{18}F]MPPF and [^{11}C]WAY-100635 BP_{ND} were reported to be influenced by the triallelic 5-HTTLPR polymorphism, which S allele is associated with depressive disorder [92, 93].

3.1. Effects of antidepressants

A small number of PET studies have examined the potential impact of chronic antidepressant medication on 5-HT_{1A} receptor binding.

Three test-retest [^{11}C]WAY-100635 studies reported no change of BP_{ND} after selective serotonin recapture inhibitor (SSRI) treatment in MDD patients [75, 94, 95]. Contrary to these findings, a reduction of [^{11}C]WAY-100635 BP_F was found in MDD patients previously treated by antidepressants (most of the antidepressant exposure ended between 21 and 14 days prior to PET scans) when compared with medication naïve MDD patients, but not when compared with healthy controls [77]. In line with this result, a decreased 5-HT_{1A} BP_{ND} was observed following at least 12 weeks of SSRI treatment in patients suffering from social phobia or panic disorder [96]. These data suggest that chronic antidepressant treatment could induce a down-regulation of 5-HT_{1A} receptors.

In a recent test-retest [^{18}F]MPPF PET study, we explored the potential dynamic changes in [^{18}F]MPPF BP_{ND} in six patients with untreated MDD, before, and after five and 30 days of SSRI treatment [97]. No change of [^{18}F]MPPF BP_{ND} after SSRI medication was observed within the raphe nuclei and a significant increase of [^{18}F]MPPF BP_{ND} from baseline to 30 days of SSRI treatment was reported primarily in the medial orbital region and the anterior cingulate gyrus. These findings are in contradiction with the three previous test-retest [^{11}C]WAY-100635 studies which have addressed this issue [75, 94, 95].

After 30 days of SSRI treatment, no more significant modification of [^{18}F]MPPF BP_{ND} was found in MDD patients compared with healthy subjects in the medial orbital region and the anterior cingulate gyrus. Thus effective SSRI treatment is associated with a trend toward normalisation of the serotoninergic function. In agreement with these human PET imaging data, no change in the in vivo [^{18}F]MPPF binding was found in the dorsal raphe nucleus, frontal cortex and hippocampus of rats undergoing chronic SSRI treatment, as measured with β-microprobes or with the small animal PET scanner YAP-(S)PET system [98, 99].

Overall these preliminary [^{18}F]MPPF data suggest the existence of SSRI-mediated serotoninergic adaptative mechanisms in patients with MDD. However, due to the small sample size, it is necessary to confirm these findings in a larger population.

Apart from the discrepancy of the used radioligands, several points of difference between our [^{18}F]MPPF study and the three previous [^{11}C]WAY-100635 studies should be noted [75, 94,

95]. Firstly, one of these [^{11}C]WAY-100635 studies did not evaluate specifically the medial orbital region and the anterior cingulate gyrus [94]. Moreover, the treatment response, the treatment duration, the polymorphism status for serotoninergic genes as well as the cortisol plasma levels [69] of the patients selected could partly explain these discrepancies. For instance, in one of the [^{11}C]WAY-100635 studies, only half of the patients studied were responders [75], whereas in our [^{18}F]MPPF study all patients were responders.

4. Depressive comorbidity in temporal lobe epilepsy

Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures, due to an abnormal, excessive, and synchronous neuronal discharges, affecting about 50 million people worldwide. Depressive disorders are the most frequent psychiatric comorbidity in epilepsy but often remain under-recognized and untreated [100-103]. The lifetime prevalence of major depression ranged from 11 and 60% in patients with recurrent seizures [103] and increased in patients with temporal lobe epilepsy (TLE), particularly in those with left TLE and possibly hippocampal sclerosis (for review see [101, 104-108]). The rate of suicide in patients with epilepsy is about two to five times that of the general population, and this rate rises to six to seven times in the case of TLE [109, 110]. In addition, comorbid depression is a strong predictor of poor quality of life in patients with epilepsy [111]. This higher incidence of depressive disorders in patients with epilepsy, in particular in those with TLE, may reflect the existence of common pathogenic mechanisms between mood disorders and epilepsy [112]. In this paragraph, we are referring to the presence of depressive symptoms in interictal period. Indeed, depressive symptoms may also occur transiently during ictal or post-ictal [103].

A large body of evidence from preclinical studies indicates an anticonvulsant and antiepileptic effect of 5-HT mediated by 5-HT_{1A} receptors [113]. The activation of 5-HT_{1A} receptors retards the development of the kindling process in rats [114] and in cats [115, 116] and inhibits epileptiform activity in various cellular models of epilepsy [117, 118]. In addition, agents that raise endogenous 5-HT levels (e.g. SSRI) have an anticonvulsant effect, mediated by 5-HT_{1A} receptors [119], in genetically epilepsy-prone rats [120], in partial seizures generated by low-frequency electrical stimulation in rats [121], as well as in kindled rats [116]. Finally, given their multiple cellular localizations, the 5-HT_{1A} receptors may mediate inhibition of excitatory neurons, but also of inhibitory neurons, leading to opposite effects on the neural network [122]. Accordingly, a possible mechanism of neuronal hyperexcitability in epilepsy could be an excitatory/inhibitory shift mediated by changes in serotoninergic transmission.

Abnormalities of the 5-HT_{1A} receptors were reported in TLE using various radioligands, including [^{11}C]WAY-100635, [^{18}F]FCWAY and [^{18}F]MPPF. All showed a BP reduction that predominated over the epileptogenic temporo-limbic structures [123-130] (see figure 2).

This reduction of 5-HT_{1A} binding on the side of the epileptogenic zone support the hypothesis of a decrease in 5-HT_{1A} receptors density in TLE. In line with these imaging studies, a decrease of binding of the agonist [^{3}H]8-OH-DPAT (8-hydroxy-2-(di-n-propylamino) tetralin) to 5-HT_{1A} receptors was reported in the hippocampus of genetically epilepsy-prone rats [131].

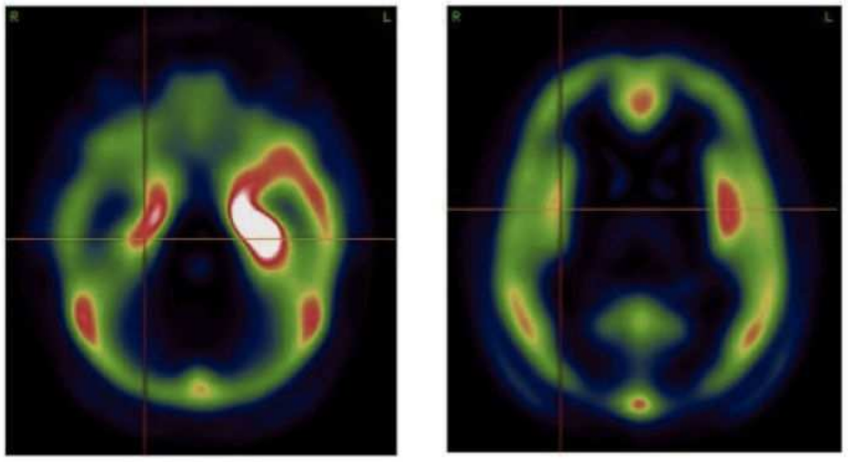

Figure 2. Typical pattern of [^{18}F]MPPF BP_{ND} in patients with TLE.

Nevertheless, it should be stressed that the P-glycoprotein (PGP) expression could compromise this interpretation of PET findings. PGP is an ATP-driven transmembrane efflux pump, which is located at the blood-brain barrier and transports a wide variety of substrates from the brain to blood and cerebrospinal fluid. [^{18}F]MPPF being a substrate for PGP, its brain uptake is modulated. An overexpression of PGP is reported in epileptic foci, probably leading to drug resistance in epilepsy [132]. Thus, the reduction of [^{18}F]MPPF BP_{ND} observed in patients with TLE could reflect a combination between decreased number of 5-HT_{1A} receptors and a more active PGP pump.

In epilepsy and depression, PET studies of the serotoninergic system focused on 5-HT_{1A} receptors in patients with TLE. Previous PET investigations of 5-HT_{1A} receptors using [^{11}C]WAY-100635 and [^{18}F]FC-WAY observed greater BP reduction in the more depressed patients with TLE, suggesting decreased expression of 5-HT_{1A} receptors [126, 127, 133, 134]. This abnormality was primarily reported ipsilateral to the epileptogenic temporal lobe, and more specifically over the anterior cingulate gyrus [126] and the hippocampus [127, 133]. Recently this finding was confirmed in a larger sample of TLE patients, reporting a significant inverse relation between Beck depression inventory (BDI) scores and [^{18}F]FC-WAY 5HT_{1A} receptor plasma free-fraction corrected volume of distribution (V/f1) in the hippocampus ipsilateral to the patient's epileptic focus [134]. In 37 TLE patients with or without hippocampal sclerosis, Hasler et al. [135] also showed lower [^{18}F]FCWAY binding in patients with a history of MDD compared with those without such a history, in hippocampus, temporal neocortex, anterior insula, anterior cingulate and raphe nuclei. However, a recent [^{11}C]WAY-100635 PET study performed in a small population of 13 TLE patients with or without hippocampal sclerosis failed to report any correlation between binding potential and depression [130].

In contrast with these findings, we observed greater BP_{ND} of [^{18}F]MPPF in the more depressed TLE patients with hippocampal sclerosis and no previous antidepressant exposure, particularly within the insula contralateral to seizure onset as well as in the raphe nuclei [8]. Interestingly, a different set of brain regions was associated with each of the main dimensions explored by the BDI-2, with the insula and raphe abnormalities being associated with symp-

toms of psychomotor anhedonia and negative cognition, whereas somatic symptoms correlated with [^{18}F]MPPF BP_{ND} in the anterior cingulate gyrus and hippocampus ipsilateral to seizure onset. Considering the sensitivity of [^{18}F]MPPF to the extra-cellular concentration of endogenous 5-HT, the greater [^{18}F]MPPF BP_{ND} observed in the more depressed patients suggests a combination of an underlying depletion in the extra-celllular concentration of 5-HT and a decreased density in 5-HT_{1A} receptors.

As previously mentioned, discordance between PET studies of 5-HT_{1A} receptors in patients with epilepsy and depression might also reflect a difference in the modeling methods used to calculate BP [79], the choice of the reference region, as well as the studied patient samples. Indeed, in our [^{18}F]MPPF PET study, we have selected a more homogeneous group of patients than those of previous [^{11}C]WAY-100635 studies; all patients were naïve to previous antidepressant exposure and showed MRI signs of hippocampal sclerosis. Conversely, the proportion of patients with hippocampal sclerosis varied in other series [126, 127, 133, 134]. The pathophysiology of epilepsy-related depression might differ between TLE patients with and without hippocampal sclerosis [136, 137]. Furthermore, the brain distribution of 5-HT_{1A} receptors would be influenced by previous antidepressant treatment [77]. Finally, it should be noted that antiepileptic drugs, such as carbamazepine [138], could modify the intracerebral concentration of 5-HT. Thus, differences in the proportion of patients with and without depressive symptoms receiving carbamazepine could also play a role in the discordances observed between [^{18}F]MPPF and [^{11}C]WAY-100635 PET findings.

5. Schizophrenia

Schizophrenia is a severely disabling and complex psychiatric disorder with a lifetime prevalence of approximately 1% in the general population [139]. The diagnosis of schizophrenia encompasses the presence of positive (delusions, hallucinations, thought disorder) and negative (emotional blunting, paucity of speech, loss of motivation, self neglect, and social withdrawal) symptoms, and cognitive deficits (deficits in attention, executive function, and memory). According to DSM-IV-TR, two or more positive symptoms have occurred for at least one month, unless hallucinations or delusions are especially bizarre, in which case one alone suffices for diagnosis. The onset of symptoms typically occurs during adolescence and young adulthood, with men having an earlier age of onset than women. Medical and psychiatric comorbidities, such as substance abuse, anxiety and depressive disorders, are frequent in patients with schizophrenia [140]. Furthermore patients with schizophrenia have higher rates of mortality in comparison to the general population [141].

Schizophrenia has a multifactorial etiology, involving a combination of genetic and environmental risk factors. Several neurotransmitters systems (dopamine, glutamate, acetylcholine, GABA, serotonin) are altered in schizophrenia. Until recently, the predominant focus of research in the pathophysiology of schizophrenia was the dopaminergic neurotransmission. The current dopamine hypothesis postulates that dopaminergic systems in schizophrenia might be characterized by a cortical/subcortical imbalance. Subcortical mesolimbic dopami-

nergic projections might be hyperactive (underlying positive symptoms), while mesocortical dopaminergic projections to the prefrontal cortex might be hypoactive (underlying negative symptoms and cognitive impairments) [142]. However, despite over 100 years of research, the precise pathophysiologic mechanisms of schizophrenia still remain unclear.

Over the years, there is increasing evidence that the serotonergic 5-HT_{1A} system is involved in the pathophysiology of schizophrenia and its treatment [143]. Abnormalities of 5-HT_{1A} receptors were reported in patients suffering from schizophrenia or schizoaffective disorder. Firstly, most post-mortem studies observed an increased 5-HT_{1A} receptor density (between 17% and 79%) in different brain regions of patients with schizophrenia, including the dorsolateral prefrontal cortex [144-148]. It should be noted that the majority of patients included in post-mortem studies had generally lengthy histories of psychiatric illness and of antipsychotic chronic treatment and/or other medications that could have an impact on the 5-HT_{1A} receptor distribution.

Only few [^{11}C]WAY-100635 PET studies were performed in patients with schizophrenia or schizoaffective disorder and have reported inconsistent results. The first [^{11}C]WAY-100635 PET study showed an increased BP_{ND} in the left medial temporal cortex in patients with schizophrenia who were untreated and never previously exposed to antipsychotic drug (APD) compared to healthy subjects [149]. However, other PET series demonstrated a decreased [^{11}C]WAY-100635 BP in the amygdala in drug-free and drug-naïve patients with schizophrenia or schizophreniform disorder (predominantly drug-naïve) [150] or failed to show BP alterations in various populations of APD-treated, untreated or never exposed to APDs patients with schizophrenia or schizoaffective disorder [151, 152]. There are several possible explanations for these discrepancies including differences in the brain regional distribution of PET changes, in the modeling methods used to calculate BP, in the selected patient samples as well as in their antipsychotic treatment.

Antipsychotic medications are used to treat schizophrenia. Since mid-1950's, numerous APDs with different pharmacological profiles were developed. In agreement with the dopamine hypothesis of schizophrenia, the first generation antipsychotics, such as haloperidol, are dopamine D_2 antagonists and are effective for reducing positive symptoms of schizophrenia. However, they are ineffective against negative symptoms and have high propensity for induction of extrapyramidal symptoms. The second generation antipsychotics, such as clozapine, olanzapine or risperidone, present enhanced efficacy in treating positive and negative symptoms and lower rates of extrapyramidal side effects [153]. The latter are potent 5-$HT_{2A/2C}$ receptor antagonists and relatively weak dopamine D_2 antagonists.

To date, the development of new APDs focuses on agonist properties at 5-HT_{1A} receptors, pharmacologic profile involved in the treatment of negative symptoms and cognitive deficits of schizophrenia and in the reduction of extrapyramidal side effects [154]. Indeed, preclinical studies reported that 5-HT_{1A} agonists reduced D_2-antagonist-induced catalepsy and increased the outflow of dopamine in the striatum [155] and in the medial prefrontal cortex [156, 157]. Aripiprazole is the first APDs with a unique pharmacologic profile combining a partial agonist activity at dopamine D_2 receptors, an antagonism at 5-HT_2 receptors and a partial agonism at 5-HT_{1A} receptors [158]. In rats, aripiprazole modulates the in-vivo 5-HT and dopamine release

in the medial prefrontal cortex through the activation of 5-HT_{1A} receptors [159]. Furthermore, aripiprazole does not induce extrapyramidal symptoms in patients with schizophrenia or schizoaffective disorder [160].

The effects of different APDs on 5-HT_{1A} receptors have been evaluated using PET and [^{11}C]WAY-100635 or [^{18}F]MPPF as radioligand, but these series reported conflicting results [151, 161-163]. Two [^{11}C]WAY-100635 PET studies showed contradictory findings in treated schizophrenic patients, reporting either no difference between patients taking clozapine or second generation antipsychotics and age-matched controls [151] or a reduction in BP_{ND} obtained after treatment with aripiprazole in comparison to age-matched controls [163]. In addition a recent test-retest study failed to observe a significant effect of chronic treatment of ziprasidone on the 5-HT_{1A} binding in six schizophrenic patients [162].

To investigate the impact of various APDs on the serotoninergic system, we performed a [^{18}F]MPPF PET study in 19 schizophrenic patients treated with either aripiprazole or second generation antipsychotics [161]. We reported a reduced [^{18}F]MPPF BP_{ND} mainly in the frontal and orbitofrontal cortex, in treated schizophrenic patients compared to age- and gender-matched healthy subjects. These findings may reflect either the pathophysiology of schizophrenia or medication effects. Furthermore, the schizophrenic patients treated with aripiprazole showed a reduction of global [^{18}F]MPPF BP_{ND} in comparison to healthy subjects and schizophrenic patients with second generation antipsychotic treatment. In addition, in comparison to matched controls, the reduction of regional [^{18}F]MPPF BP_{ND} was more marked in the schizophrenic patients treated with aripiprazole in comparison to those receiving second generation antipsychotic treatment. These abnormalities were localized in larger clusters encompassing the right and left frontal and orbitofrontal cortex, precunei and cingulate regions, the left temporal region as well as the raphe nuclei. These findings could be due to either occupancy by aripiprazole at 5-HT_{1A} receptors or a decreased 5-HT_{1A} receptor density. These findings may possibly reflect the partial agonist of aripiprazole activity at 5-HT_{1A} receptors. However, no modifications of 5-HT_{1A} receptor density and mRNA expression were found in limbic regions in rats after 12 weeks of aripiprazole treatment [164]. In our opinion, our [^{18}F]MPPF PET data most likely reflect the partial agonist activity of aripiprazole at 5-HT_{1A} receptors. Importantly, in contrast with previous [^{11}C]WAY-100635 PET studies, we take into account cortical atrophy as a confounding factor, by excluding the affected clusters in the right temporal gyrus and insula from our [^{18}F]MPPF PET analyses. These contradictory 5-HT_{1A} receptors PET findings could be attributable to differences in the used radioligands, the choice of the reference region, in sample populations, including duration of illness, as well as the in vivo agonist properties at the 5-HT_{1A} receptors of studied APDs.

6. Conclusion

Discordance between [^{18}F]MPPF and [^{11}C]WAY-100635 PET studies of 5-HT_{1A} receptors might reflect their differential sensitivity to extracellular concentration of endogenous 5-HT and to

the internalization of 5-HT_{1A} autoreceptors, but also differences in the data modeling strategies used to calculate BP, including the choice of the reference region (inclusion of cerebellar vermis and gray matter in the reference region)[79], and the population studied. We should also bear in mind that the genetic background for each subject and the gene-by-environment interaction can have a significant influence in different directions on [^{18}F]MPPF and [^{11}C]WAY-100635 PET findings, which is difficult to control for in the small samples of patients and healthy subjects included in PET studies [41-46].

In future PET studies of 5-HT_{1A} receptors, a more detailed clinical description of studied patients would improve the understanding of discrepancies between studies. Furthermore, particular attention should be paid to the constitution of a group of healthy subjects matched for confounding factors, such as age and sex. For instance, a PET study reported a lower cortical trapping of the alpha-[^{11}C]Methyl-L-Tryptophan (AMT) in women compared to men [165].

Future studies should aim at disentangling these issues by using a traditional multi-injection [^{18}F]MPPF protocol that enables a precise quantification of binding parameters (B'MAX; Kd) and the estimation of extracellular 5-HT concentration [166] or by coupling [^{18}F]MPPF and [^{11}C]WAY-100635 PET studies in the same individuals taking advantage of their different affinities for 5-HT_{1A} receptors. Another future challenge will be to image endogenous 5HT release in humans [167].

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Author details

Amélie Lothe[1*], Sandrine Bouvard[1] and Philippe Ryvlin[1,2]

*Address all correspondence to: amelie.lothe@cermep.fr

1 INSERM U1028, CNRS UMR5292, and University Claude Bernard Lyon 1, Lyon Neuroscience Research Center, Translational and Integrative Group in Epilepsy Research (TIGER), Lyon, France

2 Department of Functional Neurology and Epileptology and Institute for Children and Adolescents with Epilepsy (IDEE), Hospices Civils de Lyon, Lyon, France

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