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4

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Contents

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Abstract

This chapter summarizes findings of a large number of molecular imaging studies in the field of unipolar and bipolar depression (BD).

Brain metabolism in depressed unipolar and bipolar patients is generally hypoactive in the middle frontal gyri, the pregenual and posterior anterior cingulate, the superior temporal gyrus, the insula, and the cerebellum, while hyperactivity exists in subcortical (caudate nucleus, thalamus), limbic (amygdala, anterior hippocampus), and medial and inferior frontal regions. Interestingly, after depletion of serotonin or noradrenalin/dopamine in vulnerable (recovered) major depressive disorder (MDD) patients, a similar response pattern in metabolism occurs.

Findings on the pre- and postsynaptic dopaminergic system show indications that, at least in subgroups of retarded MDD patients, presynaptic dopaminergic markers may be decreased, while postsynaptic markers may be increased. The findings regarding serotonin synthesis, pre- and postsynaptic imaging can be integrated to a presumable loss of serotonin in MDD, while this remains unclear in BD. This reduction of serotonin and dopamine in MDD was recently summarized in a revised version of the monoamine hypothesis, which focuses more on a dysfunction at the level of the MAO enzyme. This should be addressed further in future studies. Nevertheless, it should be acknowledged that the serotonergic and dopaminergic systems appear adaptive; therefore, it remains difficult to distinguish state and trait abnormalities. Therefore, future longitudinal molecular imaging studies in the same subjects at different clinical mood states (preferably with different tracers and imaging modalities) are needed to clarify whether the observed changes in transporters and receptors are compensatory reactions or reflect different, potentially causal mechanisms. Several suggestions for future developments are also provided at the end of this chapter.

4.1 Introduction

A depressive episode is characterized by lowered mood, anhedonia, sleeping and eating disturbances, psychomotor agitation and/or retardation, extreme fatigue, cognitive dysfunction, feelings of worthlessness, guilt, and suicidal ideation. Depressive

episodes occur as a mood episode in unipolar major depressive disorder (MDD) or bipolar disorder (BD); in the latter, depressive episodes are interspersed by manic episodes.

MDD and BD are disabling diseases with a lifetime prevalence of ≥20% and a high risk of recurrences after a first episode (Bockting et al. 2005; Geddes et al. 2003; Hollon et al. 2005; Rush et al. 2006; Ten Doesschate et al. 2010; Vittengl et al. 2007; Sim et al. 2015; Brouwer et al. 2019). In the adult population, MDD and BD have a year prevalence of 5 and 1%, respectively. Both disorders cause tremendous suffering. MDD is expected to be the second cause of disability in 2030 (Mathers and Loncar 2006; GBD collaborators 2017). Antidepressants (ADs) are often used for treatment of depressive episodes; mostly selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) are used (American Psychiatric Association 2000; Anderson et al. 2000; Kennedy et al. 2001; Mulrow et al. 1999; Cipriani et al. 2018), while monoamine oxidase inhibitors (MAOI) and electroconvulsive therapy (ECT) are used in treatment-resistant cases. For BD these ADs are routinely used in combination with mood-stabilizing drugs like lithium, antiepileptic agents, or atypical antipsychotics, although with less efficacy (Goodwin 2003; Nivoli et al. 2011; Yatham et al. 2009; Bowden and Singh 2016; Grande et al. 2016).

In the 1950s, the serendipitous finding that iproniazid (Crane 1956) and imipramine (Kuhn 1958) improved depressive episodes led to the monoamine hypothesis. The monoamine hypothesis stipulates that "depressive episodes are *caused* by a lack of serotonin, noradrenalin, and dopamine," which is an overt simplification (Ruhe et al. 2007). The monoamine hypothesis dominated research in MDD and BD for the past decades. In the field of nuclear medicine, many radioligands have been developed for the serotonergic and dopaminergic systems and more recently for the MAO-A enzyme, which is the major enzyme responsible for the breakdown of the monoamines. Noradrenergic ligands for the norepinephrine transporter (NET) have recently been developed to evaluate in vivo NET occupancy in the brain by psychotropic drugs, but have not yet been used often.

In this chapter we will summarize the outcomes of the efforts with molecular imaging techniques to clarify the pathophysiology of MDD and BD. Because imaging of cerebral blood flow and brain function is currently studied most by (functional) MRI, we will mainly focus on transporter and receptor imaging, as—to our opinion—this is most important in studying depression with molecular imaging techniques. For BD we will restrict ourselves to report findings about the depressed state. For a more thorough comparison of findings in depressed and manic states in BD, we refer to Chap. 7.

Despite large advances by research, to date the pathophysiology behind MDD and BD cannot be fully explained. This could be due to insufficient acknowledgment of the heterogeneity of the clinical phenotypes of depression and inclusion of comorbid disorders in small samples or indicate that other mechanisms must be investigated in addition, for which some new, interesting perspectives will be mentioned at the end of this chapter.

4.2 Metabolism and Cerebral Blood Flow

From the 1990s of the last century onward, the quantification of cerebral metabolism and blood flow by radioligands was also applied to MDD and BD. We will briefly summarize this literature and refer to the referenced reviews and meta-analyses for more in-depth reading.

In general, for MDD, studies of resting state metabolism revealed overactivity of limbic structures versus a decreased activity in the prefrontal cortex (cognitive, regulatory regions) (Drevets 1998, 2000; Drevets and Raichle 1992). The first meta-analysis comprised studies until 2006, including positron-emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) (all resting state and treatment studies were PET/SPECT studies) (Fitzgerald et al. 2008). The authors reported limited overlap across imaging paradigms, but in general found hypoactivity in bilateral middle frontal gyri (dorsolateral prefrontal cortex, DLPFC), the pregenual anterior cingulate cortex (ACC; pgACC), posterior ACC, left superior temporal gyrus, insula, and the cerebellum, while hyperactivity existed in subcortical (caudate nucleus, thalamus), limbic (amygdala, anterior hippocampus), and medial and inferior frontal regions. Treatment with SSRIs increases resting activity in the hypoactive regions (i.e., the DLPFC, dorsal, and posterior ACC) and decreases activity in hyperactive regions like insula, (para)hippocampus, pregenual ACC (pgACC), subgenual ACC (sgACC), and medial frontal regions (Fitzgerald et al. 2008). However, a more recent meta-analysis comprising four [^{18}F]FDG PET studies which used a data-driven whole-brain approach showed *increased* glucose metabolism in the (right) subgenual ACC and pgACC (Sacher et al. 2012b). Of note, these authors excluded studies with a region-of-interest approach, in their attempt to avoid publication bias, but vice versa they thus also limited the number of studies that contribute to the knowledge base. The apparent difference between these two meta-analyses regarding pgACC activity might reflect differences between included studies, e.g., differences in response rates between studied populations. In a more recent meta-analysis, including 10 whole-brain-based [^{18}F]FDG-PET studies with 188 MDD patients versus 69 controls, using an activation likelihood estimation analysis, in MDD patients a decrease in metabolism in the bilateral insula, left lentiform nucleus of the putamen, extra-nuclear, right caudate, and cingulate gyrus was found, while increased activation was seen in the right pulvinar (thalamus) and the anterior and posterior lobe of the cerebellum (Su et al. 2014).

In a meta-analysis increased pgACC activity was associated with increased chances of response to treatment (Pizzagalli 2011), but see Brody et al. (1999, 2001), Konarski et al. (2009), and Milak et al. (2009). Reductions of pretreatment [^{18}F]FDG glucose metabolism within the right posterior insula correlated with reductions in depression scores in 16 MDD patients receiving 16 weekly sessions of brief psychodynamic psychotherapy (Roffman et al. 2014). Regarding increased sgACC activity, especially after corrections for partial volumes (Drevets 1999), persistent increased sgACC metabolism has been reported especially in nonresponsive patients (Mayberg 2003). However, this could not be replicated in 33 drug-free

MDD patients scanned before 3 months of treatment with antidepressants (Milak et al. 2009). Higher activity of sgACC as measured with [^{18}F]FDG PET was associated with treatment response to accelerated high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) in 15 antidepressant-free unipolar, melancholic, treatment-resistant MDD patients, where clinical response was associated with a decrease in activity in the sgACC after the 2 weeks of treatment (Baeken et al. 2015). Based on the increased activity in sgACC metabolism in nonresponders (Mayberg 2003), this region has been targeted with deep brain stimulation (Lozano et al. 2008; Mayberg et al. 2005). Interestingly, during sad mood induction in healthy volunteers, also increases in activity in sgACC and insula have been described in combination with decreased activity in the DLPFC (Mayberg et al. 1999). These cingulate increases are not found in depressed patients after sad mood induction. Instead, unique dorsal ACC increases and medial and orbital frontal (OFC) decreases are reported (Mayberg 2003). Given these inconsistencies and the additional report that an index of the connectivity of the sgACC with the left anterior ventrolateral prefrontal cortex/insula, dorsal midbrain, and left ventromedial prefrontal cortex (measured with 7.5 min of resting state fMRI) showed differential predictive properties for treatment outcomes of cognitive behavioral therapy versus antidepressants (Dunlop et al. 2017), the search for prospective biomarkers for treatment response based on [^{18}F]FDG PET metabolism might better (and cheaper) be pursued with different (non-molecular) imaging modalities.

In BD in the depressed state, comparable dysfunction was found, although not consistently (Gonul et al. 2009). Globally reduced glucose metabolism was reported in depressed BD patients versus manic patients and controls. Region-wise, in the frontal cortex, metabolism was reduced in depressed BD, while the sgACC activity was increased, especially when measurements were corrected for smaller (partial) volumes (Drevets 1999), but again reports were not unequivocal (Gonul et al. 2009). Since abnormal ACC metabolism was also reported for manic and euthymic BD patients, this might represent more a trait marker for BD. For the caudate nucleus and thalamus, early PET/SPECT studies showed a reduced glucose metabolism, while later PET studies showed increased striatal activity in combination with increased activity of the amygdala and (para)hippocampus. Striatal and amygdala activity was linearly associated with depression severity. These findings can be interpreted as being indicative of a loss of inhibitory control by the PFC (Gonul et al. 2009).

4.3 Imaging of Monoamine Systems

4.3.1 Serotonin

The serotonergic system governs a multitude of normal psychophysiological functions such as sleep, appetite, stress responses, affective cognition, aggression, and impulsivity, many of which are disturbed during a depressive (or manic) episode. Serotonin in the brain is mainly synthesized in the raphe nuclei (Purves et al. 2001).

Serotonin has been associated with depression for decades, and this association was the basis for the monoamine hypothesis in depression. There is hardly any doubt that this system is important in the pathophysiology and treatment of depression, although the question remains how it contributes to depression symptomatology. Each and every serotonin receptor has its own unique distribution pattern in the brain and is involved in different physiological processes in the body. In relation to depression, almost all receptor subtypes seem to be involved in stress-related reactions or the efficacy of antidepressants. PET and SPECT can measure these receptor levels and in vivo processes in a noninvasive way.

4.3.1.1 Serotonin Synthesis

Serotonin is synthesized from the amino acid tryptophan. Tryptophan is transported over the blood–brain barrier (BBB) by the large amino acid transporter. Inside neurons, especially terminals, tryptophan is hydroxylated by tryptophan hydroxylase (TPH2) to 5-hydroxy-tryptophan (5-HTP). In turn, 5-HTP is decarboxylated to 5-hydroxy-tryptamine (5-HT), or serotonin, by aromatic amino acid decarboxylase (AADC). Produced 5-HT is taken up in vesicles by the monoamine vesicular transporter. These vesicles fuse with the synaptic membrane, and serotonin is released into the synaptic cleft. 5-HT can be taken up back into the neuron, by the serotonin transporter (SERT). Eventually, 5-HT is metabolized to 5-hydroxyindoleacitic acid (5-HIAA), which is extracted from the brain through the cerebrospinal fluid.

Besides being used for the production of 5-HT, tryptophan is used for the production of kynurenine by the enzyme indoleamine 2,3-deoxygenase (IDO). Increases in this process could reduce 5-HT synthesis, as tryptophan is used to produce kynurenine instead of 5-HT and tryptophan availability is rate limiting for 5-HT production.

Levels of 5-HT have been linked to the pathophysiology of depression and the efficacy of antidepressants. When tryptophan is artificially decreased by an amino acid drink, devoid of this precursor of 5-HT, people that are sensitive to developing depression experience a reduction in mood (Fusar-Poli et al. 2006; Ruhe et al. 2007; van Steenbergen et al. 2012).

The hypothesis of the involvement of serotonin in depression started with measurements of serotonin levels and its metabolites by Van Praag and Korf. Depressive patients appeared to have reduced 5-HT turnover levels in the brain. This was shown by performing the probenecid test, where 5-HIAA transport is prevented (van Praag and Korf 1974). However, another study showed contradictory results, where 5-HIAA levels, directly measured in the jugular vein, were actually increased, suggesting increased 5-HT turnover. This increase was greater in people carrying the low-expressing variant of the 5-HTTLPR gene compared to the high-expressing genotype, and the increase in turnover was abolished by SSRI treatment (Barton et al. 2008). As discussed further in Sect. 4.3.3, the increase in 5-HT turnover may also be explained by an increase in the enzyme MAO-A, increasing the degradation of 5-HT to 5-HIAA and thereby depleting the brain of 5-HT (Meyer et al. 2006a, 2009).

As results are contradictory, turnover rates do not necessarily reflect 5-HT synthesis and the measurement of 5-HT and 5-HIAA levels in CSF is invasive; a more sufficient way of measuring 5-HT synthesis is needed. With PET, direct measurements of synthesis rates could be obtained by labeling the precursors of 5-HT: tryptophan or 5-HTP. Currently, there are no SPECT tracers to measure 5-HT synthesis.

Nowadays, two radiotracers for measuring 5-HT synthesis are used; these are α-[^{11}C]methyltryptophan ([^{11}C]AMT) and 5-hydroxy-l-[β-^{11}C]tryptophan ([^{11}C]5-HTP). Most studies that measure 5-HT synthesis in the brain are performed with [^{11}C]AMT, while [^{11}C]5-HTP is additionally used to visualize pancreatic islet tumors. Notably, [^{11}C]AMT is a substrate for both AADC and IDO; therefore, it not only measures 5-HT synthesis rates but also the production of kynurenine (Batista et al. 2009). In relation to depression, this may also be interesting, as IDO activity is upregulated under inflammatory conditions; however, this tracer will not solely measure 5-HT synthesis rates. [^{11}C]5-HTP on the other hand is difficult to produce as the production involves enzymatic steps (Neels et al. 2006).

Only three imaging studies have been performed in patients with MDD, but most studies indicate a decrease in 5-HT synthesis rate in the prefrontal cortex and cingulate cortex (Agren et al. 1991; Agren and Reibring 1994; Rosa-Neto et al. 2004) (Table 4.1). In addition, one study studied the effects of treatment with the SSRI citalopram and augmentation with the beta-blocker and 5-HT$_{1A}$ antagonist pindolol on 5-HT synthesis in depressed patients (Berney et al. 2008).

The first [^{11}C]5-HTP study found a reduction in uptake of [^{11}C]5-HTP over the BBB in the whole brain. The most profound decrease was observed in the dorsolateral prefrontal cortex (effect size 0.83) (Agren et al. 1991). Thereafter, the same group of subjects was used to estimate AADC activity by using a reference tissue kinetic model. With this method, the authors found an opposite effect; the AADC activity was increased in the medial prefrontal cortex of MDD patients. This discrepancy might reflect a compensatory mechanism for the decrease in precursor uptake (Agren and Reibring 1994), but the reference tissue kinetic model is compromised as [^{11}C]5-HTP has no actual reference tissue.

With [^{11}C]AMT it was found that the 5-HT synthesis rate was reduced in MDD patients, mainly in the cingulate cortex, and this effect was more robust in women (Rosa-Neto et al. 2004). With this tracer it was additionally shown that the SSRI citalopram could elevate the 5-HT synthesis rate in patients with major depression in the medial prefrontal cortex, extending to the cingulate cortex (Berney et al. 2008). Increases were only seen after 24 days of treatment and could be accelerated by augmenting the effect with pindolol, a nonselective 5-HT$_{1A}$ antagonist. Interestingly, after 10 days, there was even a decrease in the right premotor area, which is in agreement with the inhibitory effects of SSRIs on 5-HT neurotransmission through 5-HT$_{1A}$ autoreceptor stimulation, causing inhibition of firing. Similar results were found with [^{14}C]AMT and autoradiography in a rat model for depression. Here acute citalopram increased synthesis rates in the terminal areas of olfactory bulbectomized rats, but decreased rates in the raphe nuclei, where the cell bodies of 5-HT neurons lie. Pindolol prevented this decrease and increased the rates in terminal areas even more (Nguyen et al. 2009). Recent in vivo molecular imaging

Table 4.1 Serotonin synthesis imaging studies (PET) in patients with major depression as compared to controls

Authors (year)	Pts/ controls	Radiotracer	MDD treatment	Change tracer trapping	Effect size (*d*)
Rosa-Neto et al. (2004)[a]	17 MDD (2 BD) 17 HC	[^{11}C]MTrp	Drug-free (>2 weeks)	Female:	
				Cingulate right: 18% ↓ K*	−1.09
				Cingulate left: 12% ↓ K*	−0.91
				Mesial temporal lobe right: 9% ↓ K* (ns)	−0.64
				Mesial temporal lobe left: 11% ↓ K*	−0.78
				Male:	
				Cingulate cortex right:3% ↓ K* (ns)	−0.21
				Cingulate cortex left: 9% ↓ K*	−0.58
Agren and Reibring (1994)[a,b]	6 MDD 8 HC	[^{11}C]5-HTP	Drug-free (>10 days)	Whole brain: 30% ↓ uptake	N/A[d]
				Medial prefrontal cortex lower level: 766% ↑ k_3-l_3[c]	4.84
				Medial prefrontal cortex upper level: 114% ↑ k_3-l_3[c]	2.59
Agren et al. (1991)[b]	6 MDD 8 HC	[^{11}C]5-HTP	Drug-free (>10 days)	Overall: 29% ↓ SUV	−0.93
				Dorsolateral prefrontal cortex: 27% ↓ SUV	−0.83
				Medial area: 26% ↓ SUV	−0.82
				Basal ganglia: 21% ↓ SUV (ns)	−0.54
				Caudate nucleus: 22% ↓ SUV (ns)	−0.57
				Lentiform nucleus: 15% ↓ (ns)	−0.38

The change in tracer trapping is estimated from several brain regions of depressive patients and compared to reported healthy control data
[a]Other statistical test than *t*-test used
[b]Same sample of patients
[c]New way of calculating vague (k_3-l_3)
[d]No individual data available to calculate the effect size

studies on serotonin synthesis in MDD are sparse, with no additional studies since 2004.

In summary, these studies indicate that 5-HT synthesis, mainly in the prefrontal cortex and cingulate cortex, probably plays a role in the pathophysiology of MDD and the efficacy of antidepressants. A decreased synthesis or an increased

breakdown of 5-HT would lead to lower levels of serotonin in the brain, putatively increasing the risk for MDD at least in some MDD subtypes. SSRIs increase 5-HT levels and may relieve some of the symptoms of depression; however, after acute administration a decrease in synthesis takes place through stimulation of autoreceptors. Blocking of 5-HT_{1A} receptors could lead to a faster and greater increase in 5-HT synthesis rates and possibly accelerate the efficacy of antidepressants. Imaging these 5-HT_{1A} autoreceptors with PET tracers is another important feature of molecular imaging in depression, which has been investigated with sustained effort as described in Sect. 4.3.1.3.

4.3.1.2 Serotonin Transporter (SERT) Imaging

The availability of the (nonspecific) SPECT tracer iodine-123-labeled 2β-carbomethoxy-3β-(4-iodophenyl)-tropane ([^{123}I]β-CIT) from 1991 onward (Innis et al. 1991) started the investigation of the SERT availability in affective disorders. [^{123}I]β-CIT and its analogue [^{123}I]nor-β-CIT (with a tenfold higher affinity to the SERT than β-CIT (Bergstrom et al. 1997a; Hiltunen et al. 1998)) do not bind selectively to SERT but also to the dopamine transporter (DAT) (Laruelle et al. 1993) and noradrenalin transporter (NET), and endogenous serotonin competes with binding (Heinz et al. 2004). Because of lower DAT density in the midbrain, binding there is considered to represent mainly SERT, while binding in the striatum will mainly represent DAT, because of the high density of DAT relative to SERT in this region (Pirker et al. 2000). Thereafter the selective PET ligand [^{11}C](+)McN5652 was developed, followed by [^{11}C]DASB. More recently the SPECT ligand [^{123}I]ADAM was developed which is also selective for SERT (Acton et al. 2001; Catafau et al. 2005; Frokjaer et al. 2008b). [^{11}C]DASB is now considered the gold standard for SERT imaging, due to its high ratio of specific to nonspecific binding (Szabo et al. 2002), although even this tracer is not perfectly suited for imaging cortical binding. [^{11}C](+)McN5652 and [^{123}I]ADAM yield slightly worse contrasts, especially in subcortical and cortical brain regions (Frankle et al. 2004; Szabo et al. 2002).

It remains unclear what pathophysiological mechanism the measurement of SERT availability exactly represents. First, SERT availability may simply represent a marker of axons/number of neurons with SERTs. From another perspective, increased SERT availability may represent more SERTs at the synaptic cleft which enhance clearance of serotonin from the synaptic cleft; reduced SERT may then result in the opposite (Meyer 2012). However, although not indisputable, SERT availability may also be influenced by the availability of intrasynaptic endogenous serotonin, with compensatory downregulation in case of reduced endogenous serotonin (Dewar et al. 1992; Frokjaer et al. 2009; Graham et al. 1987; Graham and Langer 1987; Meyer 2007; Rattray et al. 1996; Rothman et al. 2003).

Until December 2019, 30 separate studies investigated the SERT in unipolar MDD (Table 4.2A) and 4 in BP (Table 4.2B). Most studies were small (18 studies with less than 20 MDD patients), which generally limits the statistical power to detect differences with less than large effect sizes (<0.8). Eighteen studies used PET tracers ([^{11}C]DASB, 4-[^{18}F]ADAM, [^{11}C]-ZIENT, or [^{11}C](+)McN5652), and 16

Table 4.2 Results of serotonin transporter (SERT) imaging studies (PET/SPECT) in patients with unipolar major depressive disorder (A) or bipolar disorder (B) as compared to controls

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size[a]
A. Unipolar depression					
Ananth et al. (2018)	26 MDD 31 HC	[^{11}C]DASB	Drug-free (6 recently tapered); consecutively treated with 8 weeks of escitalopram 10–20 mg	Lower Amygd SERT binding in final remitters vs. controls (p = .03) but not in non-remitters vs. controls (p = .97), final remitters and non-remitters not significantly different (p = .06)[d]	–
				Differences in Midbr, Thal, dorsal putamen, Hippoc, ACC nonsignificant	
				No sign. association between baseline Amygd SERT and posttreatment HDRS-24 score (p = .39)	
Hahn et al. (2014) Sample also described in: Lanzenberger et al. (2012), Kraus et al. (2014)	20 MDD 20 HC	[^{11}C]DASB	Drug-free ≥3 months	Midbr: 1%↑ (p = .92) in MDD	0.03
				N accumbens: −6%↓ (p = .15) in MDD	−0.5
				Caudate: −6%↓ (p = .16) in MDD	−0.5
				Putamen: −5%↓ (p = .17) in MDD	−0.5
				Thal: −9%↓ (p = .03) in MDD	−0.7
				ACC: −9%↓ (p = .25) in MDD	−0.4
				Insula: −11%↓ (p = .04) in MDD	−0.7
				Amygd: −9%↓ (p = .10) in MDD	−0.5
				Hippoc: −2%↓ (p = .72) in MDD	−0.1
				Neg. associations of SERT availability and age in Thal, insula, medial PFC, middle/posterior ACC in controls and with insula and caudate in MDD patients (p < .001); not in Midbr or striatum. No associations with duration or treatment of MDD	

Yeh et al. (2014, 2015)	17 MDD (8 with suicide attempt) 17 HC	4-[^{18}F] ADAM	Antidepressant naive	Lower SERT in Midbr ($p < .001$), Thal ($p < .001$), Striat ($p = .005$)[d]	–
				SERT availability in Midbr and Thal especially lower in MDD patients with suicidal behavior	
				Significant correlation between lower Midbr SERT availability and higher HDRS score ($p < .05$) Significant correlation between higher SERT and decrease in HDRS at week 3 (but not week 6) in Thal ($p = .016$) and Striat ($p = .047$)	
Ho et al. (2013)	40 MDD 12 HC	[^{123}I]ADAM	Drug-free ≥4 months	Striat: −9%↓ ($p = .159$) in MDD	−0.3
				Thal: −24%↓ ($p = .036$) in MDD	−0.7
				Midbr: −12%↓ ($p = .139$) in MDD	−0.4
				Pons: −14%↓ ($p = .078$) in MDD	−0.5
				No association of SERT availability in any region with MDD severity (HDRS) or SLC6A4, STin2, age, gender	
Miller et al. (2013a)	51 MDD (15 with attempted suicide) 31 HC	[^{11}C]DASB	Drug-free ≥2 weeks (11 drug-naive)	Midbr: −11%↓ ($p = .025$) in MDD	−0.5
				Thal: −7%↓ ($p = .21$) in MDD	−0.3
				Amygd: −12%↓ ($p = .021$) in MDD	−0.5
				ACC: −14%↓ ($p = .06$) in MDD	−0.4
				Dorsal putamen: −7%↓ ($p = .07$) in MDD	−0.4
				Hippocampus: −11%↓ ($p = .15$) in MDD	−0.3
				MDD suicide attempters had lower Midbr binding than both MDD nonattempters ($p = .031$) and HC ($p = .0093$)	
				No relationship between age or depression severity (HDRS) and SERT availability across the six ROIs	

(continued)

Table 4.2 (continued)

Nye et al. (2013)	11 MDD + suicide attempt 10 HC	[^{11}C]ZIENT	Drug-free ≥6 weeks	Midbr/pons: −47%↓ (p = .03) in MDD	−1.4
				Putamen: −25%↓ (p = .04) in MDD	−0.6
				Amygd: 0%↓ (p = .50) in MDD	0
				Caudate: −23%↓ (p = .21) in MDD	−0.5
				Thal: −23%↓ (p = .08) in MDD	−0.6
				Frontal cortex: −20%↓ (p = .11) in MDD	−0.5
				Cingulate: 20%↑ (p = .89) in MDD	0.4
				No sign. effect of age on mean SERT availability, but because of differences between MDD and HC, used as covariate	
Newberg et al. (2012) Amsterdam et al. (2013)	20 MDD 10 HC	[^{123}I]ADAM	Drug-free ≥1 year (10 drug-naive)	Midbr: −9%↓ (p < .005) in MDD	−1.2
				Basal ganglia: −12%↓ (p < .0.03) in MDD	−1.0
				Temporal lobe: −15%↓ (p < .005) in MDD	−1.3
				No sign. effect of age, gender, illness duration, prior antidepressant drug exposure, or symptom severity on mean SERT availability After cognitive therapy, MDD patients had a sign. increase in SERT availability in Midbr and temporal lobes (p < .01), especially in responders	
Selvaraj et al. (2011)	12 MDD	[^{11}C]DASB	Drug-free ≥4 months (4 drug-naive)	Amygd: 0%↓ (p = .99) in MDD	0.0
	24 HC (males only)			ACC: −10%↓ (p = .31) in MDD	−0.3
				Midbr: −23%↓ (p = .00001) in MDD	−1.2
				Caudate: −23%↓ (p = .06) in MDD	−0.6
				PFC: −13%↓ (p = .30) in MDD	−0.4
				Hippoc: 7%↑ (p = .58) in MDD	0.2
				Insula: −4%↓ (p = .67) in MDD	−0.1

				Putamen: −14%↓ (p = .11) in MDD	−0.5
				Thal: −24%↓ (p = .01) in MDD	−0.8
				Possible (uncorrected) pos. correlation with age of onset (caudate, PFC + p < .05) and neg. association with severity (PFC; p = .02)	
Hsieh et al. (2010)	13 MDD 26 HC	[^{123}I]-ADAM	Drug-free >3 months	Midbr: 3%↑ (p = .76) in MDD	0.2
Ruhe et al. (2009a, c)	49 MDD	[^{123}I]β-CIT	Drug-free ≥4 weeks (34 drug-naive)	Midbr: 2%↓ (p = .73) in MDD	−0.1
	49 HC			Thal: 6%↑ (p = .27) in MDD	0.2
				Midbr male: 16%↓ (p = .09) in MDD[b]	−0.5
				Midbr female: 10%↑ (p = .37) in MDD[b]	0.3
				Thal male smoke +: 23%↓ (p = .01) in MDD[b,c]	−1.5
				Thal male smoke −: 13%↓ (p = .18) in MDD[b,c]	−0.6
				Thal Fem. smoke +: 5%↑ (p = .54) in MDD[b,c]	0.3
				Thal Fem. smoke − : 21%↑ (p = .003) in MDD[b,c]	1.0
				In winter in Midbr: 18%↑ SERT (p = .04)	
				No differences in Midbr, Thal SERT for 5-HTTLPR polymorphisms (Ruhe et al. 2009c)	
Lundgren et al. 2009	7 MDD	[^{123}I]-ADAM	Drug-free >3 weeks	Midbr: 18%↓ (p = .001) in MDD	−3.0
	6 NES (BDI <19)			L/R temp lobe: 15%↓ (p < .01) in MDD	−2.0
				L/R Bas. ganglia: 3%↓ (n.s.) in MDD	−0.2
Reimold et al. (2008)	10 MDD	[^{11}C]DASB	Drug-free >5 half-lives of previous drugs	Thal: 16%↓ (p = .005) in MDD	−1.1
	19 HC			Midbr: 6%↓ (p = .26) in MDD	−0.3
				Amygd: 1%↓ (p = .45) in MDD	−0.0

(continued)

Table 4.2 (continued)

				Thal SERT inversely correlated with anxiety (p = .02) and age, but not with depression severity (n.s.)	
Bhagwagar et al. (2007)	24 MDD (recovered)	[^{11}C]DASB	Drug-free >3 months (9 drug-naive)	No overall differences (p = 0.28)	
	20 HC (males only)			Amygd: 0%↑ (n.s.) in MDD	0.0
				ACC: 0%↑ (n.s.) in MDD	0.0
				Caudate: 9%↑ (n.s.) in MDD	0.3
				PFC: 5%↑ (n.s.) in MDD	0.2
				Hippoc: 7%↑ (n.s.) in MDD	0.3
				Insula: 0%↑ (n.s.) in MDD	0.0
				Thalamus: 4%↑ (n.s.) in MDD	0.1
				Dorsal raphe: 15%↑ (n.s.) in MDD	0.4
				No association with DAS scores	
Cannon et al. (2006b, 2007), Laje et al. (2010), Liu et al. (2011)	18 MDD	[^{11}C]DASB	Drug-free >3 weeks	Midbr: 8%↑ (n.s.) in MDD	0.4
	18 BD			Thal: 27%↑ (p = .0001) in MDD	1.4
	34 HC			Striat: 12%↑ (p = .04) in MDD	0.8
				Insula: 15%↑ (p=.02) in MDD	1.1
				PAG: 22%↑ (p = .009) in MDD	1.0
				pgACC: 16%↑ (p=.06) in MDD	0.7
				Negative correlation with MDD severity and Thal, insula, DCC SERT	
				Lower SERT in Thal associated with 5-HT$_{2A}$ rs7333412 AA polymorphism (Laje et al. 2010)	

				Increased SERT associated with galactose mutarotase polymorphism independent of diagnosis; replicated in another sample (Liu et al. 2011)	
Lehto et al. (2006, 2008b), Joensuu et al. (2007, 2010)	29 MDD	[^{123}I]nor β-CIT	Drug-naive	Midbr: 10%↓ (p = .0002) in MDD	−1.1
	19 HC			No correlation with MDD severity	
				Linear inverse correlation with atypical score (Lehto et al. 2006)	
	Subgroup: 8 MDD+ dysthymia vs. 11 MDD			In MDD in MPFC 26%↓ (p = .024) in SS vs. other genotypes; in Midbr 1%↓ (n.s.)	−1.2
				Midbr: 10%↓ (p = .004) in MDD	−1.0
				Midbr: 12%↓ (p = .004) in MDD + dysthymia (Lehto et al. 2008b)	−1.5
Miller et al. (2008, 2009b), Parsey et al. (2006a, b)	25 MDD	[^{11}C] McN5652	Drug-free ≥2 weeks (12 drug-naive)	BP ↓ (p < .02) over all regions in MDD	
	43 HC			Amygd: 19%↓ (p < .03) in MDD	−0.5
				Midbr: 21%↓ (p < .03) in MDD	−0.6
				No correlation with MDD severity. SERT↓ in ACC, Amygd, putamen, Hippoc, Midbr, and Thal (p < .046) in MDD with childhood abuse (Miller et al. 2009b)	

(continued)

Table 4.2 (continued)

				SERT↓ in Amygd, Midbr, and ACC in non-remitters (at 1 year; $p = .013$); higher Amygd SERT predicted lower final HDRS score ($p = .035$) (Miller et al. 2008)	
				No differences in any region for 5-HTTLPR polymorphisms (Parsey et al. 2006a)	
Staley et al. (2006)	32 MDD	[^{123}I]β-CIT	Drug-free	Females: Thal 22%↓ ($p = .005$) in MDD[b]	−1.0
	32 HC			Males: Thal 1% ≈ (n.s.) in MDD[b]	0.1
				Midbr: 1% ≈ (n.s.) in MDD (no interaction with gender)	0.0
				Age is neg. correlated with SERT; but pos. correlated with SERT in MDD females in the thalamus	
Herold et al. (2006)	21 MDD	[^{123}I]-ADAM	Drug-free	Midbr: 21%↑ ($p = 0.07$) in MDD	0.4
	12 HC			In MDD males < females (n.s.)	
				No correlation with MDD severity	
Catafau et al. (2006)	10 MDD	[^{123}I]-ADAM	Drug-free >6 months	Midbr: 4%↓ ($p = .52$) in MDD	−0.3
	10 HC			Thal: 11%↓ ($p = .09$) in MDD	−0.8
				Striat: 5%↑ ($p = .62$) in MDD	0.3
Uebelhack et al. (2006)	30 MDD (unknown number with schizo-affective disorder) 14 HC	[^{123}I]-ADAM	Drug-free >2 months (10 drug-naive)	Midbr: 9%↑ ($p = .51$) in MDD	0.2
Newberg et al. (2005)	7 MDD	[^{123}I]-ADAM	Drug-free >3 weeks	Midbr: 7%↓ ($p = .01$) in MDD	−1.4
	6 HC			Sign. correlation with MDD severity	
Meyer et al. (2004a)	20 MDD 20 HC	[^{11}C]DASB	Drug-free >3 months	MPFC, DLPFC, ACC, caudate, putamen, Thal, Midbr ≈ ($p > .24$)[d]	–

				Significant increase in SERT in patients vs. controls in all regions for 8 patients with high DAS scores. In MDD (but not HC) sign. correlations between increased DAS scores and increased SERT	
Meyer et al. (2004b)	37 MDD 35 HC	[^{11}C]DASB	Drug-free >1 month	Striat ≈ (p = .59) difference	0
Reivich et al. (2004)	4 MDD	[^{11}C](+) McN5652	Drug-free for	L PFC: 17%↑ (p = .013) in MDD	2.9
	4 HC		≥5 half-lives	R ACC: 24%↑ (p = .043) in MDD	1.9
				Thal: 17%↑ (n.s.) in MDD	0.4
				Midbr: 25%↑ (n.s.) in MDD	0.8
Ahonen et al. (2004)	10 MDD 14 HC	[^{123}I]-ADAM	Drug-free	Midbr: 7%↑ (n.s.) in MDD	0.5
Ichimiya et al. (2002)	7 MDD and 6 BD	[^{11}C](+) McN5652	Drug-free	Thal: 23%↑ (p = .002) in MDD/BD	1.0
	21 HC (males only)			Midbr: −2% ≈ (n.s.)	0.1
Meyer et al. (2001c)	13 MDD	[^{11}C]DASB	Drug-free (11 drug-naive)	Striat no differences (p = .82)[d]	–
	13 HC			Significant effect of age (p = .04)	
Dahlstrom et al. (2000)	31 MDD 10 non-MDD pts Children/adolescents	[^{123}I]β-CIT	Drug-naive	Midbr: 8%↑ in MDD at 1 h (p = .02), 9%↑ at 4 h (p = .08)	0.9 (1 h)
				PFC n.s.	0.8 (4 h)
				Thal n.s.	– –
Willeit et al. (2000)	11 SAD	[^{123}I]β-CIT	Drug-free ≥6 months	Midbr: 2%↑ (p = .95) in MDD (4 h)	0.2

(continued)

Table 4.2 (continued)

	11 HC			Thal: 7%↓ (p = .31) in MDD (4 h)	−0.6
				Midbr: 7%↓ (p = .39) in MDD (24 h)	−0.5
				Thal: 15%↓ (p = .026) in MDD (24 h)	−1.2
Kugaya et al. (2004), Malison et al. (1998b)	15 MDD	[^{123}I]β-CIT	Drug-free	Midbr: 18%↓ (p = .02) in MDD	−0.8
	15 HC			No correlation with MDD severity	
				Higher SERT predicted treatment response (Kugaya et al. 2004)	
B. Bipolar depression					
Chou et al. (2010)	24 BD (10 BP-I) (euthymic)	[^{123}I]-ADAM	Mood stabilizers and antipsychotics allowed; no SSRI/SNRI >1 year	Midbr: 8%↓ (p = .27) in BD-I+BD-II	−0.3
				Midbr: 25%↓ (p = .042) in BD-I	1.2
	28 HC			Midbr: 3%↑ (n.s.) in BD-II	0.1
				In BD-I SERT correlated inversely with duration of illness	
Oquendo et al. (2007)	18 BD (10 BP-I)	[^{11}C](+) McN5652	Drug-free ≥2 weeks (2 drug-naive)	Midbr: 27%↓ (p = .02) in BD[e]	−0.8[e]
	41 HC			Amygd: 26%↓ (p = .02) in BD	−0.6
				Hippoc: 23%↓ (p = .02) in BD	−0.7
				Thal: 23%↓ (p = .02) in BD	−0.8
				Putamen: 16%↓ (p = .02) in BD	−0.3
				ACC: 23%↓ (p = .02) in BD	−0.6
				No correlation with severity. No effect of 5-HTTLPR genotype	

Cannon et al. (2006b), Laje et al. (2010)	18 BD (5 BP-I)	[^{11}C]DASB	Drug-free ≥1 month (1 drug-naive)	Thal: 14% ↑ (p = .003) in BD	0.9
	37 HC			Insula: 13% ↑ (p = .015) in BD	0.7
				pgACC: 16% ↑ (p = .017) in BD	0.8
				sgACC: 9% ↑ (n.s.) in BD	0.4
				Striat: 8% ↑ (p = .06) in BD	0.5
				Midbr: 5% ↓ (n.s.) in BD	−0.4
				DCC: 19% ↑ (p = .004) in BD	0.8
				PCC: 14% ↑ (p = .05) in BD	0.6
				No correlation with severity. Pos. correlation between anxiety and SERT in insula and DCC	
				Comorbid OCD associated with increased SERT in insula and DCC; more pronounced differences in BD without previous mood stabilizers; lower SERT in midbrain of patients with attempted suicides	
				Lower SERT in Thal associated with 5-HT$_{2A}$ rs7333412 AA polymorphism (Laje et al. 2010)	
Ichimiya et al. (2002)	7 MDD and 6 BD	[^{11}C](+) McN5652	Drug-free	Thal 23%↑ (p = .002) in MDD/BD	1.0
	21 HC (males only)			Midbr −2% ≈ (n.s.)	0.1

Abbreviations: *5-HTTLPR* Serotonin transporter promoter region, *Amygd* Amygdala, *BDI* Beck Depression Inventory, *HDRS* Hamilton Depression Rating Scale, *Midbr* Midbrain, *ACC* Anterior cingulate cortex, *pg* Pregenual, *sg* Subgenual, *DAS* Dysfunctional Attitude Scale, *DCC* Dorsal cingulate cortex, *L* Left, *Midbr* Midbrain, *NES* Night eating syndrome, *PAG* Periaqueductal gray matter, *PCC* Posterior cingulate cortex, *PFC* Prefrontal cortex, *M* Medial, *DL* Dorsolateral, *R* Right, *SAD* Seasonal affective disorder, *Striat* Striatum, *Thal* Thalamus

Notes/remarks:

[a]The differences and effect sizes (vs. controls) have been estimated from tables and text (or graphs), based on specific binding potential relative to non-displaceable binding (BP_{ND}, V3″, or analogous measures), unless specified differently (Innis et al. 2007)

[b]Significant disease group by gender interaction ($p < .05$)

[c]Significant gender by smoking interaction ($p < .04$)

[d]Only statistics provided

[e]BP_P reported instead of BP_{ND}

studies used SPECT tracers ([^{123}I]β-CIT, [^{123}I]nor-β-CIT, or [^{123}I]ADAM). In most studies both males and females were included, although three studies (Bhagwagar et al. 2007; Ichimiya et al. 2002; Selvaraj et al. 2011) investigated males only. We will first summarize the findings of these studies for unipolar and bipolar depression separately and try to synthesize these thereafter.

Unipolar Depression

With PET, 295 MDD patients have been investigated in total versus 342 controls. All studies investigated drug-free depressed patients (of whom 55/271 were reported drug-naive), except one study which investigated remitted patients (of whom 9/24 were drug-naive) (Bhagwagar et al. 2007).

The PET ligand [^{11}C]DASB was used in ten studies (Bhagwagar et al. 2007; Cannon et al. 2007; Meyer et al. 2001c, 2004a, b; Reimold et al. 2008; Selvaraj et al. 2011; Miller et al. 2013a; Hahn et al. 2014; Ananth et al. 2018). Other PET ligands were 4-[^{18}F]ADAM (Yeh et al. 2014, 2015), [^{11}C]ZIENT (Nye et al. 2013), and [^{11}C]McN5652 (Ichimiya et al. 2002; Reivich et al. 2004; Miller et al. 2008, 2009b; Parsey et al. 2006a, b).

Many brain regions have been investigated: the thalamus, striatum, and midbrain (including the dorsal raphe) were investigated most, followed by more incidental reporting of SERT availability in the amygdala, anterior cingulate cortex (ACC; including the pre- and subgenual parts), caudate nucleus, putamen, prefrontal cortex (PFC; including the medial and dorsolateral parts), hippocampus, insula, and periaqueductal gray (PAG). The results are mixed.

In the midbrain five studies (n = 116 patients) reported a decrease in SERT availability (Parsey et al. 2006b; Selvaraj et al. 2011; Nye et al. 2013; Miller et al. 2013a; Yeh et al. 2014, 2015), and seven studies (n = 105 patients) reported no difference (Cannon et al. 2007; Ichimiya et al. 2002; Meyer et al. 2004a; Reimold et al. 2008; Reivich et al. 2004; Hahn et al. 2014; Ananth et al. 2018). One small study (n = 4 patients) was underpowered to distinguish an effect size of 0.8 *increase* in midbrain SERT availability (Reivich et al. 2004). Interestingly, three studies (n = 79 patients) reported that midbrain SERT availability was especially lower in patients with a history of suicide attempts (n = 34) (Nye et al. 2013; Miller et al. 2013a; Yeh et al. 2014, 2015).

In the thalamus, five studies (n = 70 patients) reported a decrease in SERT availability (Reimold et al. 2008; Selvaraj et al. 2011; Nye et al. 2013; Yeh et al. 2014, 2015; Hahn et al. 2014), while four studies (n = 101 patients) reported no difference (Meyer et al. 2004a; Reivich et al. 2004; Miller et al. 2013a; Ananth et al. 2018) and two studies (n = 25 patients) an increase (Cannon et al. 2007; Ichimiya et al. 2002).

In the striatum, five studies (n = 108) reported no difference in SERT availability (Meyer et al. 2001c, 2004a, b; Selvaraj et al. 2011; Ananth et al. 2018), three studies (n = 82 patients) reported nonsignificant lower SERT availability (Nye et al. 2013; Miller et al. 2013a; Hahn et al. 2014), while one study (n = 17 patients) reported significantly lower SERT availability in MDD (Yeh et al. 2014, 2015).

SERT availability in the amygdala was reported in seven studies (n = 130 patients), with no (significant) change in five studies (n = 67 patients) (Reimold

et al. 2008; Selvaraj et al. 2011; Nye et al. 2013; Hahn et al. 2014; Ananth et al. 2018) but significantly lower SERT availability in MDD in two studies (n = 76) (Miller et al. 2008, 2009b; Miller et al. 2013a). Interestingly, lower amygdala SERT availability was associated with remission of MDD after treatment with escitalopram (Ananth et al. 2018).

Age was negatively correlated with SERT availability in striatum (Meyer et al. 2001c; Hahn et al. 2014). In other regions only significant increases were reported in the right ACC (Reivich et al. 2004), PAG (Cannon et al. 2007), and insula (Hahn et al. 2014).

In remitted patients no differences in midbrain, thalamus, or striatal SERT availability were found, although for the midbrain and striatum, effect sizes of 0.4 and 0.3 (increased vs. controls) were reported (Bhagwagar et al. 2007). Another study of the same research group in another sample of depressed patients found a decrease in SERT availability in the midbrain and thalamus. These results are indicative of state-dependent changes in SERT availability in the course of MDD (Selvaraj et al. 2011).

Interestingly, Meyer et al. reported that in a subgroup of eight depressed patients with high dysfunctional attitude scores (DAS), an increased SERT availability in the midbrain, thalamus, striatum, PFC, and ACC existed (Meyer et al. 2004a). DAS scores also showed a significant correlation with SERT availability, which was not found in the remitted patients (Bhagwagar et al. 2007). Severity of depression was negatively correlated with SERT availability in the PFC (Selvaraj et al. 2011), thalamus, insula, dorsal ACC (Cannon et al. 2007), and midbrain (Yeh et al. 2014, 2015) (lower SERT, higher severity), which was not replicated in other PET studies. Of note is one study specifically investigating the effect of anxiety symptoms; this study demonstrated that more anxiety symptoms were associated with lower SERT availability in the thalamus (Reimold et al. 2008). Childhood abuse appeared to be associated with lower SERT availability in the midbrain, thalamus, ACC, amygdala, putamen, and hippocampus in a secondary analysis of 23 MDD patients (Miller et al. 2009b).

The original finding of Kugaya et al., who reported that higher SERT availability in the midbrain (measured by [^{123}I]β-CIT) appeared predictive of later response to antidepressants (Kugaya et al. 2004), was not replicated with PET (but see the association of lower SERT availability in the amygdala above (Ananth et al. 2018)). Some support that antidepressant treatment may depend on high SERT availability in the depressed state was found later: final non-remitters after 1 year of antidepressant treatment had lower SERT availability in the midbrain, ACC, and amygdala before follow-up (compared to final remitters), and higher amygdala SERT availability predicted lower posttreatment Hamilton (HDRS) scores (Miller et al. 2008). In addition, Lanzenberger et al. reported that the ratio of SERT binding in the amygdala/hippocampus complex, sgACC, and habenula relative to the SERT binding median raphe nuclei (MRN) was predictive for a response after ≥3 weeks of (es) citalopram (Lanzenberger et al. 2012). The higher the SERT binding in terminal regions in relation to the MRN SERT binding, the better the treatment outcome. If replicated and validated as a prognostic test, this study might herald the first

PET-based biomarker ([^{11}C]DASB binding in sgACC/habenula/amygdala–hippocampus complex relative to MRN) for the prediction of SSRI treatment outcome.

Despite the higher resolution in PET, many studies used the less expensive, easier to handle, alternative SPECT imaging, with a total of 318 MDD patients versus 230 healthy controls being scanned. All studies investigated depressed drug-free patients (of whom 114/318 were reported drug-naive). One study without healthy controls was omitted (Lundgren et al. 2009); one study included nondepressed patients as controls, but will be discussed further (Dahlstrom et al. 2000).

All studies with these SPECT ligands reported on SERT availability in SERT-rich regions of interest: mostly results were reported for the midbrain, sometimes for the thalamus/diencephalon, and occasionally for the MPFC (Joensuu et al. 2010) and temporal lobe (Newberg et al. 2012). Results are mixed, which might be explained by methodological issues. First, a ratio method overestimates SERT availability during a transient equilibrium, with the largest errors in high-binding regions. Second, the time point of (transient) equilibrium is later in regions with high binding. Third, plasma clearance rates may vary from subject to subject, and this may be even worse between patients and controls. For example, [^{123}I]ADAM studies in humans showed poor test–retest outcomes for the ratio method, with intrasubject variability of >13% (Frokjaer et al. 2008b).

In the midbrain, four studies ($n = 71$ patients) reported a decrease in SERT (Lehto et al. 2006; Malison et al. 1998b; Newberg et al. 2005; Newberg et al. 2012), and ten studies ($n = 247$ patients) found no (significant) difference (Ahonen et al. 2004; Catafau et al. 2006; Dahlstrom et al. 2000; Herold et al. 2006; Uebelhack et al. 2006; Hsieh et al. 2010; Ruhe et al. 2009a; Staley et al. 2006; Willeit et al. 2000; Ho et al. 2013) in direct comparisons of patients and controls. Of note is that four of the studies, which were poorly powered and reported no difference, in fact reported nonsignificant increases in SERT availability in MDD patients ($n = 92$ patients) (Ahonen et al. 2004; Dahlstrom et al. 2000; Herold et al. 2006; Uebelhack et al. 2006). One study reported a significant negative correlation between midbrain SERT and depression severity (Newberg et al. 2005). In one study MDD patients had a significant increase in SERT availability in midbrain (and temporal lobes; $p < .01$) after cognitive therapy, which was especially seen in responders (Newberg et al. 2012; Amsterdam et al. 2013).

In the thalamus, two studies ($n = 72$ patients) reported a decrease in SERT (Staley et al. 2006; Ho et al. 2013) and four studies ($n = 101$ patients) no difference (Catafau et al. 2006; Dahlstrom et al. 2000; Ruhe et al. 2009a; Willeit et al. 2000) in direct comparisons of patients and controls.

Importantly, two larger studies ($n = 81$ MDD patients) that reported no overall differences in direct comparisons between MDD patients and controls reported an interaction of gender by disease status (Ruhe et al. 2009a; Staley et al. 2006), albeit with opposite interaction effects. Staley et al. reported significantly lower thalamus SERT availability for depressed females versus controls and no difference in males (Staley et al. 2006). Both in the thalamus and midbrain, there was an age by gender interaction (lower SERT availability at higher age in males versus higher SERT availability in older females). In their sample no gender by disease status interaction

was found for midbrain SERT availability. However, Ruhe et al. reported a significant interaction of lower midbrain SERT availability in depressed males and an increase of SERT availability in depressed females (vs. controls). They also found an interaction of smoking by gender and gender by disease status for SERT availability in the thalamus. Relative to controls, smoking increased SERT availability in males, while this difference was not significant in females. In a recent study, in a mix of controls and a group of patients with different psychiatric disorders, smoking status significantly interacted with 5-HTTLPR genotype: active smoking was associated with reduced 5-HTT availability only in LL subjects but not in carriers of the S-allele (Smolka et al. 2019). Furthermore, like in the midbrain, SERT availability was lower in depressed males but higher in depressed females (Ruhe et al. 2009a).

Bipolar Depression

BP was investigated sparsely, with no additional studies since 2012, with three PET studies and one SPECT study (Table 4.2B). In total 56 BP patients were studied, of whom at least 25 were suffering from bipolar I disorder. One study did not report separate analyses for unipolar and bipolar subjects (Ichimiya et al. 2002), but found increased SERT availability in the thalamus. This was also found by Cannon et al., who also reported significantly increased SERT availability in the insula, pgACC, and DCC, with a trend for increased SERT in the striatum and no change in the midbrain (Cannon et al. 2006b). However, Oquendo et al. reported the opposite: lower SERT availability in the midbrain, thalamus, amygdala, ACC, putamen, and hippocampus in BD patients (Oquendo et al. 2007), although with a different tracer ([^{11}C](+)McN5652) and a different definition of the binding potential (BP_P). The authors reported no significant differences for BP_{ND}, but argue that the BP_P value is more precise due to differences in SERT availability in the cerebellum reference region between BD patients and controls. Finally, Chou et al. reported significantly reduced SERT availability, which correlated inversely with duration of illness (Chou et al. 2010), but only in bipolar I patients. No associations between SERT availability and SERT 5-HTTLPR polymorphisms were found nor with severity of depression, although Cannon et al. reported increased SERT availability in the insula and dorsal cingulate associated with anxiety and OCD comorbidity and lower SERT availability in the midbrain of patients with attempted suicide (Cannon et al. 2006b).

SERT Availability in Unipolar and Bipolar Depression

The inconsistencies in the reported studies have been discussed previously (Meyer 2012; Oquendo et al. 2007) and have also been meta-analyzed recently (Gryglewski et al. 2014; Kambeitz and Howes 2015; Nikolaus et al. 2016), but merit a further discussion here to synthesize the above findings. Possible explanations consist of differences in selectivity of ligands (with concomitant binding to DAT in the substantia nigra in the midbrain for [^{123}I]β-CIT) or artifacts by differential displaceable binding of (low) SERT availability in the reference region (cerebellum) as put forward by Oquendo et al. (2007) and Selvaraj et al. (2011). In order to overcome this problem, these authors suggest to measure BP in conjunction with arterial input modeling, which might increase the sensitivity of measurements.

Selection of studied patients (with or without anxiety or comorbid anxiety disorders (Cannon et al. 2006b; Meyer 2007; Reimold et al. 2008); early–late onset of the first episode (before/after 40 years of age) (Meyer 2012); previous use of antidepressants (Meyer 2012; Parsey et al. 2006b) or mood stabilizers (Cannon et al. 2006b); or suicidality (Cannon et al. 2006b; Nye et al. 2013; Miller et al. 2013a; Yeh et al. 2014, 2015)) or healthy controls (with/without screening for familial vulnerability for MDD (Ruhe et al. 2007)) might furthermore have influenced results.

Genetic polymorphisms might influence SERT availability. First, the well-studied 5-HTTLPR polymorphism (Risch et al. 2009) was not correlated with SERT availability in single studies of controls (Shioe et al. 2003; Van Dyck et al. 2004; Willeit et al. 2001), although the LL genotype was associated with more SERT availability in the raphe in one small study (Heinz et al. 2000) and associated with increased SERT availability in the putamen in a study by Praschak-Rieder et al. (most prominent in Caucasian participants) (Praschak-Rieder et al. 2007). Nevertheless, in a review Willeit et al. concluded that by genotyping the tri-allelic variant of the 5-HTTLPR, a small to moderate effect could be shown, with the L_A/L_A carriers having slightly higher cerebral [^{11}C]DASB SERT binding (Willeit and Praschak-Rieder 2010). Therefore, small genotype effects cannot be ruled out in the above comparisons between patients and controls. The effects of 5-HTTLPR were also studied in MDD and BD patients: Parsey et al. did not find an association between genotype and SERT availability in the midbrain, putamen, amygdala, thalamus, hippocampus, or ACC of unipolar patients (Parsey et al. 2006a). Ruhe et al. reported no differences in SERT availability by genotype in the midbrain and thalamus (Ruhe et al. 2009c), as did Ho et al. (2013) for the striatum, thalamus, midbrain, and pons. However, Joensuu et al. reported lower SERT availability in the MPFC, but not in the midbrain for the SS carriers (Joensuu et al. 2010). Oquendo et al. found no indication of differences in SERT availability in the midbrain, putamen, amygdala, thalamus, hippocampus, or ACC between genotypes in BD patients (Oquendo et al. 2007). Second, in the population originally studied by Cannon et al. (2007), lower SERT availability in the thalamus was associated with the AA variant of the 5-HT_{2A} rs7333412 polymorphism (Laje et al. 2010). This polymorphism was previously associated with nonresponse to citalopram treatment of MDD (McMahon et al. 2006). Third, in a genome-wide association study in the same population, SERT availability was independently associated with a polymorphism of galactose mutarotase (GALM; rs6741892; T-allele vs. AA homozygotes) in controls and patients with unipolar or bipolar depression, which was replicated in an independent sample (Liu et al. 2011). GALM might increase local serotonin release and membrane trafficking and N-glycosylation of SERT which are related to the surface expression of SERT. These genetic differences might very well have influenced the findings in the above (nonrandomized) studies and were not (but neither could be) taken into account in most analyses. Furthermore, gene–environment interactions (e.g., the association of the s/s SERT genotype with seasonal influence on SERT availability (Kalbitzer et al. 2010)) also have not been addressed in patient samples.

Finally, as an explanation of inconsistencies, confounding by the season when scans were obtained might also have obscured differences. Seasonal change in SERT availability was well demonstrated, with higher SERT availability when daylight is reduced (winter) (Buchert et al. 2006; Kalbitzer et al. 2010; Praschak-Rieder et al. 2008; Ruhe et al. 2009a). Furthermore, the observed gender by disease status interactions, although only reported for SPECT studies (Ruhe et al. 2009a; Staley et al. 2006), might have obscured differences between MDD patients and controls as well. These factors can only be reassessed when original data at a patient level is available.

Interestingly, in seasonal affective disorder (SAD), global SERT availability (measured with [^{11}C]DASB PET) was comparable between SAD patients and controls in summer, but in their symptomatic phase in winter, SERT availability was higher than in controls (Mc Mahon et al. 2016). In a comparable study, Tyrer et al. (2016a) also observed larger increases in SERT availability in winter in the PFC and ACC but also in the dorsal putamen, thalamus, striatum, midbrain, and hippocampus of (most severe) SAD patients. In both studies the seasonal change in SERT availability was positively correlated with increase of symptom severity. Treatment with light therapy reduced [^{11}C]DASB PET SERT availability (Tyrer et al. 2016b). Moreover, in people resilient for SAD, a decrease of SERT availability was observed in winter, suggesting an adaptation to winter in the healthy states (Mc Mahon et al. 2018).

Also in BP patients, the mixed results could at first be attributed to different radioligands and the method how SERT availability was measured, but in addition to the abovementioned confounders, also differences in duration of illness between the studied populations and type of BP patients might be explanative. Bipolar I patients in the study by Chou showed most spread in disease duration, with lower SERT availability in patients with longer disease duration (Chou et al. 2010). Patients in the study by Oquendo et al. (with 10/18 bipolar I patients) appeared more chronically ill (Oquendo et al. 2007) than patients in the study by Cannon et al., who also investigated mostly bipolar II patients (13/18) (Cannon et al. 2006b). Furthermore, with these small samples, no conclusions can be made about confounding by season nor about interactions of gender by disease or gender by smoking. Due to the limited number of studies in bipolar patients with conflicting results and a suggestion of different SERT availabilities between bipolar I and II subtypes, no definite conclusions regarding bipolar depression can yet be drawn.

Notwithstanding the abovementioned concerns, although, in general, the majority of studies in unipolar depressed patients reported no differences in SERT availability in the midbrain, when considering the number of patients investigated, there is an indication that the midbrain of MDD patients displays lower SERT availability. Indeed, the methodologically most appropriate and updated meta-analysis of 25 in vivo imaging (PET and SPECT) studies showed significantly lower SERT availability in the brain stem of MDD patients (pooled Hedges' g = −0.31 [95% CI −0.55 to −0.08] (Kambeitz and Howes 2015), which was also concluded by the earlier meta-analyses by Gryglewski et al. (2014), including18 studies, and Nikolaus et al. (2016), who identified 38 studies until 2015, but poorly described their methods

(e.g., pooling and handling of different study sizes). More equivocal changes (decrease, no difference, increase) appear from studies reporting about the thalamus, striatum, and amygdala. The meta-analysis by Kambeitz and Howes (2015) indicated no significant difference in SERT availability between MDD patients and controls in the thalamus (Hedges' $g = -0.31$ [95% CI −0.65 to 0.03]), but a significant reduction in SERT availability in MDD patients in the striatum (Hedges' $g = -0.39$ [95% CI −0.62 to −0.17]) and also amygdala (Hedges' $g = -0.34$ [95% CI −0.61 to −0.13]).

As noted, several underpowered studies in fact indicated an *increase* in SERT availability in the midbrain (Ahonen et al. 2004; Cannon et al. 2006b, 2007; Dahlstrom et al. 2000; Herold et al. 2006; Reivich et al. 2004), which was also reported in females as a result of the gender by disease status interaction (Ruhe et al. 2009a). Increases of SERT availability may result in enhanced clearance of endogenous serotonin from the synaptic cleft. In addition to this potentially increased SERT availability, Meyer et al. reported that increased SERT availability in the midbrain, thalamus, striatum, PFC, and ACC showed a significant correlation with more pessimistic DAS scores (Meyer et al. 2004a). This group also showed that in patients with higher DAS scores, 5-HT_{2A} receptor density was increased (Meyer et al. 2004b). Taken together with the fact that long-term depletion of serotonin increases 5-HT_{2A} receptor density in rats (Stockmeier and Kellar 1986), it might be concluded that increased SERT availability in specific patients might lead to decreased intrasynaptic serotonin, high depressive dysfunctional attitudes, and an upregulation of 5-HT_{2A} receptors (Meyer 2007, 2012).

From another perspective, decreases in SERT availability may reflect high competitive binding of endogenous serotonin with the tracer, a deficit of serotonergic neurons in the raphe nuclei, less projections from these neurons to various brain regions, and deficits in SERT in the synapses of these projections but also a compensatory response to lower intrasynaptic serotonin, as proposed by Miller et al. (2009b). Increased endogenous serotonin competitive binding is unlikely, because in humans reductions of serotonin did not affect binding of [^{11}C]-DASB (Praschak-Rieder et al. 2005; Talbot et al. 2005; Kambeitz and Howes 2015). The compensatory response to lower intrasynaptic serotonin is more probable since the observed differences in SERT availability in the midbrain and thalamus (and possibly also in the caudate nucleus/striatum) between depressed and euthymic patients and the observations in SAD patients (Mc Mahon et al. 2016; Tyrer et al. 2016a) suggest compensatory flexibility of the SERT expression (Bhagwagar et al. 2007; Selvaraj et al. 2011). However, it cannot be ruled out that the results in MDD patients (Bhagwagar et al. 2007; Selvaraj et al. 2011) are incomparable because of selection bias of the different groups under study. Furthermore, the compensatory hypothesis is not unequivocally supported by serotonergic manipulations in rats, with some studies showing no alteration (Dewar et al. 1992; Graham et al. 1987; Graham and Langer 1987; Meyer 2007) of SERT availability after prolonged depletion states, while others reported a downregulation of SERT availability (Rattray et al. 1996; Rothman et al. 2003). A recent study of (drug-naive) never-depressed co-twins with high familial risk for MDD (defined as MDD or BD in the other co-twin) showed a

decrease in DLPFC SERT availability, but no differences in SERT availability in the midbrain (Frokjaer et al. 2009). This finding could be interpreted as a compensatory modulation of SERT density in the nerve terminals in the DLPFC, keeping the serotonergic tone at a required level.

However, the findings that childhood abuse, like in macaques who were raised deprived of their mothers (Ichise et al. 2006), reduces SERT availability in a widespread manner, including the midbrain (Miller et al. 2009b), are suggestive of a deficit of serotonergic neurons in the raphe nuclei that might be programmed in interaction with the environment during brain maturation in early childhood. This, in combination with associations with poorer MDD treatment response in patients with childhood abuse, the observation that lower SERT availability (Kugaya et al. 2004; Miller et al. 2008) was associated with non-remission (but see Ananth et al. (2018)), and the reports of reduced midbrain SERT availability (Lehto et al. 2006; Malison et al. 1998b; Newberg et al. 2005; Parsey et al. 2006b; Selvaraj et al. 2011; Newberg et al. 2012; Nye et al. 2013; Miller et al. 2013a; Yeh et al. 2014, 2015), is suggestive of a subgroup of patients in whom a (potential) serotonergic deficit is present as a vulnerability factor. It would be interesting to investigate whether these patients could be identified by more specific clinical features (e.g., treatment resistance and/or past treatment with antidepressants,, longer duration of depressive episodes, severity of depression and/or suicidal ideation, higher levels of childhood adversity, high recurrence rates, early age of onset) and/or by being more susceptible for depressed mood after, e.g., tryptophan depletion (Ruhe et al. 2007). It would only be possible to assess this in the current studies when mega-analyses of individual patient data could be done, requiring (mostly) complete data on these features. Alternatively, future prospective studies with large and specifically sampled individuals to address these uncertainties would be necessary.

SERT Occupancy During Antidepressant Treatment

The SERT is the primary target for many serotonin reuptake inhibiting antidepressants. With the availability of SERT tracers, the measurement of SERT availability before and after antidepressant treatment provides a measure of the dynamics of SERT occupancy that is reached during antidepressant treatment. This was primarily used to establish specificity of ligands for the SERT in single-dose SSRI blocking experiments during tracer development (six studies in controls). However, thereafter 8 and 12 studies investigated the dynamics of short- and long-term (>2 weeks) treatment with antidepressants, respectively (Table 4.3). Most studies scanned patients before and after treatment, although five studies used BP_{ND} obtained in controls as a reference (Lundberg et al. 2012; Pirker et al. 1995; Suhara et al. 2003; Tauscher et al. 1999; Voineskos et al. 2007), and one study compared BP_{ND} in responders and nonresponders to antidepressants without occupancy measures (Cavanagh et al. 2006).

SERT occupancy is a nonlinear function of drug serum/plasma concentration described by an E_{max} curve (Fig. 4.1). The rapid increase in occupancy occurs at clinically (very) low doses of the antidepressants, while at therapeutic doses, a maximum occupancy is reached at around 80–90%. Initial studies with SSRIs reported

Table 4.3 Results of serotonin transporter (SERT) occupancy imaging studies (PET/SPECT) in healthy controls and patients with major depression during treatment

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Rominger et al. (2015)	19 MDD	[^{123}I]β-CIT	6 weeks EsCIT 10–20 mg	Occ EsCIT:
				Thal: 42.2%
				Midbr: 53.4%
				A significant negative correlation existed between Thal (but not Midbr) SERT occupancy and change in DAT-weighted striatal BP_{ND} ($R = -0.62$; $p = .005$)[d] No association with SERT occupancy and change in HDRS
Lundberg et al. (2012)	20 MDD 26 HC	[^{11}C] MADAM	≥2 months (13 patients >1 year)	Occ[b] putamen:
			AMI 30 and 67.5 mg ($n = 2$)	AMI + CLOM: 61% SSRI: 70%
			CLOM 40–100 mg ($n = 3$)	
			VLX 150–300 mg ($n = 3$)	
			CIT 20–60 mg ($n = 4$)	
			FLX 20–60 mg ($n = 3$)	
			SER 50–200 ($n = 4$)	
			MIR (30 mg)	
Smith et al. (2011)	7 MDD (geriatric)	[^{11}C]DASB	8–10 weeks CIT 20–40 mg	Occ[c] CIT:
				Striatum: 73%
				Thal: 76%
Ruhe et al. (2009b, c), Ruhé et al. 2014, Simoons et al. (2020)	42 MDD (32 randomized after 6 weeks)	[^{123}I]β-CIT	6 weeks PAR 20 mg	Occ (6 weeks PAR 20 mg):
			In 32 nonresponders after 6 weeks, PAR 20 mg was randomized to another 6 weeks placebo-*increase* (= PAR 20 mg) or PAR-*increase* (PAR 30–50 mg)	Midbr: 71.1%
				Thal: 61.3%
				Amygd: 59% ($n = 15$)

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
				Occ (placebo-increase PAR 20 mg):
				Midbr: 84.6%–>87.7%
				Thal: 72.2%–>66.4%
				Occ (PAR-increase PAR 30–50 mg):
				Midbr: 76.2%–>78.6%
				Thal: 64.3%–>66.2%
Voineskos et al. (2007)	12 MDD 12 HC	[^{11}C]DASB	>4 weeks VLX 225–450 mg, SER 150–200 mg, CIT 60–80 mg	Occ[b] VLX, SER, CIT:
				Striat: 85.8%, 85.8%, 85.4%
				Midbr: 99.5%, 98.2%, 95.7
				Thal: 77.6%, 76.3%, 82.2%
Kasper et al. (2009), Klein et al. (2007)	15 HC (males only)	[^{123}I]-ADAM	10 days EsCIT 10 mg or CIT 20 mg	Occ in Midbr EsCIT: 81.5%, CIT 64.0%
				Sign. lower binding by CIT after 10 days probably attributable to accumulation of R-enantiomer over time
Shang et al. (2007)	8 HC	[^{123}I]β-CIT	9 days VLX 150 mg (4 days stable dose)	Occ[d] in Thal: 52.5%
				Occ Midbr: 55.7%
Catafau et al. (2006)	10 MDD	[^{11}C] MADAM	4–6 weeks PAR 20 mg	Occ: Midbr 66.4%, Thal 63.0%, Striat 61.3%
Herold et al. (2006)	21 MDD	[^{11}C] MADAM	1 week CIT 10 mg	Occ in Midbr 61%
Kasper et al. (2009), Klein et al. (2006)	25 HC (males only)	[^{11}C] MADAM	Single-dose EsCIT (5, 10, 20 mg) or CIT (10 or 20 mg)	Occ in Midbr EsCIT: 60% (5 mg), 64% (10 mg), and 75% (20 mg). CIT: 65% (10 mg) and 70% (20 mg)

(continued)

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Takano et al. (2006b)	15 HC (males only)	[^{11}C]DASB	Single-dose DLX (5, 20, 40, or 60 mg) (n = 12)	Occ Thal: 43.6% (5 mg), 71.3% (20 mg), 80.6% (40 mg), 81.8% (60 mg)
			DLX 60 mg for 7 days and then stopped (n = 3)	Occ Thal: 84.3% (7 days), 71.9% (9 days), 47.1% (11 days)
Takano et al. (2006a)	6 HC (males only)	[^{11}C]DASB	FLV 50 mg once	Occ: Thal 71.8%, Amygd 71.6%, Striat 70.5%, PFC 74.6%, Hippoc 75.9%
Cavanagh et al. (2006)	24 MDD	[^{123}I]β-CIT	Monotherapy (n = 17): VLX 75–300 mg, SSRIs 20–60 mg, tricyclic 150 mg, MIR 30 mg; combinations of 2 antidepressants, addition of lithium, valproate, carbamazepine, T3, or antipsychotics. Dosages unchanged for ≥2 weeks	No occupancy percentages available. No significant difference in SERT residual activity between responders and nonresponders. Wide range of SERT availability
Parsey et al. (2006c)	17 HC	[^{11}C]DASB	4–6 days SER 25, 50, and 100 mg (4 days at designated dose)	Occ average across 15 ROIs: max 106.8%
				Occ range: OFC 126.9% to Thal 79.3%; no exact data for separate ROIs provided
Erlandsson et al. (2005)	16 HC (males only)	[^{123}I]-ADAM	CIT at different dosages (10–60 mg) for different durations (2–7 days)	Occ Midbr: max 84%
				No mean occupancy for separate dosing regimens given

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Meyer et al. (2004b)	29 MDD 16 MDD + anxiety disorder 37 HC	[^{11}C]DASB	4 weeks open treatment: CIT 20–60 mg, FLX 20–60 mg, SER 50–200 mg, PAR 20–60 mg, VLX 75–225 mg In HC: CIT 1–10 mg, FLX 1–10 mg, SER 5–25 mg, PAR 5–10 mg, VLX 2.4–37.5 mg	Mean CIT, FLX, SER, PAR, VLX Occ:
				Striatum: 81.4%, 76.2%, 85.0%, 84.5%, 83.7%
				Thal: 72.3%, 69.1%, 76.8%, 74.7%, 71.3%
				Midbr: 87.5%, 82.3%, 91.8%, 93.4%, 91.0%
				No relation between striatal occupancy and clinical remission or percentage change in Hamilton depression scores
Kugaya et al. (2003, 2004)	10 MDD	[^{123}I]β-CIT	6 weeks PAR 20 mg	Occ at 1–3 weeks: Midbr 36.5%, Thal 29.1%
				Occ at 6 weeks: Midbr 32.6%, Thal 23.4%
	9 HC		CIT 40 mg (8 days), CIT 40 mg + bupropion 100 mg (8–16 days)	Occ CIT (8 days): Midbr 51.4%, Thal 39.4%; no sign. change thereafter
				Bupropion did not sign. alter SERT Occ
Suhara et al. (2003)	10 MDD	[^{11}C] McN5652	CLOM 20–250 mg, FLV 25–200 mg (long term)	Occ[b] Thal: CLOM ≥61.3–100%; FLV ≥76.6–93.6%
	27 HC		CLOM 5–50 mg, FLV 12.5–50 mg (single dose)	Occ Thal: CLOM ≥83.9–100%; FLV ≥7.7–87.7%

(continued)

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Meyer et al. (2001c)	12 MDD	[^{11}C]DASB	4 weeks open treatment: PAR 20 mg (n = 7), 10 mg (n = 1), or CIT 20 mg (n = 4)	Occupancy after PAR/CIT 20 mg:
	17 HC			Striat 83%/77%
				Thal 75–78%/65–70%
				CingA 76–77%/77–79%
				No relationship between HDRS score and occupancy level
				Striatal Occ increased with higher serum levels of paroxetine, with app. 85% Occ at serum levels of 28 µg/L
Parsey et al. (2000)	2 HC (males only)	[^{11}C] McN5652	PAR 60 or 80 mg single dose prior to 2nd scan	Occ PAR 60 mg (n = 1):
				Amygd 64.8%, Hip 46.0%, Thal 38.4%, Midbr 83.9%, CingA 26.4%
				Occ PAR 80 mg (n = 1): data not reported
Tauscher et al. (1999)	1 patient with MDD and bulimia	[^{123}I]β-CIT	FLX 60 mg (no baseline)	Occ[b] of app. 41% in Thal and Hypothal was estimated
Hiltunen et al. (1998)	5 HC	[^{123}I] nor-β-CIT	CIT 30 mg 3 h *prior* to injection (n = 1); CIT 20 mg (n = 1), VLX 37.5 mg (n = 1) 1 h *after* injection vs. untreated (n = 2)	CIT 30 mg 3 h *prior* to injection BP_{ND} midbrain 52% less than in untreated subjects. For venlafaxine and citalopram 20 mg, no data given

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Pirker et al. (1995)	13 MDD 11 HC	[^{123}I]β-CIT	≥1 week CIT 20 mg (n = 5), 40 mg (n = 6), and 60 mg (n = 1); one untreated patient	CIT-treated patients showed sign. decrease in Thal, Hypothal, and Midbr BP_{ND} compared to controls[b]
				No difference in binding between CIT 20 and 40 mg

Abbreviations: *Amygd* Amygdala, *CIT* Citalopram, *CLOM* Clomipramine, *DLX* Duloxetine, *EsCIT* Escitalopram, *FLV* Fluvoxamine, *FLX* Fluoxetine, *Hypothal* Hypothalamus, *Midbr* Midbrain, *Occ* Occupancy, *OFC* Orbitofrontal cortex, *PAR* Paroxetine, *SER* Sertraline, *Thal* Thalamus/diencephalon, *VLX* Venlafaxine

[a]The change in binding ratios is estimated as the change in BP_{ND} after treatment relative to the before treatment scan unless stated otherwise

[b]No baseline scan; occupancy relative to BP_{ND} in untreated healthy controls

[c]Three different tracer kinetic models revealed similar outcomes

[d]Scans obtained 20–24 h after injection of radioligand

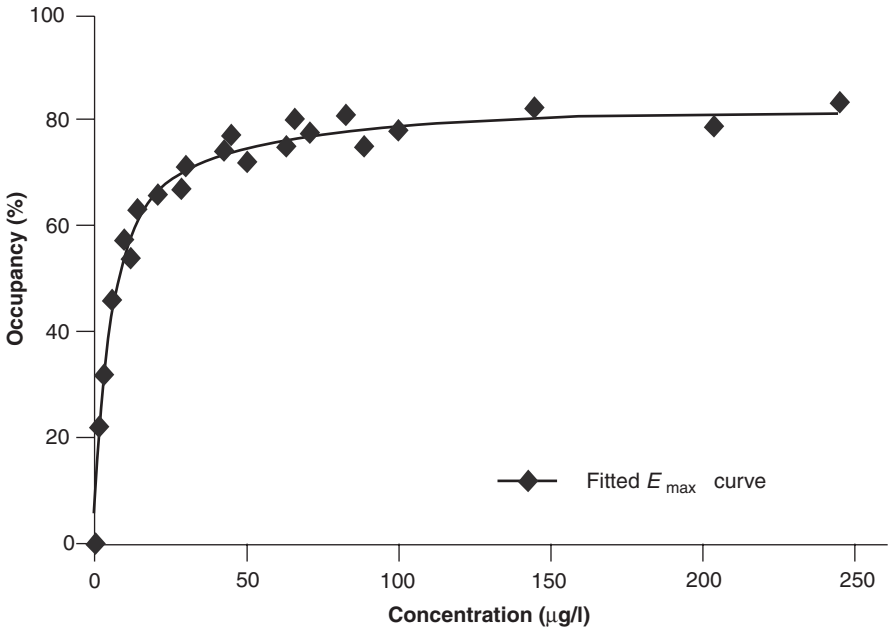

Fig. 4.1 Concentration–occupancy curve. This figure shows a hypothetical E_{max} curve. The curve is defined with the formula $y = (a*x)/(b + x)$, in which a represents the maximum binding (B_{max}) and b the concentration with 50% occupancy (EC_{50}). Here B_{max} = 82.8% ± 0.85 (SE) and EC_{50} = 5.09 µg/L ± 0.32 (SE)

that the lowest therapeutic doses of SSRIs were associated with ≥80% occupancy in the striatum, which was assumed to be necessary for a clinical response (Meyer et al. 2001c, 2004b; Suhara et al. 2003). However, later studies did not unequivocally replicate this finding (Catafau et al. 2006; Kugaya et al. 2004; Ruhe et al. 2009b, c; Smith et al. 2011; Rominger et al. 2015), which might also be attributable to the difference in radiotracers ([^{11}C]DASB versus [^{123}I]β-CIT) or an elderly population (Smith et al. 2011).

Clinical response was not associated with occupancy of SERT in the striatum, thalamus, or midbrain (Cavanagh et al. 2006; Meyer et al. 2004b; Ruhe et al. 2009b, c; Rominger et al. 2015). However, in a voxel-wise analysis in elderly patients, Smith et al. found significant associations of SERT occupancy with decrease in HDRS scores in the ACC; middle and inferior frontal, temporal, and parahippocampal gyrus; and cuneus. These regions also showed a change in glucose metabolism, which—in addition—was associated with decreases in HDRS scores (Smith et al. 2011). One study showed an association between SERT occupancy by the SSRI paroxetine (20 mg/day) and decrease in HDRS scores, but only in carriers of the L_A/L_A SERT promoter polymorphism. Higher occupancy was associated with more decrease in HDRS ($p < .001$) (Ruhe et al. 2009c). Previously, the L/L polymorphism had been associated with superior treatment effects (Serretti et al. 2007), while non-S/S carriers showed more favorable structural and functional anatomy of the amygdala–cingulate feedback circuitry (Pezawas et al. 2005). A possible explanation could be that the limbic–cortical network and the serotonergic innervations are developed more flexibly in non-S/S carriers. The significant association between higher SERT occupancy and increased reduction of symptoms in L_A/L_A carriers might be indicative for this broader range of regulation for the serotonergic system. Higher SERT occupancy might then result in more effects of serotonergic antidepressants in L_A/L_A carriers.

Our group also investigated the increase of SERT occupancy in a randomized, placebo-controlled dose-escalation study. This study showed that increasing the dose of paroxetine to 50 mg/day did not increase response rates nor improve changes in HDRS scores. Moreover, the SERT occupancy did not increase more after true dose escalation relative to the placebo dose escalation (Ruhe et al. 2009b). This study thus provided a rationale for the observed flat dose–response relationship for SSRIs (Adli et al. 2005; Corruble and Guelfi 2000; Ruhe et al. 2006). In the same study, we examined whether four polymorphisms of the ABCB1 gene coding for the P-glycoprotein efflux pump, responsible for the intracerebral concentrations of paroxetine and antidepressants in general (Cordon-Cardo et al. 1989), influenced SERT occupancy in 38 MDD patients after 6 weeks of paroxetine treatment (20 mg/day). Although we found significantly higher maximum SERT occupancies in the E_{max} curves for the rs1128503 and rs2032582 SNPs (C-carriers and G-carriers, respectively), this did not affect clinical responses (Simoons et al. 2020). Since previous meta-analyses showed equivocal or nonexisting associations of these SNPs with clinical response as well, the clinical relevance of our differences in SERT occupancy curves remains to be elucidated further (Breitenstein et al. 2015; Niitsu et al. 2013). In addition, in a smaller subsample ($n = 15$ patients) of this study, we showed

that higher SERT occupancy by paroxetine (20–50 mg/day) in both amygdalae was associated with greater attenuation of left amygdala activation by negative facial expressions as measured with fMRI (Ruhé et al. 2014). Given that the change in left amygdala activation was significantly correlated with (proportional) change in HDRS, this finding may provide a rationale for decreased limbic activity seen during treatment of MDD. It might also explain the rapid decrease in negative attentional bias and amygdala activation caused by SSRIs.

Finally, occupancy studies are increasingly used in the development and evaluation of the effects of antidepressants. First, several SERT occupancy studies indicated that the relationship between the in vitro affinity for SERT of SSRIs and their in vivo occupancy is poor. Therefore, with phase I occupancy studies, a minimal effective dose of new antidepressants might be determined better. Second, differences between isoforms of new antidepressants can be investigated. For example, Kasper et al. (2009) combined two occupancy studies (Klein et al. 2006, 2007) with an interesting approach: they compared the occupancy curves of citalopram and escitalopram (which contains only the S-enantiomer, while citalopram contains both the S-enantiomer and the pharmacologically inactive R-enantiomer) during acute and prolonged treatment and showed that although doses were equivalent, prolonged treatment for 10 days with escitalopram resulted in significantly higher occupancy values (81.5 ± 5.4%) than citalopram (64 ± 12.7%; $p < .01$). Furthermore, they observed a trend that, relative to acute single doses, after prolonged treatment the E_{max} of SERT occupancy by serum level curves increased in escitalopram, while it decreased for citalopram. This could be explained by the longer half-life of the R-enantiomer, which will accumulate over time and will compete more for binding to the SERT (despite its lower affinity relative to the S-enantiomer). Because the R-enantiomer binds to a low-affinity allosteric site on the SERT (Mansari et al. 2007), this will preclude binding of the S-enantiomer to the primary 5-HT binding site (but not the ligand), resulting in lower SERT blockade in the end.

In conclusion, occupancy studies are useful in the development of new tracers, in the study of the properties and dosing of new antidepressants, and in the study of the relationship between clinical and neurobiological effects of antidepressants.

4.3.1.3 Serotonin Receptor Imaging

5-HT_{1A}

The 5-HT_{1A} receptors are presynaptically localized on serotonergic cell bodies situated in the raphe nuclei in the midbrain and postsynaptically in terminal areas. These receptors are G-protein-coupled receptors that have an inhibitory influence on neuronal firing (Barnes and Sharp 1999). Therefore, antidepressants like SSRIs that increase synaptic 5-HT in the projection areas may inhibit 5-HT neuronal activity in early stages of treatment, and this inhibition can be prevented by administration of a 5-HT_{1A} antagonist like WAY-100635 (Gartside et al. 1997) or pindolol.

In vivo imaging of 5-HT_{1A} receptors by PET can therefore contribute to the understanding of the mechanisms of antidepressant drugs and elucidate underlying mechanisms of nonresponders to SSRIs and the involvement of desensitization of

autoreceptors. So far, mainly PET tracers for 5-HT_{1A} receptor have been developed (Passchier and van Waarde 2001). However, only [*carbonyl*-^{11}C]WAY-100635 (or [^{11}C]WAY-100635) has been used for studies which compare healthy controls to patients with MDD. WAY-100635 is a highly selective antagonist for the 5-HT_{1A} receptor; however, the synthesis of [^{11}C]WAY-100635 is technically challenging. Another 5-HT_{1A} antagonistic tracer used is [^{18}F]MPPF; this tracer has lower affinity for the 5-HT_{1A} receptor and lower brain uptake, probably because it is a substrate for P-glycoprotein, an efflux pump in the BBB. As the cerebellum is almost devoid of 5-HT_{1A} receptors, it was proposed that this region could be used as a reference region for kinetic analysis. Nevertheless, the outcome measures of the kinetic model used to analyze BP can differ depending on which activity measure is used as a reference: BP_{ND} (specific binding in respect to non-displaceable radioligand in tissue), BP_F (specific binding in respect to free radioligand in tissue), or BP_P (specific binding in respect to total parent radioligand in plasma) (Innis et al. 2007).

Twelve studies found an overall decrease in BP_{ND} or BP_P in several brain areas expressing postsynaptic 5-HT_{1A} receptors, and especially in the DRN, which expresses presynaptic 5-HT_{1A} receptors (Table 4.4A, B). In contrast six studies found an increase notably when BP_F was used as an outcome measure. One study did not detect an effect.

The most pronounced effects were found by Drevets et al. (effect size >1); this study also included patients with BD (Drevets et al. 1999, 2007). The largest decreases in BP_{ND} were found in the mesiotemporal cortex (−28%), hippocampus (−25%), and raphe nuclei (−42%). Another study in remitted MDD patients also found large effects in cortical areas, but no effect in the raphe nuclei (Bhagwagar et al. 2004). Sargent et al. also found that there is a reduction in 5-HT_{1A} binding in the medial temporal cortex, temporal pole, orbitofrontal cortex, anterior cingulate cortex, and insula cortex of MDD patients, which did not change when patients used antidepressants (Sargent et al. 2000). Similar results were found in MDD patients on SSRIs that additionally received electroconvulsive therapy. A reduction in BP_{ND} in the raphe nuclei was found in these patients, and this was not normalized after electroconvulsive therapy (Saijo et al. 2010). Hirvonen et al. found an overall decrease in BP_P, but not in BP_{ND}, and there was no significant difference in any individual brain region (Hirvonen et al. 2008a). In this same cohort, they tested the effect of the SSRI fluoxetine or psychotherapy on 5-HT_{1A} binding and found that psychotherapy increased BP_{ND} (with the cerebellum as reference tissue) compared to fluoxetine treatment and healthy controls. Fluoxetine did not induce any changes compared to healthy controls, although the clinical outcome was the same as in the patients treated with psychotherapy (Karlsson et al. 2010). Another study found only an effect on BP in the raphe nuclei (Meltzer et al. 2004). In postpartum depression (including patients with bipolar depression), there also seems to be a reduction of 5-HT_{1A} BP_{ND} in various cortical areas like the orbitofrontal, cingulate, temporal, and occipital cortex (Moses-Kolko et al. 2012). In addition a reduction in 5-HT_{1A} binding in the raphe nucleus was reported.

Table 4.4 Results of 5-$HT_{1A/B}$ imaging studies (PET) in patients with major depression as compared to controls

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
A. Unipolar depression 5-HT_{1A}					
Miller et al. (2013b)	21/51	[^{11}C] WAY-100635	Unmedicated	Raphe nuclei: 56% ↑ BP_F Amygdala: 37% ↑ BP_F Hippocampus: 29% ↑ BP_F Parahippocampal gyrus: 45% ↑ BP_F Temporal cortex: 39% ↑ BP_F Anterior cingulate: 28% ↑ BP_F Cingulate: 43% ↑ BP_F Dorsolat. prefront. cortex: 40% ↑ BP_F Medial prefrontal cortex: 26% ↑ BP_F Ventral prefrontal cortex: 38% ↑ BP_F Insula: 32% ↑ BP_F Occipital cortex: 44% ↑ BP_F Parietal cortex: 44% ↑ BP_F	1.33 1.02 0.94 1.37 1.19 1.20 1.33 1.15 0.99 1.15 1.06 1.26 1.24
Lothe et al. (2012)	6/18	[^{18}F]MPPF	Naive	Medial orbital cortex: 25% ↓ BP_{ND}	1.36
				Perigenual anterior cingulate cortex: 23% ↓ BP_{ND}	1.39
				Dorsal anterior cingulate cortex: 22% ↓ BP_{ND}	1.31
				Raphe nuclei: 30% ↓ BP_{ND}	1.18

(continued)

Table 4.4 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
Saijo et al. (2010)	9/9	[^{11}C] WAY-100635	Paroxetine/ fluvoxamine	Prefrontal cortex: 5.8% ↓ BP_{ND} (ns)	0.24
				Medial frontal cortex: 6.2% ↓ BP_{ND} (ns)	0.22
				Temporal cortex: 4.4% ↓ BP_{ND} (ns)	0.19
				Parietal cortex: 2.2% ↓ BP_{ND} (ns)	0.08
				Occipital cortex: 1.9% ↑ BP_{ND} (ns)	0.06
				Anterior cingulate: 7.9% ↓ BP_{ND} (ns)	0.34
				Insula: 7.9% ↓ BP_{ND} (ns)	0.31
				Amygdala: 4.6% ↑ BP_{ND} (ns)	0.21
				Hippocampus: 7.8% ↓ BP_{ND} (ns)	0.37
				Midbrain raphe: 32% ↓ BP_{ND}	1.36
Parsey et al. (2010)	22/9	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Overall: ↑ BP_F (no exact values given)	0.85
Miller et al. (2009a)[a]	28[b] (15 remitted, 13 naive)/51 (healthy)	[^{11}C] WAY-100635	Drug-free (>6 months)	Overall: ↑ BP_F (no exact values given)[c]	[d]
				Overall: 11.4% ↑ BP_{ND} with cerebellar white matter as ref (ns)	
				Overall: 22.6% ↓ BP_{ND} with cerebellar gray matter as ref	
Hirvonen et al. (2008a)[a]	21/15	[^{11}C] WAY-100635	Drug-free (>4 months)	Overall: 19% ↓ BP_P	0.69
Mickey et al. (2008)	14/17		Drug-free (>6 months)	Overall: no effect	[d]

Table 4.4 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
Moses-Kolko et al. (2008)	9 postpartum (4 BD)/7		Drug-free (>3 weeks)	Left lateral orbitofrontal cortex:18% ↓ BP_{ND}	1.35
				Right lateral orbitofrontal cortex: 23% ↓ BP_{ND}	1.96
				Mesiotemporal cortex: 22% ↓ BP_{ND}	2.38
				Subgenual anterior cingulate: 28% ↓ BP_{ND}	2.46
				Pregenual anterior cingulate: 23% ↓ BP_{ND}	2.10
				Postcentral gyrus: 19% ↓ BP_{ND}	1.26
				Occipital cortex: 19% ↓ BP_{ND}	1.42
				Raphe nucleus: 11% ↓ BP_{ND}	0.78
Drevets et al. (2007)	16 (2 BD)/8	[^{11}C] WAY-100635	Drug-free (>3 weeks)	Mesiotemporal cortex: 28% ↓ BP_{ND}	1.19
				Raphe: 42% ↓ BP_{ND}	1.96
Parsey et al. (2006d)[a]	22[b] (13 remitted)/43	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Overall: ↑ BP_F unremitted vs. remitted	[d]
Parsey et al. (2006e)[a]	28[b] (13 naive)/43	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Overall: ↑ BP_F drug-naive	[d]
Bhagwagar et al. (2004)[a]	14 (remitted)/18	[^{11}C] WAY-100635	Drug-free (>6 months)	Several cortical areas: 17% ↓ BP_{ND}	4
				Raphe: 1% ↓ BP_{ND} (ns)	0.22
Meltzer et al. (2004)[a]	17 (late-life)/17	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Raphe: 34% ↓ BP_{ND}	0.98
				Lateral orbitofrontal cortex: 8% ↓ (ns)	0.32
				Pregenual cingulate: 4% ↓ (ns)	0.13
				Subgenual cingulate: 2% ↓ (ns)	0.06
				Hippocampus: 15% ↓ (ns)	0.32
				Mesial temporal cortex: 8% ↓ (ns)	0.20
				Occipital cortex: 1% ↓ (ns)	0.03

(continued)

Table 4.4 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
Rabiner et al. (2004)[a]	7/7	[^{11}C] WAY-100635	Venlafaxine	Raphe: 10% ↓ BP_F (ns)	0.74
				Rest: 17% ↑ BP_F	1.28
Sargent et al. (2000)	15/18	[^{11}C] WAY-100635	Drug-free (>3 months)	Overall: 10.8% ↓ BP_{ND} Medial temporal cortex right: 10.3% ↓ BP_{ND}	0.69
				Temporal pole right : 8.8% ↓ BP_{ND}	0.85
				Temporal pole left: 12.1% ↓ BP_{ND}	1.04
				Orbitofrontal cortex right: 15.8% ↓ BP_{ND}	1.06
				Orbitofrontal cortex left: 12.9% ↓ BP_{ND}	0.79
				Ventral anterior cingulate cortex right: 17% ↓ BP_{ND}	0.88
				Dorsal anterior cingulate cortex right: 15.1% ↓ BP_{ND}	0.79
				Dorsal anterior cingulate cortex left: 14% ↓ BP_{ND}	0.94
				Insula cortex right: 12.9% ↓ BP_{ND}	0.88
				Insula cortex left: 13% ↓ BP_{ND}	0.88
				Dorsolateral prefrontal cortex left: 11.4% ↓ BP_{ND}	0.59
B. Bipolar depression 5-HT_{1A}					
Nugent et al. (2013)	26 (BD)/37	[^{18}F] FCWAY	Unmedicated	Amygdala and hippocampus: 12% ↓ BP_{ND}	[d]
Sargent et al. (2010)[a]	8 (euthymic BD)/8	[^{11}C] WAY-100635	On different drugs	Overall: 2% ↓ BP_{ND} (ns)	0.12
Sullivan et al. (2009)[a]	32 (BD)/47	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Overall: 25.1% ↑ BP_F	[d]
				Male	
				Raphe: 102% ↑ BP_F	

Table 4.4 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
				Forebrain: 29–50% ↑ BP_F	
Drevets et al. (1999)	12 (4 BD)/8	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Mesiotemporal cortex: 27% ↓ BP_{ND} Raphe: 42% ↓ BP_{ND} Hippocampus: 25% ↓ BP_{ND}	1.16 1.27 1.12
C. Unipolar depression 5-HT_{1B}					
Murrough et al. (2011)	10/10	[^{11}C]P943 (5-HT_{1B})	Drug-free (>4 weeks)	Ventral striatum/ pallidum left: 16.1% ↓ BP_{ND}	1.85
				Ventral striatum/ pallidum right: 21.1% ↓ BP_{ND}	1.49

The change in binding ratios is estimated from several brain regions of depressive patients and compared to reported healthy control data

[a]Other statistical test than *t*-test used

[b]Same sample of patients

[c]Values given reflect comparison of patients in remission and healthy controls; comparable results are found for drug-naive MDD patients

[d]No individual data available to calculate the effect size

Only one study used [^{18}F]MPPF as a tracer to compare controls with depressive patients and effects of treatment. As a pilot study, the sample size was small, but a general decrease in BP_{ND} in depressive patients was found. Moreover, 30 days of SSRI treatment increased the reduced BP_{ND} to control levels in the medial orbital cortex (Lothe et al. 2012). Intriguingly, two recent studies have linked 5-HT_{1A} receptor binding to specific cognitive features of MDD (Schneck et al. 2020; Langenecker et al. 2019).

Several studies found an overall increase of BP_F in the brain when healthy controls were compared to MDD patients. The most striking effects were found in patients with BD where an increase in BP_F of 102% was found in the raphe nuclei and 29–50% in the forebrain. Interestingly, this difference was only present in males and not in females (Sullivan et al. 2009).

Other studies also found an increase in BP_F, although heterogeneous results were found in respect to remission and the effects of treatment. Miller and colleagues showed that the increase in 5-HT_{1A} BP_F was similar in patients with symptomatic MDD and patients who had recurrent MDD, but were in remission (Miller et al. 2009a). This is in line with results found by Rabiner et al., who still found an increase in patients who were currently treated with venlafaxine (Rabiner et al. 2004). Contradictorily, Parsey et al. found a significant increase in BP_F in MDD patients that were drug-naive, but as soon as patients had used antidepressants in their lives, the effect was gone (Parsey et al. 2006e). These authors replicated their

findings in a new cohort, where depressive patients who had not recently received antidepressants were compared with healthy controls (Parsey et al. 2010). Additionally, a higher BP_F was observed in non-remitted patients compared to remitted patients after treatment (Parsey et al. 2006d), perhaps an indication that 5-HT_{1A} binding is related to SSRI treatment response. Only two studies did not find any effect on 5-HT_{1A} binding in depressive patients. One study included euthymic patients with BD who used different kinds of medication and did not find differences (Sargent et al. 2010). The second study included non-medicated depressive patients and reported a relation between MAO-A genotype (the enzyme that deaminates serotonin) and 5-HT_{1A} binding in women (Mickey et al. 2008). The difference was apparent in brain regions like the medulla, midbrain, frontal cortex, hippocampus, and amygdala. The different MAO genotypes were not related to disease, which questions whether these genotypes and the related difference in 5-HT_{1A} binding are indeed related to MDD.

Some studies found a relationship to scores of depressive severity as measured by the HDRS (Meltzer et al. 2004; Rabiner et al. 2004). Rabiner et al. discovered that healthy controls showed a higher occupancy of pindolol. This preferential occupancy was negatively correlated to depression severity on HDRS (Rabiner et al. 2004).

Antidepressant treatments appear to decrease 5-HT_{1A} binding. This has been shown for SSRIs in a PET study of 19 MDD patients before and after 5–9-week treatment with either paroxetine, citalopram, or escitalopram, where raphe nuclei [^{11}C]WAY-100635 binding was lower posttreatment irrespective of the magnitude of antidepressant treatment response (Gray et al. 2013). Such an antidepressant-associated downregulation of 5-HT_{1A} autoreceptor binding appears to reverse within 2 weeks of medication discontinuation (Metts et al. 2019). Moreover, a [^{11}C]WAY-100635 PET study in 12 patients with severe MDD undergoing electroconvulsive therapy (ECT) (of whom 10 were responders) showed global decreases in serotonin 5-HT_{1A} binding in the projection areas. No correlation with the magnitude of antidepressant response was detected though (Lanzenberger et al. 2013). On the other hand, in bipolar depression, mood stabilizers (lithium or divalproex) seem to decrease 5-HT_{1A} receptor binding, most prominently in the amygdala and hippocampus (Nugent et al. 2013).

Finally, a few studies have suggested that 5-HT_{1A} receptor binding at baseline can help predict antidepressant treatment response in unipolar depression. Miller et al. (2013b) showed that patients with the highest binding at baseline were most likely to respond successfully to escitalopram treatment. Likewise, in a naturalistic study in bipolar depression (n = 41), higher 5-HT_{1A} receptor binding at baseline predicted remission with treatment with mixed pharmacological approaches (Lan et al. 2013). Also in bipolar depression (n = 27), lithium monotherapy treatment response was related to baseline serotonergic markers including 5-HT_{1A} receptor binding ([^{11}C]-CUMI-101) and 5-HTT binding ([^{11}C]-DASB) such that, in contrast to unipolar depression, the lower the binding, the better response (Ananth et al. 2020). In this study, 5-HT_{1A} binding was able to predict remission with 85% accuracy (87% sensitivity, 80% specificity).

In summary, it appears that 5-HT_{1A} receptors play a role in symptomatology and recovery of depression in some patient groups. Because not all patient groups are similar and almost none of the patients are drug-naive, interpretation of this collection of 5-HT_{1A} studies remains problematic. Although PET imaging shows that there probably is a difference in 5-HT_{1A} receptor binding in depressed patients, the direction of this change appears to be dependent on the kinetic model used.

Several of the studies mentioned above show a trend toward a difference in distribution volume in the cerebellum between healthy controls and depressed patients (Hirvonen et al. 2008a; Meltzer et al. 2004; Miller et al. 2009a). This could severely compromise the results when the cerebellum is used as a reference tissue for kinetic analysis. Indeed, Miller and colleagues compared different outcome parameters to relate to previously performed studies where BP_{ND} was measured instead of BP_F. While they found an increase in BP_F, they found a nonsignificant increase in BP_{ND} when cerebellar white matter was used as a reference tissue, a significant decrease in BP_{ND} when cerebellar gray matter was used as a reference tissue, and no effect when BP_P was used as an outcome measure. These conclusions were also drawn by their colleagues (Parsey et al. 2010). They additionally showed that the BP_{ND} in cerebellar gray matter decreases when the 5-HT_{1A} antagonist pindolol is applied, while this does not account for cerebellar white matter. Therefore, we conclude that the decrease in BP_{ND} found in most studies using the cerebellum as a reference tissue is due to changes in specific binding in the cerebellum. When considering studies that used an arterial input function only, a higher 5-HT_{1A} availability has been observed and replicated (Parsey et al. 2006d, e; Miller et al. 2013b). Therefore, most probably, MDD is associated with an increase in binding to 5-HT_{1A} receptors, which is in line with the observation that both SSRIs and ECT antidepressant treatment of MDD lower 5-HT_{1A} receptor binding as mentioned above and that 5-HT_{1A} binding might be useful to predict treatment outcome (although inconsistent findings exist). It remains difficult to judge whether the observed differences reflect state or trait effect, as some studies do not find an effect of remission or treatment while others do.

Also postmortem studies show contradictory results. Some studies show a reduction in mRNA or radioligand binding (Arango et al. 2001; Lopez et al. 1998), while others show an increase in 5-HT_{1A} receptor binding (Stockmeier et al. 1998).

5-HT_{1B}

The 5-HT_{1B} receptor is another serotonergic autoreceptor, which is present on serotonergic neurons in terminal regions and regulates the release of 5-HT in these regions. Activation of this receptor decreases the amount of 5-HT released in the synapse. Indeed, the amount of 5-HT released in the extracellular space by an SSRI, as measured with microdialysis in rats, is greatly increased by simultaneous 5-HT_{1B} antagonism (Cremers et al. 2000). However, it seems that overexpression of these receptors in the dorsal raphe nuclei actually reduces fear and depressive-like behavior in rats, which is contradictory to the hypothesis that antagonism and the consequential increase in 5-HT would lead to higher efficacy of antidepressants (McDevitt et al. 2011). An experimental study in mice suggested that the antidepressant

properties of the 5-HT_{1B} agonist anpirtoline depend on 5-HT_{1B} heteroreceptors present in the substantia nigra and striatum, but not on the autoreceptors present on 5-HT neurons (Chenu et al. 2008). Interestingly, in the ventral tegmental area and nucleus accumbens, 5-HT_{1B} receptor agonists are known to increase dopamine release, possibly through inhibiting GABA release from interneurons (Yan et al. 2004; Yan and Yan 2001). These preclinical data suggest a role for 5-HT_{1B} receptors in antidepressant effects; at least some of the antidepressant effects may be related to the interaction with the dopaminergic system. In addition, single nucleotide polymorphisms in the 5-HT_{1B} receptor gene seem to be related to antidepressant response in patients with major depression (Villafuerte et al. 2009; Xu et al. 2012). Antidepressant treatment mechanisms may also include reduced 5-HT_{1B} receptor binding in the dorsal brain stem as shown in response to cognitive behavioral therapy of MDD (Tiger et al. 2014).

Only one recent study with a recently developed PET radioligand ([^{11}C]P943) examined the binding of 5-HT_{1B} receptors in MDD patients (Table 4.4C). In this study, a decrease in BP_{ND} was found in the left and right ventral striatum/pallidum, with effect sizes of 1.85 and 1.49, respectively (Murrough et al. 2011). These findings are in accordance with the results of Chenu et al., who found that the antidepressant effect of a 5-HT_{1B} agonist depends on stimulation of heteroreceptors and not on the stimulation of autoreceptors (Chenu et al. 2008).

5-HT_{2A}

The role of the serotonin 2A receptor (5-HT_{2A}) in MDD has been extensively studied in cross-sectional settings, but in BD no studies on 5-HT_{2A} have been done yet. Investigations in MDD have been partly motivated by the fact that serotonergic neurotransmission is critical in the mechanisms of action of antidepressants. Those actions include direct 5-HT_{2A} receptor inhibition and 5-HT_{2A} receptor downregulation, for example, as seen with the SSRIs (Carr and Lucki 2011; Gray and Roth 2001; Meyer et al. 2001a). Also, the 5-HT_{2A} receptor has been one of the few serotonin receptor subtypes in the serotonergic neurotransmitter system where several PET and SPECT tracers have been available for selective mapping and quantification in the living human brain (Paterson et al. 2013). Five radioligands for the 5-HT_{2A} receptor have been used successfully in human studies: the SPECT radioligand [^{123}I]R91150 and the PET radioligands [^{18}F]setoperone, [^{18}F]altanserin, [^{18}F]deuteroaltanserin, and [^{11}C]MDL 100,907. Even though [^{123}I]R91150 displays a lower signal-to-noise ratio and SPECT provides lower resolution compared to the available PET methods, it offers some advantages due to the more widespread availability of SPECT facilities. However, it has not directly been used to study the pathophysiology of MDD or BD. Radiosynthesis of the ^{18}F-labeled R91150 is complicated and therefore has not been feasible in clinical studies. The radioligand [^{18}F]setoperone is less selective than [^{18}F]altanserin and [^{11}C]MDL 100,907 due to a relative high affinity for dopamine D_2 receptors. Nevertheless, due to the differential localization of the 5-HT_{2A} relative to D_2 receptors, [^{18}F]setoperone has been applied successfully in several studies. Of the PET radioligands, [^{18}F]altanserin has continued to be the most widely used, despite its lipophilic radiometabolite. This use is

especially due to its longer-lived ^{18}F-label, which enables the application of a bolus/infusion paradigm that allows for acquisition under steady-state conditions and overcomes the modeling issue with the lipophilic metabolites. [^{18}F]deuteroaltanserin was developed in order to identify a ligand with no lipophilic metabolites crossing the blood–brain barrier; however, with the steady-state modeling of [^{18}F]altanserin, this was no longer needed. [^{11}C]MDL 100,907 is a more selective 5-HT$_{2A}$ ligand than [^{18}F]altanserin in vitro, but is much less widely used as a 5-HT$_{2A}$ radioligand for in vivo studies than [^{18}F]altanserin. The reason for this might be the shorter-lived ^{11}C-label and more demanding modeling requirements for [^{11}C]MDL 100,907 that under ideal circumstances necessitate arterial blood sampling. However, seemingly, reference tissue modeling methods may be feasible for larger group comparisons in populations that tolerate the longer acquisition time of 90–120 min as compared to 40 min for bolus/infusion [^{18}F]altanserin (Talbot et al. 2012). In summary, at the current state of tracer evolution, [^{18}F]altanserin PET and [^{11}C]MDL100,907 PET are the best tools for selective 5-HT$_{2A}$ receptor imaging though with some limitations in subcortical regions where signal-to-noise ratio is low (Paterson et al. 2013). However, these tracers are antagonist ligands and bind to the total pool of both membrane-bound and internalized 5-HT$_{2A}$ receptors. As such, the interpretations of the imaging findings are limited with respect to understanding the role of the biologically active part of the 5-HT$_{2A}$ receptor system which is highly relevant for the pathophysiology of MDD (also see Sect. 4.4.1).

Hereafter, we will outline how postmortem data, data from at-risk individuals, and recent in vivo imaging data, based on highly selective tracers and patients that were not recently medicated, are converging to support that high prefrontal 5-HT$_{2A}$ receptor binding is implicated in MDD. The majority of postmortem studies in suicide victims of major depression report increased 5-HT$_{2A}$ receptor binding in the prefrontal cortex particularly in the Brodmann areas 8 and 9 (Arango et al. 1997; Stockmeier 2003). Table 4.5 summarizes the main findings of in vivo brain imaging studies of 5-HT$_{2A}$ in patients with current or remitted major depression relative to healthy controls.

Initial findings of in vivo receptor imaging studies were contradictory (Attar-Levy et al. 1999; Biver et al. 1997; D'haenen and Bossuyt 1994; Meltzer et al. 1999; Messa et al. 2003; Meyer et al. 1999, 2003; Yatham et al. 2000) with two studies reporting increased, four studies decreased, and three studies similar 5-HT$_{2A}$ availability in MDD patients versus controls. However, two recent studies with selective PET tracers and good control of treatment bias confirmed the postmortem observations in recovered, unmedicated remitted patients with a history of MDD (Bhagwagar et al. 2006) and in unmedicated patients (drug-free >6 months) with severe depression and high levels of dysfunctional attitudes (Meyer et al. 2003), showing increased 5-HT$_{2A}$ availability in MDD patients relative to controls. Furthermore, higher dysfunctional attitudes were correlated with higher 5-HT$_{2A}$ availability. However, one study with the highly selective PET tracer [^{18}F]altanserin by Mintun et al. reported an isolated decrease in hippocampal 5-HT$_{2A}$ receptor binding but no significant differences in cortical regions in depressed patients compared to controls (Mintun et al. 2004). Interestingly, a

Table 4.5 Results of serotonin receptor 2A (5-HT_{2A}) imaging studies (PET/SPECT) in patients with current or remitted MDD as compared to controls

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
Bhagwagar et al. (2006)[a]	20 remitted MDD	[^{11}C]MDL	Medication-free >6 months	Frontal 19%↑	NA
	20 HC			Parietal 25%↑	
				Occipital 19%↑	
				Temporal no difference →	
				Positive correlation with dysfunctional attitudes in recovered patients	
Mintun et al. (2004)	46 MDD 29 HC	[^{18}F] altanserin	Medication-free (4 weeks)	Hippocampus 29% ↓	−0.71
				Pregenual AC 17%↓	−0.36
				Subgenual AC 21% ↓	−0.41
				Gyrus rectus 14% ↓	−0.30
				Dorsolateral prefrontal 16% ↓	−0.36
				Lateral temporal 12% ↓	−0.31
				Superior parietal 17% ↓	−0.38
				Occipital 9% ↓	−0.21
Meyer et al. (2003)	22 MDD	[^{18}F] setoperone	Medication-free (6 months)	No differences between the total groups	NA
	22 HC			Cortex↑ by 21–29% (particularly middle frontal gyrus bilaterally) in severe depression, $N = 11$	NA
				Positive association with dysfunctional attitudes	NA

Table 4.5 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
Messa et al. (2003)[b]	19 MDD	[^{18}F] fluoroethyl-spiperone	Antidepressant naive	Frontal 26%↓	−1.03
	20 HC		Benzodiazepines	AC 22%↓	−0.79
				Temporal 22%↓	−1.12
				Occipital 22%↓	−0.92
				Striatum 7%↓	−0.48
	15 MDD on medication		Paroxetine treatment (4th week)	Frontal 5%↓	−0.19
				AC 6%↓	−0.24
	20 HC			Temporal 4%↓	−0.14
				Occipital 4%↑	0.12
				Striatum 1%↓	−0.08
Yatham et al. (2000)	20 MDD	[^{18}F] setoperone	Medication-free (2 weeks)	Left inf. frontal gyrus 23%↓	−0.82
	20 HC			Right AC 27%↓	−0.93
				Left fusiform gyrus 22%↓	−0.88
				Right inf. temporal gyrus 22%↓	−0.83
				Right medial frontal gyrus 24%↓	−0.87
				Right cingulate gyrus 27%↓	−0.91
				Left sup. temporal gyrus 25%↓	−0.85
Attar-Levy et al. (1999)	7 MDD	[^{18}F] setoperone	Antidepressant-free >2 weeks	Frontal 6%↓	−0.26
	7 HC		Benzodiazepines	Temporal 1%↓	−0.05
				Parietal 3%↓	−0.16
				Occipital 16%↑	0.70
	7 MDD treated		Clomipramine 150 mg for 3 weeks	Frontal 25%↓	−1.10
	7 HC			Temporal 20%↓	−1.09
				Parietal 21%↓	−1.15
				Occipital 5%↓	−0.22
Meltzer et al. (1999)[c]	11 MDD	[^{18}F] altanserin	Untreated	No difference in all regions assessed →	NA
	10 HC				

(continued)

Table 4.5 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
Meyer et al. (1999)	14 MDD	[^{18}F] setoperone	Medication-free (>6 months)	Prefrontal cortex 11%↓	−0.31
	19 HC			Right/left ratio prefrontal cortex 1%↑	0.025
Biver et al. (1997)	8 MDD	[^{18}F] altanserin	Medication-free (10 days)	Right orbitofrontal-insular cortex 17%↓	−1.08
	22 HC				
D'haenen et al. (1992)	19 MDD	[^{123}I] ketanserin	Medication-free >7 days (10 pts > 3 weeks)	Sup. frontal 14%↑	0.49
				Central sulcus 1%↑	0.03
				Parietal 21% ↑	1.48
	10 HC			Prefrontal 7%↓	−0.32
				Infero-frontal 7%↑	0.36
				Anterior temporal 1%↓	−0.03
				Posterior temporal1% ↑	0.08
				Occipital 4% ↓	−0.16
				Right/left ratio infero-frontal cortex↑	NA

Outcome represents the change in binding potential as estimated from several cortical regions, anterior cingulate, and hippocampus and compared to reported control data. *Arrows* indicate directions of changes calculated as MDD relative to healthy individuals. Effect size is given as Cohen's *d*. NA, not applicable for calculation of Cohen's *d* based on reported measures from the study

Abbreviations: *MDD* Major depressive disorder, *HC* Healthy controls, *Nr* Number, *pts* Patients, *AC* Anterior cingulate

[a]This study included remitted patients with prior, recurrent depression ≥2 episodes

[b]Two groups of patients were compared with the same group of healthy controls; 20 antidepressant naive and 15 patients treated for 4 weeks with paroxetine

[c]Late-life depression

decrease in hippocampal 5-HT$_{2A}$ receptor availability in depressed patients finds some support in the postmortem literature, however, not consistently (Stockmeier 2003). Although Mintun et al. included a large number of patients, a power analysis of [^{18}F]altanserin PET data showed that in order to avoid type II errors, robust detection of differences in the hippocampus would require a sample size twice as large as their study sample (Haugbol et al. 2007). Furthermore, treatment effects may have biased that study since patients were only off medication for 4 weeks. Therefore, we think that the available imaging data is insufficient to conclude on the potential involvement of hippocampal 5-HT$_{2A}$ receptor disbalances in the pathophysiology of major depression.

Treatment effects and scar effects of prior depressive episodes might bias the data provided from cross-sectional studies in patients with a history of depression.

Therefore, studies linking risk factors for developing MDD and PET markers of serotonergic neurotransmission, in the absence of depressive symptoms, may provide important insight to early pathophysiological mechanisms in the development of MDD. Such studies in healthy, never-medicated individuals have pointed toward an association between high frontal 5-HT_{2A} receptor binding and increased risk (represented by higher neuroticism scores (Fanous et al. 2007; Kendler et al. 1993)) (Frokjaer et al. 2008a), or the combination of high neuroticism scores and familial risk for mood disorders (Frokjaer et al. 2010).

In summary, this postmortem data, data from at-risk individuals, and recent in vivo imaging data are converging to support that high prefrontal 5-HT_{2A} receptor binding is implicated in MDD. This may be due to upregulation of 5-HT_{2A} receptors in cortical regions as a compensatory response to disturbances in serotonin homeostasis with low levels of extracellular serotonin. Indeed, sustained low levels of serotonin upregulate 5-HT_{2A} receptor levels in rodents (Cahir et al. 2007; Heal et al. 1985; Reneman et al. 2002). Generalization of these results and this explanation of possible mechanisms remain speculative, because synaptic levels of serotonin cannot be measured in vivo in humans. Rather than being compensatory to low levels of serotonin, a primary high frontal 5-HT_{2A} receptor setting might also, in itself, be adverse in the context of mood disorders. For example, 5-HT_{2A} receptor agonism stimulates cortisol excretion (Van de Kar et al. 2001), and enhanced cortical 5-HT_{2A} receptor signaling is accompanied by a tendency to perceive or judge an environment as risky (Weisstaub et al. 2006).

As indicated above, some data suggest that hippocampal 5-HT_{2A} receptor binding may be low in MDD. This may relate to the consequences of dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis leading to elevated cortisol excretion observed in individuals at familial risk for mood disorders (Mannie et al. 2007; Modell et al. 1998; Vreeburg et al. 2009) and in both recovered and currently depressed patients (Bhagwagar et al. 2003, 2005; Vreeburg et al. 2009). Indeed, animal models support a differential regulation of 5-HT_{2A} receptor levels induced by chronic stress, with upregulation in the frontal cortex and downregulation in the hippocampus, but only in rats prone to develop learned helplessness—a behavioral model of vulnerability to depression (Dwivedi et al. 2005). However, some of these findings may be due to hippocampal volume loss known to be a vulnerability factor in mood disorders (Gilbertson et al. 2002) and a consequence of long-lasting disease processes (MacQueen and Frodl 2011) rather than specific loss of 5-HT_{2A} receptors.

Even though a high prefrontal 5-HT_{2A} receptor binding appears to be associated with risk factors for developing major depression and with the depressed or remitted state, it is not clear if this is predictive of the risk for developing future major depression in healthy at-risk individuals or relapse in remitted patients. Longitudinal studies with clinical follow-up in high-risk populations and non-medicated patients are needed to explore such potential predictive properties of prefrontal 5-HT_{2A} receptor availability.

4.3.2 Dopamine

Depression is also related to the dopaminergic system. Psychomotor speed, motivation, memory, concentration, and the ability to experience pleasure (hedonia) are all regulated, at least in part, by dopaminergic circuits in the brain. These functions are also prominent clinical features of major depression (Dunlop and Nemeroff 2007). Also, in patients suffering from neuropsychiatric diseases which are characterized by loss of dopaminergic neurons, depression is a prominent feature. Indeed, depression may occur in about one out of three patients suffering from Parkinson's disease (PD) where it is often persistent (Aarsland et al. 2012). Finally, although most antidepressants target serotonin and/or norepinephrine transporters, which may indirectly affect the dopaminergic system, new broad-spectrum antidepressants (triple reuptake inhibitors) or second-generation inhibitors targeting primarily the dopamine and norepinephrine transporter (e.g., bupropion) also increase dopamine levels directly (Nutt et al. 2007; Prins et al. 2011). In this regard, it has been suggested that antidepressants that also increase dopamine signaling may be attractive to treat subgroups of depressed patients, e.g., atypical depression, melancholic depression, and/or treatment-resistant depression (Dunlop and Nemeroff 2007; Nutt et al. 2007; Prins et al. 2011). Therefore MDD (or subgroups of depressed patients) may be characterized by a hypodopaminergic neurotransmission (Dunlop and Nemeroff 2007).

Dopamine has also been linked to BD (Gerner et al. 1976). Mania and depression have been considered as a hyperdopaminergic and hypodopaminergic state, respectively (Cousins et al. 2009). Indeed, psychostimulants can increase dopaminergic activity in the brain (Laruelle et al. 1995, 1997b) and induce behavioral effects similar to mania (Jacobs and Silverstone 1986). Also, most second-generation antipsychotics do block dopamine receptors and have demonstrated efficacy in the treatment of mania (El-Mallakh et al. 2010).

Here, we will review the results of PET and SPECT studies in MDD and (depressed) BD that focused on the dopaminergic system. We will also discuss shortly results of molecular imaging studies on the relationship of an altered dopaminergic system and depression in neuropsychiatric disorders other than MDD/BD, as well as the relationship between dopaminergic markers and depressive symptoms in healthy controls. In addition, we will consider some possibilities to use dopaminergic imaging to evaluate the mechanism of action of antidepressants or other treatments.

4.3.2.1 Dopamine Synthesis

Tracers like [^{18}F]DOPA quantify the integrity and dopamine synthesis of presynaptic dopaminergic neurons in vivo in several brain areas (Booij et al. 1999; Booij and Berendse 2011; Kumakura and Cumming 2009). DOPA can be taken up by dopaminergic neurons via the amino acid transporter and is then decarboxylated to fluorodopamine and temporally stored in vesicles (Booij et al. 2014).

DOPA PET studies in MDD patients are scarce. However, striatal DOPA uptake may be similar in depressed patients and healthy controls (Agren et al. 1992). On

the other hand, in a small study, Martinot et al. (2001) showed decreased dopaminergic synthesis in the left caudate nucleus of depressed patients with affective flattening and psychomotor retardation. These findings again highlight that dopaminergic deficits in depression may be restricted to subgroups of patients. Though, as compared to DAT SPECT studies, DOPA PET offers the opportunity to also measure uptake in extrastriatal dopaminergic brain areas. In this regard it is of interest that Agren and co-workers reported on a decreased DOPA uptake in the medial prefrontal cortex in depressed patients, a key region in a circuit involved in the regulation of emotion and reward (Price and Drevets 2012).

Like DOPA PET studies in MDD patients, DOPA PET studies in BP are scarce. Yatham and co-workers found no significant differences in striatal [^{18}F]DOPA uptake rate constants between manic patients and healthy controls. After treatment with divalproex sodium, however, these rate constants were significantly reduced in the patients and were lower in the patients than in the controls (Yatham et al. 2002b).

4.3.2.2 Dopamine Transporter Imaging

MDD Patients Versus Controls

The presynaptic dopaminergic system can be imaged by using tracers for the dopamine transporter (DAT) for PET ([^{11}C]RTI-32, [^{11}C]CFT, [^{18}F]FE-PE2I) and SPECT ([^{123}I]β-CIT, [^{123}I]nor-β-CIT, [^{123}I]FP-CIT, [^{99m}Tc]TRODAT). The DAT is expressed exclusively in terminals of dopaminergic neurons (Miller et al. 1997). Another possibility is to use radiotracers that bind to the vesicular monoamine transporters (i.e., radiotracers derived from tetrabenazine), because in several brain areas (e.g., the striatum), uptake of these tracers reflects primarily binding to dopaminergic neurons (Okamura et al. 2010).

The results of imaging studies of the DAT in MDD are described in Table 4.6A, excluding one study, because mean and SD could not be extracted (Hellwig et al. 2018). Approximately half of these studies did not find statistically significant differences in striatal DAT binding versus age-matched controls. Also, while six studies showed a significant increase of DAT binding in MDD (Amsterdam et al. 2012; Amsterdam and Newberg 2007; Brunswick et al. 2003; Laasonen-Balk et al. 2004; Yang et al. 2008; Hsiao et al. 2013), six studies found the opposite or no effect (Meyer et al. 2001b; Sarchiapone et al. 2006; Wu et al. 2011; Camardese et al. 2014; Helwig et al. 2016; Pizzagalli et al. 2019). It is not likely that this discrepancy is caused by the use of different techniques, because, e.g., the same tracer was used in studies that showed significant increases (Amsterdam and Newberg 2007) or decreases (Wu et al. 2011) of striatal DAT binding. Also, our observations are in line with the results of a recent meta-analysis (Li et al. 2015). Of note, one study did include only anhedonic depressed patients (Sarchiapone et al. 2006). In this regard it is of interest that another study compared depressed patients with and without anhedonia directly and showed lower striatal DAT binding in patients with anhedonia (Camardese et al. 2014).

Most studies did not find a significant correlation between striatal DAT binding and symptomatology (Camardese et al. 2014; Hsiao et al. 2013; Laasonen-Balk

Table 4.6 Results of dopamine transporter imaging studies (PET/SPECT) in patients with unipolar major depression (A) or bipolar disorder (B) as compared to controls

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change DAT binding	Effect size
A. Unipolar depression					
Pizzagalli et al. (2019)[a]	25 MDD 23 HC	[^{11}C] altropane	Drug-free (>2 weeks)	Put: 8% decrease	-0.66
				VTA: 11% decrease	-0.71
Hsiao et al. (2013)	23 MDD 20 HC	[^{99m}Tc] TRODAT	Drug-free (>6 months)	Put R: 24% increase	1.59
				Put L: 25% increase	1.68
				Caudate R: 24% increase	1.40
				Caudate L: 19% increase	1.26
Camardese et al. (2014)	10 MDD[b] 10 HC	[^{123}I]FP-CIT	Drug-free interval not described	Put R: 16% decrease	0.94
				Put L: 16% decrease	0.87
				Caudate R: 14% decrease	0.82
				Caudate L: 16% decrease	0.99
Amsterdam et al. (2012)	24 MDD	[^{99m}Tc] TRODAT	Drug-free (>6 months)	7% increase (put right)	0.47
	84 HC			12% increase (put left)	1.11
				1% decrease (caudate right) (ns)	−0.16
				2% increase (caudate left) (ns)	0.20
Wu et al. (2011)	13 MDD	[^{99m}Tc] TRODAT	Drug-free (>2 years)	35% decrease (striatum right)	−4.89
	10 HC			35% decrease (striatum left)	−4.65
Lehto et al. (2008b)[c]	11 MDD	[^{123}I] nor-β-CIT	Drug-naive	0.1% decrease (striatum) (ns)	−0.06
	19 HC				
Yang et al. (2008)	10 MDD	[^{99m}Tc] TRODAT	Drug-free (>3 months)	12% increase	1.06
	10 HC				

Table 4.6 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change DAT binding	Effect size
Amsterdam and Newberg 2007	10 MDD	[^{99m}Tc] TRODAT	Drug-free (>1 week)	30% increase (put right ant)	1.59
	46 HC			47% increase (put right post)	1.39
				10% increase (put left ant)	0.46
				27% increase (put left post)	0.89
				12% increase (caudate right)	0.72
				18% increase (caudate left)	1.12
Argyelán et al. (2005)	16 MDD	[^{99m}Tc] TRODAT	9 drug-free (>2 weeks)	7% decrease (ns)	−0.23
	12 HC		7 drug-naive		
Staley et al. (2006)	32 MDD	[^{123}I]β-CIT	14 drug-naive	1% decrease in women (ns)	−0.29
	32 HC		15 drug-free	3% increase in men (ns)	0.59
			3 history unknown		
Sarchiapone et al. (2006)[d]	11 MDD	[^{123}I]FP-CIT	Drug-free (period not described)	20% decrease (put right)	−1.04
	9 HC			23% decrease (left and right)	−1.19
				17% decrease (caudate right)	−0.85
				18% decrease (caudate right)	−1.09
Brunswick et al. (2003)	15 MDD[e] 46 HC	[^{99m}Tc] TRODAT	Drug-free (>1 week)	25% increase (put ant right)	1.26
				9% increase (put ant left)	0.49
				41% increase (put post right)	1.26
				18% increase (put post left)	0.57
				2% increase (caudate right)	0.09
				13% increase (caudate left)	0.86

(continued)

Table 4.6 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change DAT binding	Effect size
Meyer et al. (2001b)	9 MDD	[^{11}C]RTI-32	5 drug-naive	16% decrease (put right)	−0.92
	23 HC		4 drug-free (>3 months)	14% decrease (put left)	−0.86
				14% decrease (caudate right)	−0.90
				12% decrease (caudate left)	−0.75
Dahlstrom et al. (2000)[f]	31 MDD	[^{123}I]β-CIT	Drug-naive	0.4% increase (ns)	0.03
	10 non-MDD				
Laasonen-Balk et al. (1999)	15 MDD	[^{123}I]β-CIT	Drug-naive	24% increase (striatum right)	1.12
Laasonen-Balk et al. (2004)	18 HC			22% increase (striatum left)	1.15
Malison et al. (1998b)	15 MDD	[^{123}I]β-CIT	6 drug-naive	11% decrease (ns)	−0.43
	15 HC				
B. Bipolar depression					
Amsterdam et al. (2012)[g]	15 BD	[^{99m}Tc] TRODAT	Drug-free (>6 months)	3% increase (caudate left)[e]	0.28
				2% decrease (caudate right)	−0.21
	84 HC			13% increase (put left)	1.15
				5% increase (put right)	0.32
Anand et al. (2011)	5 BD euthymic 6 BD depressed (8 BP-I) 13 HC	[^{11}C]CFT	Drug-free (>2 weeks)	20% decrease (caudate left)[f]	−1.38
				21% decrease (caudate right)	−0.78
				14% decrease (put left)	−0.88
				17% decrease (put right) (ns)	−0.57
				7% decrease (ventr str left) (ns)	−0.28
				1% decrease (ventr str right) (ns)	−0.01

Table 4.6 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change DAT binding	Effect size
Chang et al. (2010)	7 BP-I 10 BP-II 17 HC	[^{99m}Tc] TRODAT	Drug-free (>2 months)	16% increase (whole striatum)[g]	1.04
Amsterdam and Newberg 2007	5 BD-II 46 HC	[^{99m}Tc] TRODAT	Drug-free (>1 week)	13% increase (caudate left)	0.91
				5% decrease (caudate right) (ns)	−0.28
				4% increase (ant put left) (ns)	0.25
				16% increase (ant put right) (ns)	0.68
				13% increase (post put left) (ns)	0.45
				34% increase (post put right)	1.23

The change in binding ratios is estimated from whole striatum data (or separately for left and right striatum), or separately for striatal subregions as data are available, and compared to reported control data

ns Not statistically significantly different from control data, *put* Putamen, *VTA* Ventral tegmental area

[a]Means estimated from figure; Cohen d values as published

[b]MDD group without anhedonia

[c]Eight patients with a co-occurrence of major depression and dysthymia ("double depression") were included. As compared to data in controls, the striatal binding ratios were 2% lower (effect size 0.16)

[d]In this study, two patients had a diagnosis of BP-II, and three had a comorbid dysthymic disorder; all were suffering from depression in which anhedonia was a prominent feature

[e]Five of the 15 depressed patients had a diagnosis of BD-II or major depression not otherwise specified

[f]Subjects were children and adolescents. Due to the radiation burden involved, the control group did not consist of healthy controls, but children/adolescents who did not suffer from a depression (but, e.g., a conduct disorder)

[g]BD-II subgroup was not significantly different from the unipolar patient group

et al. 2004; Malison et al. 1998b; Sarchiapone et al. 2006; Staley et al. 2006; Yang et al. 2008), or did not report on it (Amsterdam et al. 2012; Amsterdam and Newberg 2007; Brunswick et al. 2003; Dahlstrom et al. 2000; Meyer et al. 2001b; Wu et al. 2011). On the other hand, Argyelán and co-workers (Argyelán et al. 2005) showed that striatal DAT binding was negatively associated with HDRS scores. Also, Meyer et al. (2001b) showed that age-corrected DAT binding was negatively correlated with scores of the Finger Tapping Test and Stroop Color-Word Test (which are known to be performed more poorly during low dopamine states). In addition, Lehto et al. (2008b) showed that age-adjusted baseline striatal DAT binding correlated inversely with the duration of both dysthymia and MDD in the group with combined MDD and dysthymia (double depression). Also, Wu et al., who showed decreased DAT binding, used a HDRS score of at least 24 plus psychomotor retardation (Wu et al. 2011). Finally, Pizzagalli et al. (2019) showed that the DAT availability in the putamen was negatively correlated with the lifetime number of major depressive episodes and DAT binding in the VTA was associated with scores on the external entrapment scale. All in all, these findings may indicate that dopaminergic deficits are not a feature of MDD per se, but may be specific for subgroups of patients (e.g., with psychomotor retardation, anhedonia, or in severely ill patients, and/or treatment-resistant depression (Camardese et al. 2014; Dunlop and Nemeroff 2007)). In contrast to this hypothesis, baseline striatal DAT binding was similar in responders and nonresponders during long-term treatment for depression (Cavanagh et al. 2006). However, as in many studies on depression, in this study the Hamilton Depression Scale was used (among others) to assess response. Since this scale not necessarily reflects dopaminergic functions, it may be of interest in future studies to include neuropsychological tests that reflect indirectly low dopamine states to unravel the link between dopamine and major depression (Meyer et al. 2001b).

BD Patients Versus Controls

The results of imaging studies of the DAT in BD are shown in Table 4.6B. While at least two studies showed an increase of striatal DAT binding in BD patients in the whole striatum (Chang et al. 2010) or in subdivisions of the striatum (Amsterdam et al. 2012; Amsterdam and Newberg 2007), another study showed a decrease of striatal DAT binding, particularly in the caudate nucleus (Anand et al. 2011). Interestingly, although the numbers of participants in each group are low, no significant differences were found between BD patients suffering from type I versus type II BD (Chang et al. 2010), or between depressed and euthymic BD patients (Anand et al. 2011).

It is remarkable that two studies that showed an increase of striatal DATs in BD patients used a nonselective tracer ([^{99m}Tc]TRODAT-1) and SPECT in most BD-II patients (Amsterdam and Newberg 2007; Chang et al. 2010), while the study that reported decreased DAT binding used a selective DAT tracer ([^{11}C]CFT) and PET (Anand et al. 2011). In two SPECT studies (Amsterdam et al. 2012; Amsterdam and Newberg 2007), the striatal DAT binding was assessed in three striatal subdivisions

(caudate nucleus, anterior and posterior putamen). These SPECT images were not coregistered with individual magnetic resonance imaging (MRI), which makes the accuracy of measurements uncertain. Two studies did not find a significant correlation between striatal DAT binding and symptomatology (Anand et al. 2011), nor duration of the bipolar disorder, nor the number of depressive or manic episodes (Chang et al. 2010), while two did not report on it (Amsterdam et al. 2012; Amsterdam and Newberg 2007).

Zubieta and colleagues assessed the central vesicular monoamine transporter (VMAT-2) with PET in BD. In a first study in euthymic patients diagnosed with bipolar disorder type I, they showed regional increases of VMAT binding in the thalamus and ventral brain stem (but not in the caudate nucleus) as compared to controls (Zubieta et al. 2000). This finding could be replicated in a second study (Zubieta et al. 2001).

DAT Imaging in Healthy Controls and Its Association with Mood

In healthy controls, a possible association between DAT binding and depressed affect was not found. One study showed higher striatal DAT binding in healthy controls with higher profile of mood states (POMS) scores as compared to subjects with low POMS scores and a positive association between DAT and POMS scores (Newberg et al. 2007). However, in a larger study, this could not be replicated (Burke et al. 2011). Finally, Hsieh and co-workers examined healthy controls with first-degree relatives with MDD, but found no change in striatal DAT binding as compared to healthy controls without a family history of MDD (Hsieh et al. 2014).

DAT Imaging in Other Neuropsychiatric Disorders and Its Association with Depression

As mentioned earlier, depression may occur in about one out of three patients suffering from PD (Aarsland et al. 2012). PD is characterized by severe loss of striatal DAT, even in early phases of the disease (Booij et al. 2001; Ponsen et al. 2004). Using [^{11}C]RTI-32 PET as an in vivo marker of dopamine and noradrenalin transporters, Remy et al. (2005) showed lower binding in depressed PD patients in the locus coeruleus and in several regions of the limbic system including the anterior cingulate cortex, the thalamus, the amygdala, and the ventral striatum. In agreement with these findings, Hesse et al. showed lower striatal DAT binding in PD patients with depression than those without depression (using [^{123}I]FP-CIT as a marker for the DAT) (Hesse et al. 2009), although this could not be replicated by other SPECT studies using [^{99m}Tc]TRODAT-1 or [^{123}I]FP-CIT (Felicio et al. 2010; Jaakkola et al. 2019). Also, Chung and co-workers showed no significant change in striatal DAT binding in depressed PD patients versus apathetic PD patients (Chung et al. 2016). Six other studies showed statistically significant correlations between depression scores and striatal DAT binding in PD patients (Eising et al. 1997; Rektorova et al. 2008; Weintraub et al. 2005; Vriend et al. 2014; Yoo et al. 2019; Ceravolo et al. 2013), although this could not be replicated in two other studies in PD (Picillo et al.

2017; Park et al. 2019b), as well as in another neurodegenerative disorder characterized by severe loss of dopaminergic neurons (i.e., (prodromal) Lewy body dementia (Roselli et al. 2009; Kasanuki et al. 2017; Siepel et al. 2016))). Interestingly, also striatal DAT binding was negatively related with depressive symptoms in cervical dystonia (Zoons et al. 2017).

The correlation between DAT binding and depression has not only been studied in neurodegenerative disorders characterized by loss of dopaminergic neurons. Interestingly, in alcoholics a significant relationship between DAT availability and Montgomery-Asberg Depression Rating Scale (MADRS) scores was found, both during withdrawal and after sobriety (Laine et al. 1999). Such a relationship (with HDRS-scores) was also found in alcoholics with comorbid depression (Yen et al. 2016). Also in acutely abstinent cocaine-abusing subjects, an inverse correlation between DAT levels and depression scores was observed (Malison et al. 1998a).

Presynaptic Markers and Treatment

Molecular imaging techniques offer the unique possibility to assess the mechanism of action of antidepressants. For example, Meyer et al. (2002) and Argyelán et al. (2005) studied the occupancy of striatal DAT by the antidepressant bupropion in depressed patients. After 3 weeks of treatment, Meyer et al. found no significant difference in DAT binding after bupropion treatment (300 mg/day) in eight MDD patients in comparison to test–retest data in eight healthy controls. The occupancy after bupropion treatment was 14% (6–22%) (Meyer et al. 2002). Argyelán et al. showed that approximately 20% of DATs were occupied after 4 weeks of treatment with bupropion (300 mg/day), but the occupancy was not correlated with clinical effectiveness (Argyelán et al. 2005).

Interestingly, a recent PET study in monkeys showed that electroconvulsive therapy (ECT) may induce an increase in striatal DAT and vesicular transporters after finalizing a 6-week electroconvulsive therapy course (Landau et al. 2011). A small human study in 11 patients showed that a change of DAT availability in the left caudate nucleus after sleep deprivation was significantly associated with antidepressant ECT response (Hellwig et al. 2018).

In depressed patients who were treated with the SSRIs paroxetine or escitalopram, a significant increase in striatal DAT binding was observed (Kugaya et al. 2003; Rominger et al. 2015). A small [^{99m}Tc]TRODAT SPECT study however could not replicate this finding (Wu et al. 2013). Also, successful psychotherapy for depression may not change presynaptic dopaminergic markers. Indeed, although the severity of depression decreased after 1 year of psychotherapy, striatal DAT binding did not change significantly in a study with ten participants (Lehto et al. 2008a).

Finally, in 14 depressed patients, who did not respond to 8 weeks of SSRI treatment and underwent DOPA PET imaging before and after aripiprazole augmentation, 11 responded to augmentation. Voxel-wise comparisons of pre- and post-aripiprazole scans revealed increased DOPA uptake in the right medial caudate nucleus of augmentation responders (Conway et al. 2014).

4.3.2.3 Postsynaptic Dopamine Receptor Imaging

MDD Patients Versus Controls

The dopamine D_1-like receptor is expressed predominantly on postsynaptic neurons and may be implicated in major depression. Using [^{11}C]NNC-112 PET to assess D1-like receptor binding in vivo, binding to this receptor was found to be reduced in the left caudate nucleus of depressed patients (Cannon et al. 2009). Also, binding correlated negatively with illness duration, and the left-to-right binding ratio correlated inversely with anhedonia ratings. This finding is of interest since the caudate nucleus is the target of afferent neural projections from the orbitofrontal and anterior cingulate cortices where neuropathological changes have been reported in major depression (Cannon et al. 2009). These data also extended a previous finding of decreased D1-like receptor binding in the striatum in patients with major depression with anger attacks (Dougherty et al. 2006). Unfortunately, a recent review demonstrated that no recent DA D_1 receptor PET studies have been performed in major depression (Cervenka 2019).

Many molecular imaging studies in major depression focused on postsynaptic dopamine $D_{2/3}$ receptors (Table 4.7A). Several of these studies did not find a significant difference in dopamine $D_{2/3}$ receptor binding between depressed patients and healthy controls. However, it is remarkable that the studies that did find significant differences between groups found increases in dopamine $D_{2/3}$ receptor binding in depressed patients in the striatum (D'haenen and Bossuyt 1994; Meyer et al. 2006b; Shah et al. 1997; Peciña et al. 2017). Also one PET study reported a significant difference in asymmetry of binding to $D_{2/3}$ receptors in the temporal cortex, with a higher asymmetry in patients than in controls (Lehto et al. 2009). In four of the five studies that showed significant differences between groups, striatal $D_{2/3}$ receptor binding did not correlate with neuropsychological scores or clinical variables (D'haenen and Bossuyt 1994; Meyer et al. 2006b; Shah et al. 1997) or a correlation was not reported (Lehto et al. 2008a, 2009). In one PET study, binding in the left nucleus accumbens/ventral pallidum was negatively associated with anxiety scores (GAD-7 scores), and the average binding in the bilateral nucleus accumbens was negatively associated with anhedonia (EAS) scores (Peciña et al. 2017). Also, Schneier and co-workers showed no association with baseline dopamine $D_{2/3}$ receptor binding and severity of depression (Schneier et al. 2018). Interestingly, psychomotor speed was negatively correlated with dopamine $D_{2/3}$ receptor binding (Meyer et al. 2006b; Shah et al. 1997), as well as with verbal fluency (Shah et al. 1997).

In a recent study, Savitz and co-workers showed that while the Taq1A polymorphism for the dopamine D_2 receptor is negatively associated with striatal dopamine $D_{2/3}$ receptor binding in healthy controls, the opposite might be true for MDD (Savitz et al. 2013), which may suggest that Taq polymorphism should be taken into account when studying dopamine $D_{2/3}$ receptor binding in MDD.

The release of endogenous dopamine by dopaminergic neurons can be assessed by SPECT or PET imaging, using radiotracers for the dopamine $D_{2/3}$ receptor (Breier et al. 1997; Laruelle et al. 1995, 1997b). By using a classic pharmacological

Table 4.7 Results of dopamine $D_{2/3}$ receptor imaging studies (PET/SPECT) in patients with unipolar major depression (A) and bipolar disorder (B) as compared to controls

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change $D_{2/3}$ binding	Effect size
A. Unipolar depression					
Schneier et al. (2018)	20 MDD 20 HC	[^{11}C]PHNO	Drug-naive	Ventral striatum: 0% difference (ns)	0.0
				Dorsal caudate nucleus: 4% decrease (ns)	0.32
				Posterior caudate: 0% difference (ns)	0.0
				Anterior putamen: 4% decrease (ns)	0.32
				Posterior putamen: 0% difference (ns)	0.0
				Globus pallidus: 4% decrease (ns)	0.28
				Midbrain: 13% decrease (ns)	1.0
				Thalamus: 0% difference (ns)	0.0
Peciña et al. (2017)	12 MDD 16 HC	[^{11}C] raclopride	Drug-free (>6 months)	NA[a]	NA[a]
Savitz et al. (2013)	12 MDD 24 HC	[^{11}C] raclopride	Drug-free (>6 weeks)	NA[a]	NA[a]
Moses-Kolko et al. (2012)	10 MDD 13 HC[b]	[^{11}C] raclopride	8 drug-naive	Anteroventral striatum: 9% decrease (ns)	0.46
			5 drug-free (>3 weeks)	Ventral putamen: 7% decrease (ns)	0.55
				Dorsal caudate: 10% decrease (ns)	0.90
				Dorsal putamen: 6% decrease (ns)	0.49
Saijo et al. (2010)	7 MDD 11 HC	[^{11}C] FLB457	On medication	Right anterior cingulate: 13% increase (ns)	0.40
Yang et al. (2008)	10 MDD 10 HC	[^{123}I]IBZM	Drug-free (>3 months)	Striatum: 2% decrease (ns)	0.23

Table 4.7 (continued)

Lehto et al. (2008a), Lehto et al. (2009)[c]	10 MDD 10 HC	[^{123}I] epidepride	Drug-free (>6 months)	Right temp cortex: 13% decrease (ns)	0.65
				Left temp cortex: 6% decrease (ns)	0.33
				Temporal asymmetry: 7%	1.56
Hirvonen et al. (2008b)	25 MDD 19 HC	[^{11}C] raclopride	Drug-free (>4 months)	Caudate: 2% increase (ns)	0.17
				Putamen: 1% decrease (ns)	0.11
				Thalamus: 3% decrease (ns)	0.24
				Ventral striatum: 4% decrease (ns)	0.46
Montgomery et al. (2007)	7 MDD 7 HC	[^{11}C] FLB457	Drug-free (>3 months)	Amygdala: 1% increase (ns)	0.05
				Hippocampus: 0% change (ns)	0.00
				Frontal cortex: 0% change (ns)	0.00
				Anterior cing cort: 1% increase (ns)	0.06
				Thalamus: 10% increase (ns)	0.45
				Brain stem: 6% increase (ns)	0.21
				Cerebellum: 5%increase (ns)	0.22
Meyer et al. (2006b), Kuroda et al. (2006)	21 MDD 21 HC	[^{11}C] raclopride	12 drug-naive 9 drug-free (>6 months)	Striatum: 6–8% increase	NA[a]
	9 MDD 16 HC	[^{11}C] raclopride	On medication	Right caudate: 1% increase (ns)	0.11
				Left caudate: 0% decrease (ns)	0.03
				Right putamen: 3% increase (ns)	0.22
				Left putamen: 5% increase (ns)	0.41
Parsey et al. (2001)	9 MDD 10 HC	[^{123}I]IBZM	Drug-free (>2 weeks)	Striatum: 6% decrease (ns)	0.55

(continued)

Table 4.7 (continued)

Klimke et al. (1999)	15 MDD 17 HC	[^{123}I]IBZM	Drug-free (>6 months)	Striatum: 1% decrease (ns)	0.06
Shah et al. (1997)	14 MDD	[^{123}I]IBZM	7 drug-free (>3 months)	Striatum right: 6% increase[d]	0.95
	15 HC[e]		8 on medication	Striatum left: 4% increase	0.52
Ebert et al. (1996)	20 MDD	[^{123}I]IBZM	10 drug-free (>6 months); 10 on medication	Striatum right: 8% increase (ns)[f]	0.55
	10 HC			Striatum left: 10% increase (ns)	0.68
D'haenen and Bossuyt (1994)	21 MDD 11 HC	[^{123}I]IBZM	Drug-free (>1 week)	Striatum: 11% increase	0.88
B. *Bipolar depression*					
Moses-Kolko et al. (2012)	7 BD	[^{11}C] raclopride	Drug-free (>3 weeks) or drug-naive	Anteroventral striatum: 5% decrease (ns)	0.34
	13 HC (females)[g]			Ventral putamen: 1% decrease (ns)	0.06
				Dorsal caudate: 3% increase (ns)	0.28
				Dorsal putamen: 5% increase (ns)	0.45
Yatham et al. (2002a)	13 BD (nonpsychot)	[^{11}C] raclopride	AP-naive	Striatum left: 9% decrease (ns)	0.51
				Striatum right: 8% decrease (ns)	0.43
	14 HC			Caudate: 7% decrease (ns)	0.37
				Putamen: 9% decrease (ns)	0.50
Anand et al. (2000)	13 BD 13 HC	[^{123}I]IBZM	AP-free (>6 months)	Striatum: 4% decrease (ns)	0.26
Wong et al. (1997)	7 BD (psychot) 24 HC	[^{11}C]NMSP	AP-naive or AP-free (>6 months)	Striatum: 9% increase (ns)	0.60
	7 BD (non-psychot) 24 HC[h]		AP-naive or AP-free (>6 months)	Striatum: 13% decrease (ns)	0.81
Pearlson et al. (1995)	7 BD (psychot) 12 HC	[^{11}C]NMSP	AP-naive or AP-free (>6 months)	Striatum: 87% increase[g]	1.27
	7 BD (non-psychot) 12 HC		AP-naive or AP-free (>6 months)	Striatum: 11% decrease (ns)[i]	0.22

Table 4.7 (continued)

The change in binding ratios is estimated from whole striatum data (or separately for left and right sides or striatal subregions), or extrastriatal brain areas, and compared to reported control data

ns Not statistically significantly different from control data

[a]In these studies, no data were available to calculate the effect size and/or change in dopamine $D_{2/3}$ receptor binding

[b]In this study only women were studied; also postpartum unipolar and bipolar patients were studied, as well as non-postpartum bipolar patients. In this table, the data of the non-postpartum patients and controls were compared

[c]Same sample of patients

[d]Ratios of binding in striatum versus frontal cortex were used to calculate differences between groups; the data of the 14 patients were compared to the 15 controls (no individual data were available to compare the subgroup of drug-free patients to the controls)

[e]Two patients had a bipolar affective disorder

[f]Ratios of binding in striatum versus cerebellum were used to calculate differences between groups; the 20 patients were compared to the 10 controls (no individual data were available to compare the subgroup of drug-free patients to the controls). Only in the small subgroup of patients with psychomotor retardation, an increased binding was observed

[g]In this study, only females were studied, including postpartum bipolar patients. In this table, the data of the non-postpartum patients and controls were compared

[h]In this study, psychotic patients suffering from bipolar disorder had significantly higher binding than nonpsychotic patients suffering from bipolar disorder

[i]In this study, the B_{max} for dopamine D_2-like receptors was assessed

paradigm, the amphetamine-induced release can be measured by assessing the decrease in dopamine $D_{2/3}$ receptor availability. Using an amphetamine challenge, Parsey et al. (2001) showed that although amphetamine administration induced a transient improvement in symptomatology in depressed patients, the amphetamine-induced dopamine release was not altered in MDD. In line with this finding, also a more recent PET study showed no significant difference in striatal dopamine release induced by amphetamine in MDD versus healthy controls (Schneier et al. 2018). However, contrary to this observation, female fibromyalgia patients with comorbid MDD may show a larger striatal DA release induced by monetary rewards assessed with ^{11}C-raclopride PET, compared to FMS patients without MDD (Ledermann et al. 2017).

BD Patients Versus Controls

Using [^{11}C]SCH23390 PET to assess D_1-like receptor binding, Suhara et al. showed that the binding of this tracer in the frontal cortex was significantly lower in bipolar patients than in healthy controls, whereas binding in the striatum was not significantly different (Suhara et al. 1992).

Five molecular imaging studies focused on the assessment of postsynaptic dopamine $D_{2/3}$ receptors in bipolar disorder (Table 4.7B). Four of these studies did not find a statistically significant difference compared to data obtained in healthy controls (Anand et al. 2000; Moses-Kolko et al. 2012; Wong et al. 1997; Yatham et al. 2002a). It is remarkable that in one study in which the B_{max} for striatal $D_{2/3}$ receptors was calculated, psychotic BD patients showed an increased B_{max} for these receptors

as compared to data obtained in healthy controls (Pearlson et al. 1995). This is of interest since a meta-analysis of imaging studies showed a significant but mild increase of striatal $D_{2/3}$ receptors in schizophrenia (Laruelle 1998), although a more recent meta-analysis suggested that this may not be evident in drug-naive patients (Howes et al. 2012).

The release of endogenous dopamine by dopaminergic neurons was assessed by Anand et al. in euthymic BD patients. These authors showed that, although amphetamine administration induced a significantly greater behavioral response in BD patients than in age-matched controls, the amphetamine-induced dopamine release was not increased (Zubieta et al. 2000).

Dopamine Receptor Imaging in Other Neuropsychiatric Disorders and Its Association with Depression

Apathy and depression occur frequently after deep brain stimulation for PD. In a prospective study, Thobois et al. showed that 17 out of the 63 included PD patients developed transient depression after subthalamic nucleus stimulation (Thobois et al. 2010). Except one, these patients also scored higher on apathy. Interestingly, presurgery [^{11}C]raclopride dopamine $D_{2/3}$ receptor binding was greater in bilateral OFC, DLPFC, posterior ACC, temporal cortices, left striatum, and right amygdala in apathetic versus non-apathic patients. This finding also underlines a link between dopaminergic deficits and depression.

Zoons and co-workers showed that striatal dopamine $D_{2/3}$ receptor binding was significantly lower in depressed patients with cervical dystonia compared to those without depression; however, the severity of depression was not correlated with dopamine $D_{2/3}$ receptor binding (Zoons et al. 2017).

In addition, Jolly and co-workers demonstrated lower dopamine $D_{2/3}$ receptor binding in the caudate nucleus in traumatic brain injury (TBI) patients with comorbid depression compared to controls, but this binding was not lower compared to TBI patients without depression (Jolly et al. 2019).

Dopamine Receptor Markers and Treatment

After treatment of MDD with an SSRI, Klimke et al. showed that the change in striatal dopamine $D_{2/3}$ receptors was positively correlated with the percentage improvement (measured by HDRS scores) (Klimke et al. 1999). In addition, baseline dopamine $D_{2/3}$ receptor binding was lower in responders ($n = 9$) than in nonresponders ($n = 6$). In contrast, Ebert et al. showed that 3-week treatment with amitriptyline (150 mg/daily) led to a decrease in $D_{2/3}$ receptor binding in the five patients who improved clinically (Ebert et al. 1996). Dopamine $D_{2/3}$ receptor binding remained unchanged in nonresponders. In a larger study, Hirvonen et al. showed in a randomized trial that 4-month treatment with fluoxetine (20–40 mg daily) or psychotherapy did not significantly change striatal $D_{2/3}$ receptor binding in the fluoxetine group ($n = 19$) nor in the psychotherapy group ($n = 21$), although treatment was successful in both groups (Hirvonen et al. 2011). In this study, fluoxetine

but not psychotherapy increased $D_{2/3}$ receptor binding in the lateral thalamus, but this increase was not correlated with clinical improvement. In line with this finding, a recent PET study in nonhuman primates showed that electroconvulsive therapy did not significantly influence dopamine $D_{2/3}$ receptors early after finalizing a 6-week electroconvulsive therapy treatment (Landau et al. 2011). However, by using [^{11}C]FLB 457 in humans, Saijo et al. showed a significant reduction of $D_{2/3}$ receptor binding in the right rostral anterior cingulate cortex following electroconvulsive therapy (Saijo et al. 2010). Interestingly, de Kwaasteniet et al. (2014) showed that in vivo striatal dopamine $D_{2/3}$ receptor binding was not significantly different between patients with treatment-resistant depression and controls.

As mentioned earlier, using an amphetamine challenge, Parsey and co-workers (Parsey et al. 2001) showed that although amphetamine administration induced a transient improvement in symptomatology in depressed patients, the amphetamine-induced dopamine release was not altered in MDD. In contrast, prefrontal repetitive transcranial magnetic stimulation in patients suffering from major depression may induce dopamine release (as measured by [^{123}I]IBZM SPECT) in the striatum (Pogarell et al. 2006). Although this small study lacked a placebo condition and a healthy control group, the included patients had a longer disease history than the ones included in the study by Parsey et al. (2001). Also this finding could not be replicated in a larger [^{11}C]raclopride PET study (Kuroda et al. 2006).

Using a high-affinity tracer for the dopamine $D_{2/3}$ receptors ([^{11}C] FLB457) and PET, Saijo et al. showed that electroconvulsive therapy induced a detectable dopamine release in the ACC (Saijo et al. 2010).

General Remarks Related to Dopaminergic Receptor Imaging in Unipolar and Bipolar Depression

The increased dopamine $D_{2/3}$ receptor binding, which was observed in some studies in depressed patients (and in one on bipolar disorder), may be caused by a reduced extracellular dopamine concentration in the synaptic cleft (D'haenen and Bossuyt 1994; Meyer et al. 2006b). Indeed, dopamine depletion can increase striatal $D_{2/3}$ receptor binding (Boot et al. 2008; Laruelle et al. 1997a). Also, dopamine D_1-like receptors measured by [^{11}C]NNC-112 may be sensitive to changes in endogenous dopamine (Guo et al. 2003). Therefore, and taking into account the findings on dopamine $D_{2/3}$ receptors, one may expect that a decrease of endogenous dopamine may cause an increased binding of [^{11}C]NNC-112. Nevertheless, the reported decreased D1-like receptor binding in MDD may not reflect changes in receptor binding associated with changes in dopamine concentrations, but rather a reduction in afferent neuronal terminals from the cortex and thus in the number of D_1-like receptors expressed postsynaptically (Cannon et al. 2009).

4.3.3 Monoamine Oxidase Imaging

The monoamine oxidase (MAO) enzyme catabolizes the major monoamines dopamine, noradrenalin, and serotonin (Shih et al. 1999; Youdim and Bakhle 2006). The

MAO-A enzyme especially catabolizes serotonin and noradrenalin, while the MAO-B enzyme catabolizes particularly dopamine. Classic irreversible MAO inhibitors (e.g., tranylcypromine and phenelzine) irreversibly damage both MAO-A and MAO-B; the reversible MAO-A inhibitor moclobemide does not affect MAO-B (Stahl and Felker 2008). Two selective, reversible PET ligands for MAO-A exist: [^{11}C]clorgyline (Fowler et al. 1987) and [^{11}C]harmine (Bergstrom et al. 1997b, c; Ginovart et al. 2006); the latter showed high brain uptake. In healthy controls, [^{11}C]harmine MAO-A density in the PFC was negatively correlated with the "angry/hostility" personality style (measured with the NEO-PI-R) (Soliman et al. 2011), which was reported before (with a different tracer and different personality scale) (Alia-Klein et al. 2008). However, the "deliberateness" personality style correlated positively with MAO-A density, which might indicate an evolutional advantage of this trait, when MAO-A density is moderately increased in healthy persons (Soliman et al. 2011). In 19 non-smoking healthy controls, MAO-A density as measured with [^{11}C]harmine appeared to be dynamic and adapted within 2.5–4 h to decreases of serotonin by tryptophan depletion (decrease of MAO-A in the PFC) and increases in dopamine by administration of carbidopa–levodopa (increase of MAO-A in the striatum) (Sacher et al. 2012a). This suggests rapid adaptation of the brain to externally induced changes in monoamine levels. Furthermore, increased MAO-A levels were found in the prefrontal and anterior cingulate cortices during acute cigarette withdrawal, which was associated with depressed mood (Bacher et al. 2011). In addition, Sacher et al. (2010) found elevated MAO-A in the PFC, ACC, thalamus, dorsal putamen, hippocampus, and midbrain in early puerperal mothers who were in the middle of their postpartum blues.

In medication-free patients with MDD, Meyer et al. (2006a) showed that MAO-A levels (more precisely: an index of MAO-A density) measured with [^{11}C]harmine PET were increased in every brain region assessed (from 27% in the midbrain to 39% in the thalamus; average magnitude 34%) (Meyer et al. 2006a). In later studies, this finding was replicated in early-onset MDD patients (Chiuccariello et al. 2014) and women with postpartum depression (Sacher et al. 2015), but not in seasonal affective disorder patients (Spies et al. 2018), nor in patients with treatment-resistant depression (TRD) (Baldinger-Melich et al. 2019). Moreover, Meyer et al. showed that MAO-A density remained elevated during 6 weeks of SSRI treatment (Meyer et al. 2009). Furthermore, after recovery, MAO-A levels were still significantly elevated in each brain region. Patients who had a recurrence in the following 6 months (despite a 1-year period of recovery and no drug treatment at baseline) had significantly higher MAO-A densities in the prefrontal and anterior cingulate cortex (and most regions assessed) than those who did not experience a recurrence (Meyer et al. 2009) (Table 4.8A).

MAO-B density in MDD was quantified with the highly selective tracer [^{11}C]SL25.1188 in one study, showing densities of MAO-B to be elevated by 13–26% in MDD patients relative to controls (Moriguchi et al. 2019). This finding is intriguing as increased MAO-B is associated with increased oxidative stress and mitochondrial dysfunction, possibly pointing at a metabolically deranged subtype of MDD (Table 4.8B).

Treatment of MDD patients with the reversible inhibitor of MAO-A (RIMA) moclobemide (600 mg) decreased MAO-A density on average by 74%, while in a hypothesized herbal treatment for MDD (St. John's wort 600 mg) and retesting of controls, no significant change of MAO-A binding was observed (Sacher et al. 2011). This reduction in MAO-A was replicated in a study using moclobemide (300–1200 mg/day) and the irreversible MAO inhibitor phenelzine (45–60 mg/day); these studies reported reductions between 63 and 85% and 80 and 86%, respectively (Chiuccariello et al. 2015). Electroconvulsive therapy, applied to patients with TRD, did not change MAO-A levels (Baldinger-Melich et al. 2019). [^{11}C]clorgyline was used in a dose-finding study with a new RIMA: CX157 (Fowler et al. 2010) (Table 4.8C).

These studies propose a revised monoamine deficiency theory for the pathogenesis of MDD and combine this with findings of increased SERT availability in patients with more severe negative dysfunctional attitudes (Meyer 2012). If patients suffer from increased levels of MAO-A enzymes, this will reduce intrasynaptic monoamines, e.g., serotonin. If there are few SERTs, the reduction in serotonin might be (partially) compensated, while subjects with high SERT availability (or during winter) will have more severe depressive symptoms (as expressed by more severe dysfunctional attitudes). Treatment with serotonin reuptake inhibitors (e.g., SSRIs/SNRIs and some TCAs) will block SERT and compensate the loss of serotonin. However, since increased MAO-A levels are only compensated but not changed by treatment, the persistently increased levels of MAO-A enzyme require prolongation of treatment after response/remission and may also explain recurrence. This is corroborated by MAO-A enzyme levels in patients with recurrence of their MDD in the forthcoming 6 months. This, in combination with the finding that MAO-A levels are not (or nonsignificantly) increased in a small group of TRD patients, suggests that further studies should aim to clarify whether [^{11}C]harmine scanning could be used to identify patients prone for recurrence and/or treatment with MAO inhibitors. Moreover, this hypothesis should be combined with the suggestion of decreased dopaminergic neurotransmission in a subgroup of depressed patients with treatment-resistant depression (Dunlop and Nemeroff 2007). Due to the limited evidence in small patient groups, more exploration is required before this theory is clinically applicable.

4.3.4 Monoamine Depletion Imaging

Tryptophan and tyrosine are essential amino acids in the formation of serotonin and noradrenalin/dopamine, respectively. Depletion of monoamines can be achieved by drinking amino acid mixtures without these essential amino acids. An alternative is blocking the enzyme that is crucial for the formation of the monoamine. Because of toxicity, this is not possible for serotonin, but for noradrenalin/dopamine the blockade of formation of noradrenalin/dopamine can be achieved with alpha-methylparatyrosine (AMPT) (Ruhe et al. 2007). Some depletion studies in

Table 4.8 Results of monoamine oxidase A (MAO-A) enzyme imaging studies (PET) in patients with major depression as compared to controls

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
A. MAO-A availability					
Baldinger-Melich et al. (2019)	16 MDD (≥2 antidepressant treatments; TRD) 16 HC	[^{11}C] harmine	Various antidepressants (MAO-A affecting drugs ≥6 months)	No significant, only numerical differences between groups, indicating slightly lower mean MAO-A VT in healthy controls compared to TRD	–
				Post hoc, increased MAO-A availability in TRD women compared to healthy controls	–
Spies et al. (2018)	24 SAD 27 HC	[^{11}C] harmine	>6 months	No sign. differences in MAO-A availability between SAD patients and HC	–
				Sign. decrease in MAO-A availability after bright light therapy in SAD patients: -7.6% ($p < .001$) In spring/summer MAO-A availability decreased in HC (−8.2%), but not in SAD ($p = .03$)	–

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Sacher et al. (2015)	15 MDD (postpartum) 12 HC (postpartum crying) 15 HC (recently pregnant) 15 HC (female)	[^{11}C] harmine	>3 months Non-smokers >1 year	Contrast MDD-postpartum vs. HC (female)	
				PFC: 18%↑ (p = .003) in MDD	1.3
				ACC: 16%↑ (p = .003) in MDD	1.0
				Ventral striatum: 18%↑ (p = .006) in MDD[b]	–
				Dorsal putamen: 14%↑ (p = .006) in MDD[b]	–
				Thal: 16%↑ (p = .006) in MDD[b]	–
				Midbr: 11%↑ (p = .006) in MDD[b]	–
				Hippoc: 13%↑ (p = .006) in MDD[b]	–

(continued)

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Chiuccariello et al. (2014) Kolla et al. (2016)	42 early-onset MDD (15 patients from Meyer et al. 2009) 37 HC	[^{11}C] harmine	Drug-free >2 weeks (n = 37 SSRI users drug-free >1 m)	PFC: 17%↑ ($p < .001$) in MDD[b]	–
				ACC: 16%↑ ($p < .001$) in MDD[b]	–
				Ventral striatum: 13%↑ ($p = .004$) in MDD[b]	–
				Dorsal putamen: 11%↑ ($p = .004$) in MDD[b]	–
				Thal: 15%↑ ($p = .004$) in MDD[b]	–
				Midbr: 17%↑ ($p = .004$) in MDD[b]	–
				Hippoc: 14%↑ ($p = .004$) in MDD[b]	–
				More severe MDD had higher MAO V_T in PFC and ACC ($p = .008$) MAO V_T was also higher in MDD patients with reverse neuro-vegetative symptoms in all regions ($p < .03$)	

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Meyer et al. (2009)	16 MDD	[^{11}C] harmine	>7 months (MDD; 9 drug-naive)	PFC: 27/22%↑ ($p < .001$) in MDD/rMDD[b]	1.6/1.4[b]
	18 rMDD (remitted) 28 HC		>1 year (rMDD)	ACC: 20/13%↑ ($p < .001$) in MDD/rMDD	1.3/0.8
				ATL: 23/15%↑ ($p < .001$) in MDD/rMDD	1.3/0.9
				Putamen: 30/23%↑ ($p < .001$) in MDD/rMDD	1.8/1.4
				Ventr. Striat: 25/21%↑ ($p < .001$) in MDD/rMDD	1.5/1.3
				Thal: 31/29%↑ ($p < .001$) in MDD/rMDD	1.7/1.6
				Midbr: 21/14%↑ ($p < .05$) in MDD/rMDD	0.9/0.7
				Hippoc: 28/28%↑ ($p < .001$) in MDD/rMDD	1.3/1.4
				$DV_T \approx$ (−1.6 to −9.2%; $p > .08$) after treatment with CIT (20–40 mg) or SER (50–100 mg)	
				rMDD with recurrence in 6 months ($n = 6$) had higher DVT in PFC, ACC ($p = .02$)	

(continued)

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Meyer et al. (2006a)	17 MDD	[^{11}C] harmine	>5 months (11 drug-naive)	PFC: 34%↑ ($p < .001$) in MDD[b,c]	2.0[b]
	17 HC			ATL: 35%↑ ($p < .001$) in MDD	2.4
				ACC: 35%↑ ($p < .001$) in MDD	1.9
				PCC: 35%↑ ($p < .001$) in MDD	2.2
				Thal: 39%↑ ($p < .001$) in MDD	2.0
				Caudate: 42%↑ ($p < .001$) in MDD	1.7
				Putamen: 30%↑ ($p < .001$) in MDD	1.3
				Hippoc: 30%↑ ($p < .001$) in MDD	1.9
				Midbr: 27%↑ ($p < .001$) in MDD	1.5
				No correlations with severity, duration of illness/ episode, AD use ($p > .1$)	

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
B. MAO-B availability					
Moriguchi et al. (2019)	20 MDD 20 HC	[^{11}C] SL25.1188	≥1 month drug-free (11 drug-naive)	PFC: 26%↑ ($p < .001$) in MDD VLPFC: 26%↑ ($p < .001$) in MDD DLPFC: 16%↑ ($p < .01$) in MDD OFC: 13%↑ ($p < .04$) in MDD Thal: 17%↑ ($p < .005$) in MDD Inf. parietal: 16%↑ ($p < .005$) in MDD MAO-B availabilities in VLPFC, DLPFC, OFC, ACC, Thal., and Inf. parietal, temporal, and occipital cortex were associated with longer duration of illness ($p < .001$)	1.4 1.1 0.9 0.7 1.0 1.0

(continued)

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
C. MAO-A occupancy/inhibition					
Baldinger-Melich et al. (2019)	16 MDD (≥2 antidepressant treatments; TRD) 16 HC	[^{11}C] harmine	Various antidepressants (MAO-A affecting drugs ≥6 months); treatment with right unilateral ECT	No significant change by ECT on MAO-A levels; the effect of ECT on MAO-A availability was −3.8%; comparable with a test–retest difference of −3.1% before ECT ($p > .24$)	−0.29
Chiuccariello et al. (2015)	22 MDD	[^{11}C] harmine	>2 week (No drug-naive not reported) 18 MDD treated with moclobemide (300, 600, 900, 1200 mg) 4 MDD treated with phenelzine (45, 60 mg)	Moclobemide Occ (300–1200 mg; $n = 20$)[b]	Phenelzine Occ (45–60 mg; $n = 4$)[b]
				PFC: −64 to −80%	−86%
				ACC: −67 to −84%	−86%
				Ventr Striat: −68 to 81%	−80%
				Dors. Putamen: −64 to −77%	−83%
				Thal: −63 to −78%	−84%
				Midbr: −64 to −76%	−83%
				Hippoc: −69 to −85%	−83%
				Occupancy in PFC and ACC (and all other regions) was predictive of remission ($p < .02$)	

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Sacher et al. (2011)	13 MDD	[^{11}C] harmine	>5 weeks (5 drug-naive) 6 MDD treated with moclobemide (600 mg) 7 MDD treated with St John's wort (1200 mg)	Moclobemide Occ (n = 6)[b,d]:	
	10 HC			PFC: −64%	
				ACC: −67%	
				ATL: −68%	
				Putamen: −64%	
				Thal: −67%	
				Hippoc: −66%	
				Midbr: −64%	
				St. John's wort Occ (n = 7): −11–4%	
				Test–retest: −9.4 to −3.2%	
Fowler et al. (2010)	15 HC	[^{11}C] clorgyline	CX157 20–80 mg administered once or 40 mg twice daily for 1 week	CX157 Occ (n = 15)	
				Administered once: 47–72% (>20 mg)	
				1 week: 48.3%	

ATL Anterior temporal cortex, *BDL* Borderline personality disorder patients, *ECT* Electroconvulsive therapy, *TRD* Treatment-resistant depression, *Ventr. Striat* Ventral striatum, *SAD* Seasonal affective disorder

[a]MAO-A binding expressed as DV_T, unless specified otherwise

[b]No exact data; estimated from figures

[c]DV_S as outcome measure

[d]Study reports an average occupancy of 74%

(recovered) MDD patient samples combined one of these approaches with molecular imaging, which will be shortly reviewed hereafter (Table 4.9).

4.3.4.1 Acute Tryptophan Depletion (ATD)

Three studies in recovered unipolar patients investigated the changes in cerebral metabolism or blood flow after depletion of tryptophan (Bremner et al. 1997; Neumeister et al. 2006; Nugent et al. 2008; Smith et al. 1999). Two [^{18}F]FDG studies reported a significant decrease in metabolism in cortical structures (in the middle frontal gyrus, DLPFC, OFC, thalamus), while significant increases were reported in the sgACC, pgACC, OFC, amygdala, (para)hippocampus, VMPFC, midbrain, and striatum (Bremner et al. 1997; Neumeister et al. 2006; Nugent et al. 2008). To some extent opposed to these changes, a $H_2{}^{15}O$ PET study showed decreased blood flow in the OFC, sgACC, caudate, and superior parietal cortex in association with increased depressive symptoms (Smith et al. 1999). Significant interactions of depletion and relapse (recurrence of depressive symptoms) were reported,

Table 4.9 Results of acute tryptophan depletion (ATD; A) and alpha-methylparatyrosine (AMPT; B) imaging studies (PET/SPECT) in patients with major depression and/or controls

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
A. ATD					
Sacher et al. (2012a)	7 HC 6 controls	[^{11}C] harmine	None	ATD: MAO-A density ↓ (−14% ± 9%) in prefrontal cortex ($p < .031$)	
Yatham et al. (2012)	17 remitted MDD	[^{18}F]–setoperone	SSRI	5-HT2 binding was significantly decreased in the depletion session versus control session in the nondepressed group (ACC $p = .005$; medial OFC $p = .02$) but not in the group who experienced a relapse	
Neumeister et al. (2006), Nugent et al. (2008)	27 rMDD (recov)	^{18}FDG	None	ATD (rMDD > HC): ↑ rCMRGlu in OFC ($p = .01$), sgACC ($p = .03$), pgACC ($p = .05$). Amygd, Hippoc, striatum (n.s.)	
	26 controls			Interaction with 5-HTTLPR polymorphism: Hippoc ($p = .03$), sgACC ($p = .048$), Amygd ($p = .08$; esp. left): ↑ rCMRGlu in L/L vs. ↓ in S carriers	
Praschak-Rieder et al. (2005)	25 HC (14 ATD; 11 test–retest)	[^{11}C]DASB	None	ATD vs. sham depletion difference: DLPFC −2.6%, mPFC 8.1%, ACC 1.4, caudate −2.0%, putamen −4.0%, Thal 1.4%, midbrain −5.6%	
				Test–retest differences: DLPFC 4.4%, mPFC −5.1%, ACC −3.7, caudate 1.6%, putamen 2.6%, Thal 2.5%, midbrain 0.3%	

Table 4.9 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
Smith et al. (2000), Smith et al. (1999)	8 rMDD (recov)	$H_2{}^{15}O$	3 SSRI, 1 AMI, 1 MAOI, 1 AMI + MAOI, 2 Li addition, 2 drug-free	Increasing HDRS scores associated with:	
				↓ activity OFC, sgACC, caudate, Sup. parietal Ctx	
				↓ activity dACC during fluency task	
Bremner et al. (1997)	21 MDD (recov)	^{18}FDG	SSRIs (1–355 weeks)	Pts with (n = 7) vs. without (n = 14) relapse after ATD:	
				↓ rCMRGlu in middle frontal gyrus/DLPFC, OFC, thalamus	
				↑ rCMRGlu in amygdala, parahippocampus, VMPFC, midbrain	
B. *AMPT*					
Hasler et al. (2008)	15 MDD (recov)	^{18}FDG	None >3 months	AMPT vs. plac: MDD > HC: ↑ metabolism in VMPFC, rThal, l Ventr. Striat, sgACC, l Sup. Temp. gyrus, l Inf. Parietal, l precentral gyrus, medACC	
	13 controls				
Bremner et al. (2003)	18 MDD patients (recov)	^{18}FDG	Desipramine 75–300 mg or nortriptyline 150 mg (for 5–46 weeks)	Metabolism AMPT < plac: DLPFC, OFC, thalamus	
				Metabolism AMPT > plac: OFC, middle frontal gyrus, (para)hippocampus, amygdala, temporal/ parietal cortex	
				Abnormalities were esp. seen in patients with relapse	

Abbreviations: *MAO-A* Monoamine oxidase A, *rMDD* Recurrent MDD, *SSRI* Selective serotonin reuptake inhibitor

indicating that these changes are only occurring in remitted patients who experienced a relapse. Of note, the same cortical and limbic regions were also identified in resting state PET and SPECT studies in MDD patients and after sad mood induction, as described in Sect. 4.2. Neumeister et al. also investigated the interaction of genetic polymorphisms of the 5-HTTLPR SERT promoter region with the effects of tryptophan depletion (Neumeister et al. 2006). Relative to controls, patients with an L_A allele had a recurrence of symptoms. Relative to sham depletion, recovered MDD patients who carried the L_A/L_A genotype showed increased metabolism during depletion in the left amygdala, the hippocampus, and the sgACC. Patients with the S/S genotype showed decreased metabolism during tryptophan depletion in the hippocampus. The authors explain these differences in the context of an interplay with 5-HT_{1A} receptors and propose that recovered MDD patients with the L_A/L_A genotype have lower postsynaptic 5-HT_{1A} receptors but increased presynaptic 5-HT_{1A} receptors, resulting in a decreased threshold that makes firing less likely. After depletion, this inhibition is released, which might explain the increase in metabolism.

Two of these studies included patients who recovered but still used the antidepressant drugs that improved their symptoms (mainly SSRIs) (Bremner et al. 1997; Smith et al. 1999). These patients are most prone to recurrences induced by tryptophan depletion (Ruhe et al. 2007), which—from a critical point of view—might not represent a full recurrence of the depressive episode, but rather reflect the direct effects of sharp decreases of serotonin induced by depletion. This phenomenon is also seen when patients forget to take their antidepressants, including sudden deteriorations of mood, and is recognized as the antidepressant discontinuation syndrome (Henry et al. 2003; Rosenbaum et al. 1998). One study investigated whether depletion of tryptophan influenced [^{11}C]DASB binding, but the observed change did not exceed test–retest differences (Praschak-Rieder et al. 2005). However, after studying dynamic, rapid changes in MAO-A levels in healthy controls, Sacher et al. (2012a) suggested that given the rapid decrease in MAO-A density following ATD (proposed as a compensatory adaptation to maintain serotonin levels), compensatory MAO-A fluctuations in healthy subjects (with normal MAO-A levels and adaptation) explain why these subjects do not show mood effects after ATD, while vulnerable subjects (with proposed increased levels of MAO-A activity (Meyer et al. 2009)) do show decreased mood after ATD (Ruhe et al. 2007). In addition, Yatham et al. (2012) measured reductions in 5-HT_2 receptors after ATD and showed that the reduction in 5-HT_2, believed to compensate for lower 5-HT levels due to ATD, did not occur in patients who experienced a relapse after ATD, while those remaining without relapse indeed showed decreased 5-HT_2 receptors after ATD. Both findings may suggest specific pharmacological interventions (MAO inhibitors and atypical antipsychotics, respectively) for pre-identifiable patients vulnerable for recurrence, which should be investigated further.

4.3.4.2 AMPT

Two [^{18}F]FDG PET studies investigated changes in metabolism after AMPT-induced noradrenalin/dopamine depletion in recovered unipolar MDD patients. One studied

drug-free patients in contrast with controls (Hasler et al. 2008); another studied relapse-related changes in metabolism in patients who used noradrenergic antidepressants (Bremner et al. 2003). Versus controls, noradrenalin/dopamine depletion resulted in increased metabolism in ventral/limbic/subcortical regions (VMPFC, right thalamus, left ventral striatum, sgACC) and some dorsal/cortical regions (medial ACC, temporal and parietal cortex) (Hasler et al. 2008). In patients who experienced a relapse after AMPT, metabolism was decreased in dorsal regions (DLPFC, OFC, and thalamus), while metabolism was increased in dorsal and limbic regions (middle frontal gyrus, (para)hippocampus, amygdala, temporal/parietal cortex). Again, these are regions that were also identified in resting state PET and SPECT studies in depressed patients (Sect. 4.2).

4.3.4.3 Depletion and Depressive Episodes

The interpretation of these ATD and AMPT findings could be that the depressed state resembles a situation in which serotonin and/or noradrenalin/dopamine is (acutely) depleted (in line with the monoamine hypothesis). However, an alternative hypothesis could be that after acute depletion the brain tries to compensate for withdrawal symptoms and impaired emotion regulation by activations that resemble the brain activity of a depressed state, but differ in the sense that they can easily be restored after the depletion experiment. In order to really understand this state versus adaptation hypothesis, the changes in mood and metabolism should be studied at several time points during prolonged depletion. Such studies are probably hard to do for ethical reasons.

4.4 New Perspectives

This chapter has provided an extensive overview of PET and SPECT imaging data drawn from studies investigating the molecular basis for the pathophysiology and treatment of MDD and BD. The majority of these studies focus on monoamine neurotransmitter systems and tracers related to their pharmacological targets. Although several monoamine tracers are approved for use in human subjects, novel tracers to image relatively less characterized monoamine targets are being evaluated on an ongoing basis. At the same time, recent pathophysiological research in mood disorders has identified several potential novel non-monoamine pharmacological targets. This has led to an upsurge in CNS drug discovery and the identification of new molecular entities that serve as ligands for such novel targets over the past decade. In vivo PET and SPECT imaging can be applied to track the pharmacokinetic and pharmacodynamic characteristics of novel compounds and, as a consequence, contribute to rational drug development by allowing optimal dose selection based on RO in clinical trials.

This section focuses on both novel monoaminergic and non-aminergic tracers that are currently under development or are already being applied in innovative pathophysiological research and CNS drug development in mood disorders.

4.4.1 Ongoing Radioligand Development for Imaging Serotonergic Neurotransmission

The 5-HT receptors are among the most diverse group of neurotransmitter receptors. At least 14 different receptor subtypes have been described so far. In addition, the SERT and 5-HT synthetic and degrading enzymes contribute to the system's function and regulation. At present, only few of these targets can be reliably imaged in vivo by PET or SPECT techniques, and even fewer are the subject of clinical imaging studies (Paterson et al. 2013). Therefore, there are many targets for future radioligand development. Recent advances for in vivo imaging in humans include PET imaging of the 5-HT_4 receptor with [^{11}C]SB207145 (Madsen et al. 2011; Marner et al. 2009; Marner et al. 2010) and a series of compounds for 5-HT_7 imaging that at present have been tested in cats and may prove useful for imaging of 5-HT_7 in humans (particularly [^{18}F]2FP3) (Andries et al. 2011; Lemoine et al. 2011).

PET imaging of the 5-HT_4 receptor with [^{11}C]SB207145 holds promise to index the serotonergic tone apart from mapping 5-HT_4 receptor per se (Haahr et al. 2014). Therefore larger studies with the tracer in both healthy individuals and patients with MDD have been initiated. Data on 5-HT_4 receptor density in healthy individuals at high risk for depression is starting to emerge (Madsen et al. 2014), and links between 5-HT_4 receptor binding and stress hormone regulation have been established (Jakobsen et al. 2016). However, no full article versions of data in clinical populations of MDD or BD have been published. Yet, recent data indicate that MDD patients display lower 5-HT_4 binding relative to controls, possibly reflecting compensatory mechanisms in terms of heightened serotonergic tone and low capacity for 5-HT_4 agonism to be implicated in the pathophysiology (Koehler-Forsberg et al. 2019).

At the current state of radioligand evolution, most 5-HT receptor imaging is acquired by the use of antagonist radioligands (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_4 receptors and SERT) (Paterson et al. 2013). However, antagonist ligands bind to receptors in their high-affinity as well as low-affinity state, and the high-affinity state represents the active form of the receptor that is coupled to G proteins. So, serotonin occupies more receptors in their high-affinity than in their low-affinity state. Therefore, one may expect that an agonist radiotracer will show an increased sensitivity to detect serotonin release compared to an antagonist radiotracer. Interestingly, agonist PET tracers for evaluation of the serotonergic system are under development (Paterson et al. 2010). Currently, [^{11}C]Cimbi-36 is the most promising agonist candidate for imaging of 5-HT_{2A} receptor binding and has been evaluated in pigs (Ettrup et al. 2011) and humans (Ettrup et al. 2014; da Cunha-Bang et al. 2019). Such tools may allow us to explore the interplay between the serotonergic neurotransmission and experimental challenges (either physiological or psychological stimuli or pharmacological interventions), such as amphetamine challenge which holds promise to measure serotonin release capacity (Erritzoe et al. 2020). For the dopamine system, methods are available to measure endogenous dopamine release using, e.g., antagonists [^{11}C]raclopride and [^{123}I]IBZM (Breier et al. 1997; Ginovart 2005; Laruelle et al. 1995, 1997b) or the DA agonist PHNO, and these methods have contributed valuable insights in dopaminergic mechanisms

in, e.g., schizophrenia and addiction. Importantly, agonist radiotracers for the dopamine D_2 receptor have been developed successfully, and indeed they may be more sensitive to detect DA release than D_2 receptor antagonist radiotracers.

Other tracers that are promising candidates to detect endogenous 5-HT release are the partial 5-HT_{1A} agonist [^{11}C]CUMI-101 (Selvaraj et al. 2012) and two 5-HT_{1B} antagonists [^{11}C]AZ10419369 (Finnema et al. 2010, 2012) and [^{11}C]p943 (Cosgrove et al. 2011; Ridler et al. 2011). A recent study in humans by Selvaraj et al. reported that SSRI infusion (citalopram 10 mg) increased [^{11}C]CUMI-101 binding with approximately 7% in cortical projection areas relative to placebo, but not in the raphe nuclei where the serotonergic neuronal cell bodies are located (Selvaraj et al. 2012). SSRI exposure may initially generate an inhibitory 5-HT_{1A} autoreceptor effect at the raphe level, which first reduces serotonergic activity (and synaptic 5-HT in projection areas), represented by increased [^{11}C]CUMI-101 binding. On the contrary, another study with a comparable setup could not confirm that [^{11}C]CUMI-101 was sensitive to citalopram infusion (Pinborg et al. 2012).

Two 5-HT_{1B} antagonist radioligands ([^{11}C]AZ10419369 and [^{11}C]p943) are reported to show dose-dependent displacement in response to a potent 5-HT-releasing challenge (fenfluramine infusion) in nonhuman primates. [^{11}C]p943 is also displaceable with an SSRI (Ridler et al. 2011). Nevertheless, even though these radioligands are now available for human studies, their sensitivity to human endogenous 5-HT release has not yet been established.

Recent and potential future advances in radioligand development for imaging the serotonergic neurotransmission thus include the identification of selective radioligands for remaining targets, potential development, and use of agonist tracers that image the biologically active pool of membrane-bound receptors and methods to measure synaptic levels of 5-HT. In the light of these advances, further exploration of the serotonergic system in vivo is in reach and, hopefully, will advance the pathophysiological insight in, e.g., MDD and BD in order to support development of better 5-HT-related treatments.

4.4.2 Imaging of the Norepinephrine System

Recent advances in ligand development provided suitable PET radioligands for NET, although improvements can still be achieved. The possibility to quantify NET occupancy is important for the development and evaluation of pharmacological agents targeting the NET, which are used for treatment of MDD, anxiety disorders, and attentional deficit hyperactivity disorder (ADHD). Especially (S,S)-2-(α-(2-[^{18}F]fluoro[$^{2}H_2$]methoxyphenoxy)-benzyl)-morpholine ((S,S)-[^{18}F]FMeNER-D_2) proved to have adequate affinity, specificity, selectivity, and binding kinetics to provide valid measurements also in regions with low density of NET (e.g., cerebellum, striatum, and insula) (Rami-Mark et al. 2013), while [^{11}C]-(S,S)-methylreboxetine ([^{11}C]MRB) had higher nonspecific binding in low-NET-containing regions (e.g., the basal ganglia/caudate nucleus) and therefore performed worse on signal to noise/sensitivity (Severance et al. 2007), making (S,S)-[^{18}F]FMeNER-D_2 the best

ligand for NET to date. However, given the long half-life of [^{18}F] tracers and the possibility of in vivo defluorination of (S,S)-[^{18}F]FMeNER-D_2 (Gallezot et al. 2011), [^{11}C]MRB may be preferred when repeated scans over days are requested.

Both ligands were tested in nonhuman primates using a variety of NET-occupying drugs (atomoxetine, clomipramine, milnacipran, venlafaxine) (Seneca et al. 2006; Takano et al. 2009; Gallezot et al. 2011; Takano et al. 2011a, b; Takano et al. 2013; Ding et al. 2014), showing dose-dependent occupancies of NET in different regions of the brain (locus coeruleus, (anterior) cingulate gyrus, mesencephalon, and thalamus).

In humans, (S,S)-[^{18}F]FMeNER-D_2 was first used in six healthy males, scanned twice before and after a single dose of nortriptyline (10–75 mg) (Sekine et al. 2010). NET occupancies in the thalamus varied between 16.4% (10 mg) and 41.1% (75 mg), while locus coeruleus occupancies varied between 41.6 and 90.3%, although not dose-dependently. In another study on 11 (male and female) healthy subjects, a single dose of methylphenidate (2.5–40 mg or placebo) was administered followed by 2 h of dynamic [^{11}C]MRB PET scanning (Hannestad et al. 2010). NET occupancies in the thalamus exceeded 80% in the locus coeruleus, raphe nuclei, and hypothalamus at 40 mg dose, while for this dose, occupancies in the thalamus varied between 50 and 60%. In nine healthy males treated for 6–8 days with variable dose of quetiapine XR (150–300 mg), repeated (S,S)-[^{18}F]FMeNER-D_2 PET scanning showed a mean NET occupancy in the thalamus of 19% at 150 mg and 35% at 300 mg, which is presumably caused by the norquetiapine metabolite (Nyberg et al. 2013).

In MDD patients, two studies have been published. First, six male patients using the dual-action antidepressant milnacipran at variable dose (25–200 mg) were investigated with a single (S,S)-[^{18}F]FMeNER-D_2 PET scan and compared to an age-matched healthy control to calculate NET occupancy in the thalamus (Nogami et al. 2013). NET occupancy varied between 25.3% at 25 mg and 49.9% at 200 mg. In the same study SERT occupancy in the thalamus was determined likewise by [^{11}C]DASB PET scans in six different patients treated with milnacipran (50–200 mg), showing SERT occupancies between 33.0% and 61.5%. Finally, in a study investigating ten MDD patients responding to treatment with variable doses of nortriptyline (75–200 mg) scanned once with (S,S)-[^{18}F]FMeNER-D_2 PET and compared to the mean NET availability of age-matched controls, NET occupancy varied between 50 and 70% with no association between residual symptoms and NET occupancy (Takano et al. 2014).

The above results indicate that future studies to investigate NET occupancy by antidepressants and other pharmacological agents targeting this transporter are possible, although the quality of the ligands is not yet comparable to those for SERT imaging. Studies in clinical samples are scarce, and prospective studies using repeated PET scanning to properly assess occupancies induced by norepinephrinergic drug treatment within patients are lacking.

4.4.3 Radioligands for Glutamate Targets

Glutamate is the main stimulatory amino acid in the human CNS and an endogenous ligand for ionotropic and metabotropic glutamate receptors. Ionotropic glutamatergic receptors (iGluRs) predominantly occur postsynaptically and include N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate (KA) receptors. AMPARs and KARs are responsible for excitatory neurotransmission, while NMDARs play a crucial role in processes mediated by synaptic plasticity such as long-term potentiation and excitotoxicity. Metabotropic glutamate receptors (mGluRs) are G-protein-coupled receptors (GPCRs) that are expressed both pre- and postsynaptically. As a result, mGluRs bind glutamate to activate diverse secondary messenger systems, which enables more complex modulatory downstream effects compared to iGluRs. Thus far eight distinct mGluRs have been identified and, based among others on sequence homology and agonist selectivity, are divided into three main groups (I, II, and III). Groups I, II, and III comprise mGluR1 and mGluR5; mGluR2 and mGluR3; and mGluR4, mGluR6, mGluR7, and mGluR8, respectively.

The widespread expression of glutamate receptors might facilitate their in vivo quantification using PET. However, tracer development for glutamate targets is often hampered by inferior in vivo results such as limited blood–brain barrier penetration, rapid clearance, and nonspecific receptor binding (Kassenbrock et al. 2016).

Despite the complexity associated with developing radioligands for iGluRs, several radiotracers have been developed to quantify the in vivo concentrations of iGluRs, as well as to investigate the distribution and pharmacology of these receptors in health and disease. Thus far PET tracers for NMDARs have been most numerous, followed by tracers for AMPARs, while only one has been reported for KARs (Fu et al. 2019). Among the iGluR imaging agents, a number of candidate ligands were successfully radiolabeled and showed promising in vitro properties such as high affinity and good receptor selectivity. However, in vivo results have been generally disappointing for reasons such as poor brain penetration, extensive metabolism, and high nonspecific binding in humans (Majo et al. 2013). Similarly, the recent PET ligand for the NMDAR ion channel site 3-(2-chloro-5-(methylthio) phenyl)-1-(3-([^{18}F]fluoromethoxy)phenyl)-1 methylguanidine ([^{18}F]PK-209) did not demonstrate sufficiently reproducible binding, effectively eliminating itself as candidate tracer (van der Aart et al. 2018). Only one SPECT ligand exists, N-(1-napthyl)-N′-(3-[(^{123})I]-iodophenyl)-N-methylguanidine ([^{123}I]CNS-1261), but has had limited success in clinical NMDAR studies due to activation by the NMDAR coactivator D-serine and high nonspecific binding, which hamper detection of small changes in receptor availability (Knol et al. 2009; Stone et al. 2008; Owens et al. 2000). No radioligands for either the glycine site or the NR2B binding site showed sufficient promise to warrant clinical studies. A recent paper reported the evaluation of N-((5-(4-fluoro-2-[^{11}C]methoxyphenyl)pyridin-3-yl)methyl)cyclopentanamin ([^{11}C]HACH242) in nonhuman primates with administration of the NR2B negative allosteric modulator radiprodil. Although [^{11}C]HACH242 demonstrated a suitable kinetic profile and low accumulation of lipophilic radiometabolites, radiprodil did

not consistently change [^{11}C]HACH242 brain uptake (van der Aart et al. 2019). Although limited progress has been achieved in the development of radiotracers for AMPARs and KARs, a PET tracer for AMPA receptors ([^{11}C]K-2) has recently been developed and studied in healthy human volunteers and patients with epilepsy, showing specific binding to AMPA receptors (Miyazaki et al. 2020). Increased understanding of AMPAR and KAR protein structures in the closed, active, and desensitized states has improved understanding of receptor–ligand interactions at the molecular level, which may lead to opportunities for future PET tracer development for iGluRs.

Tracer development for iGluRs is relevant given the observation that the non-competitive NMDA antagonist ketamine acts as a rapid antidepressant in treatment-resistant depression (TRD) (Aan het Rot et al. 2012; Park et al. 2019a). This provided an important impetus to the hypothesis that glutamate may play a crucial role in the pathophysiology of (persistent) unipolar mood disorders. Although such evidence is still mounting, the (S)-enantiomer of ketamine has recently been approved by regulatory authorities for the treatment of TRD. However, due to undesirable (psychomimetic) side-effects associated with ketamine, efforts are underway to develop compounds that modulate the NMDAR via alternative sites, such as the channel blocker site (lanicemine/AZD 6765), the glycine site (rapastinel/GLYX-13), and the NR2B subunit of the NMDAR (traxoprodil/CP-101,606 and CERC-301/MK-0657) (Ionescu and Papakostas 2017; Kadriu et al. 2019). Apart from mechanisms of action involving iGluRs, several metabotropic receptor modulators such as the mGluR5 antagonist basimglurant (RG7090 or RO4917523) and the mGluR2/3 antagonist decoglurant (RG1578 or RO4995819) have been developed (Kadriu et al. 2019).

In contrast to the scenario with NMDARs, several PET ligands for group I mGluRs have been developed and have demonstrated promising results in clinical studies. Among the mGluR5 imaging agents, 3-(6-methyl-pyridin-2-ylethynyl)-cyclohex-2-enone-O-^{11}C-methyl-oxime ([^{11}C]ABP-688), ^{18}F-3-fluoro-5-(pyridin-2-ylethynyl)benzonitrile ([^{18}F]FPEB), and 3-fluoro-5-(2-(2-[^{18}F](fluoromethyl)-thiazol-4-yl)ethynyl) ([^{18}F]-SP203) benzonitrile have been the most successful PET radioligands and are currently being investigated in clinical trials, including the evaluation of mGluR5 availability in disease states (Fuchigami et al. 2015; Esterlis et al. 2018). Recently, the mGluR2 PET ligand [^{11}C]JNJ-42491293 was evaluated in vivo, and although it initially appeared promising, its development seems to have been abandoned due to off-target binding (Leurquin-Sterk et al. 2017). Based on results from preliminary animal PET studies, [^{18}F]MK-1312 holds promise as suitable imaging agent for mGluR1 (Fuchigami et al. 2015). PET radioligands for mGluR1, such as 4-[^{18}F]fluoro-*N*-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-*N*-methylbenzamide ([^{18}F]FITM), *N*-(4-(6-(isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-4-[^{11}C]methoxy-*N*-methylbenzamide ([^{11}C]ITMM), N-(4-(6-(isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-*N*-methyl-4-[^{11}C]methylbenzamide ([^{11}C]ITDM), and 4-(^{18}F)fluoranyl-*N*-methyl-*N*-[4-[6-(methylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]benzamide ([^{18}F]FIMX), have proven useful in clinical PET studies (Fuchigami et al. 2015; Zanotti-Fregonara et al. 2016). One of

the limiting factors for developing PET tracers for group III mGluRs has been the lack of availability of subtype-selective high-affinity ligands, necessitating the future development of high-affinity and selective ligands for these receptors.

4.4.4 Imaging of the Central Opioid System

The endogenous opioid neuropeptides β-endorphin, enkephalins, and dynorphins act preferentially at the μ (MOR), δ (DOR), and κ (KOR) opioid receptors, respectively (Lutz and Kieffer 2013). The nociception opioid peptide receptor (NOR), also known as the nociceptin/orphanin FQ (N/OFQ) receptor or kappa-type 3 opioid receptor, is a fourth related opioid receptor that binds nociceptin (Meunier et al. 1995). The σ receptor was previously considered an opioid receptor, but since it rather binds drugs that are unrelated to opioids and it is not blocked by opioid receptor antagonists, its functional significance remains poorly understood (Corbett et al. 2006). Together these receptors represent a subfamily of GPCRs that are ubiquitously expressed in the CNS and peripheral nervous system. Physiologically, the opioid system is increasingly recognized as an important modulator of processes such as mood regulation, reward and aversion, pain, responsivity to stressful stimuli, and adverse environmental experiences. In fact, a multidimensional model for opioid receptor involvement in depression is currently emerging: although MOR and DOR agonism can improve mood, KOR antagonists may be capable of reversing depressed mood since endogenous KOR activation is associated with dysphoria. Taken together, the endogenous opioid system is a potentially promising avenue to pursue in search of novel antidepressants (Jacobson et al. 2020).

Morphine-like opioids preferentially bind to MORs, which are concentrated in regions associated with descending analgesic pathways, such as the periaqueductal gray, rostroventral medulla, medial thalamus, and dorsal horn of the spinal cord. Importantly, these regions significantly overlap with neurocircuits that have been implicated in emotion regulation, and MORs occur in reward-related regions including the ventral tegmental area (VTA) of the midbrain and the nucleus accumbens. MORs are therefore believed to mediate the hedonic effects of natural rewards and, as a consequence, the addictive effects of opiates. In addition, MORs are expressed in the dorsal striatum and in the locus coeruleus (LC), where they mediate aspects of physical opioid dependence and withdrawal (Peciña et al. 2019). The selective MOR PET ligand [^{11}C]carfentanil has been applied to investigate the relationship between opioid neurotransmission and emotion regulation. In 2003, Zubieta et al. studied 14 healthy women with a mood induction and [^{11}C]carfentanil PET scans. During the sad mood, a significant increase of mu-opioid binding (representing deactivation of neurotransmission) occurred in the rostral ACC, ventral pallidum, amygdala, and inferior temporal cortex, which correlated with the ratings of affect (Zubieta et al. 2003). However, in 2013, Hsu et al. also applied in vivo measures of MORs during a sadness induction paradigm and demonstrated reduced endogenous opioid neurotransmission in a diffuse network of regions implicated in emotion

regulation (Hsu et al. 2013). In addition, several studies have identified baseline measures of MOR availability as a predictor for monoaminergic antidepressant response (Peciña et al. 2019). Finally, human neuroimaging studies suggest that the endogenous opioid system, in particular MORs, plays a key role in the processing of social cues, which seems to be particularly altered in patients with MDD (Hsu et al. 2013).

KORs in particular have been associated with maintenance of hedonic tone (Lutz and Kieffer 2013). PET has therefore been applied to identify changes in KOR binding potential in patients with MDD and in drug development programs involving KOR antagonists as potential ADs and/or anxiolytics (Carroll and Carlezon Jr. 2013). Several selective KOR radioligands are available for clinical use and have been applied in studies with both mood and stress-related disorders. Agonist ligands include ^{11}C-methyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate ([^{11}C]-GR89696) and (-)-4-[^{11}C]methoxycarbonyl-2-[(1-pyrrolidinylmethyl]-1-[(3,4-dichlorophenyl)acetyl]-piperidine ([^{11}C]-GR103545), while antagonist ligands comprise (3R)-7-hydroxy-N-((1S)-1-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide ([^{11}C]-MeJDTic), carbonyl-^{11}C] (*S*)-3-chloro-4-(4-((2-(pyridine-3-yl)pyrrolidin-1-yl)methyl)phenoxy)benzamide ([^{11}C]-LY2795050), and [^{11}C]-LY2459989 (Richards et al. 2016). Using [^{11}C]LY2795050, low KOR expression in the amygdala–anterior cingulate cortex (ACC)–ventral striatal circuit was related to severity of loss-related symptoms in trauma-exposed individuals (Pietrzak et al. 2014). However, decreased KOR availability within the insula, caudate, thalamus, and hypothalamus was negatively related to severity of loss-related symptoms (Van't Veer and Carlezon Jr 2013). However, in a separate study with the selective KOR agonist radiotracer [^{11}C]GR103535, no effects of MDD on KOR binding within the amygdala, hippocampus, raphe nucleus, or ventral striatum were detected (Miller et al. 2018).

Several different KOR antagonists exist, including irreversible, long-acting, and short-acting compounds (Carroll and Carlezon Jr. 2013; Carlezon and Krystal 2016; Urbano et al. 2014). The prototypical selective KOR antagonists include 5-acetamidinoethylnaltrindole (ANTI), 5-guanidinonaltrindole (GNTI), (3R,4R)-dimethyl-4-(3-hydroxyphenyl) piperidine-based JDTic, and norbinaltorphimine (nor-BNI). Preclinically, these compounds have demonstrated low brain penetration and a slow onset of antagonist activity (peak at approximately 24 h), a long duration of action in vivo (up to 3–4 weeks following a single systemic exposure), and undesirable side effects. In addition, GNTI has poor oral bioavailability (Mague et al. 2003), and DIPPA binds KOR irreversibly (Carroll and Carlezon Jr. 2013). Their long duration of action and irreversibility make these compounds less suitable for clinical use. Novel KOR antagonists with a shorter duration of action and faster absorption would be more applicable to clinical trials. These include JNJ-67953964, LY2444296, zyklophin, PF-04455242, and AZ-MTAB. However, AZ-MTAB has poor brain penetration and high hERG activity which is associated with QT-interval prolongation (Urbano et al. 2014), and PF-04455242 was terminated after phase I studies due to toxicity. In addition, several mixed opioid antagonists also have

substantial affinity for KORs, including buprenorphine, the buprenorphine derivative BU10119, ALKS-5461, naltrexone, and m-trifluoromethyl-diphenyl diselenide [(m-CF3-PhSe)2]. Currently, CERC-501(LY-2456302) and ALKS 5461 survived and entered into phases II and III, respectively (Li et al). The development of KOR antagonists suitable for clinical use in the treatment of MDD is obviously still in its infancy, but steady progress is being made.

The localization of DORs in the amygdala, cortex, and hippocampus may be consistent with modulation of mood regulation, fear, and anxiety (Torregrossa et al. 2004). The selective DOR antagonist [^{11}C]-methyl-naltrindole is available for human use, but has not yet been applied to mood disorders (Madar et al. 1996). Although still in early development, DOR agonists including UFP-512 (Vergura et al. 2008) and AZD2327 (NCT00759395) (Richards et al. 2016) show potential since both preclinical and clinical studies have found positive antidepressant-like effects. However, the mechanisms through which DOR are involved in mood disorders in humans are unclear.

In summary, despite the availability of several compounds which modulate the endogenous opioid system, the limited availability of acceptable radiotracers hampers grasping the relevance of these systems to MDD and their potential as future therapeutic targets.

4.4.5 Imaging Inflammation and Depression

Given the heterogeneity of symptoms of MDD, the complexity of the affected neurotransmitter systems as described above, and the failure to successfully treat MDD based on these systems, alternative metabolic theories of depression should be considered (Gardner and Boles 2011). One of the emerging hypotheses on MDD relies on inflammatory mechanisms.

Treating nondepressed patients with pro-inflammatory cytokines, such as interferon alpha, can induce depression. In these cases, a peripheral induction of inflammation has central nervous system effects and induces depression (Dantzer et al. 2008). Furthermore, central nervous system inflammatory diseases such as multiple sclerosis (MS) have also profound effects on mood and may cause depression by direct release of pro-inflammatory cytokines in the CNS. In hepatitis C patients, depression occurs frequently and is sometimes aggravated or caused by interferon treatments (although a direct effect of the virus on the brain cannot be ruled out).

Activation of microglia, the immune-competent cells in the brain, is a well-described feature of severe diseases that are accompanied by depressive symptoms. Microglia activation can be visualized with tracers binding to the translocator protein (TSPO, previously known as peripheral benzodiazepine receptor (PBR)) (Doorduin et al. 2008), since TSPO expression is associated with a pro-inflammatory state. Current tracers used to visualize microglia activation are [^{11}C]PK11195, [^{11}C]-PBR28, and [^{18}F]-FEPPA. The affinity of [^{11}C]-PBR28 and [^{18}F]-FEPPA depends on a single polymorphism (SNP, rs6971) in the TSPO gene, which is not the case for [^{11}C]PK11195 (Owen et al. 2012). In practice, use of ligands with

dependence on this SNP requires methodological or statistical adjustments, but these ligands tend to be more sensitive than [^{11}C]PK11195.

Earlier, with [^{11}C]PK11195, patients with chronic hepatitis C virus infections were shown to have inflammatory lesions (Grover et al. 2012). In MS, inflammatory lesions in the white matter are well defined and accompanied by microglia activation. In Alzheimer's disease, microglia activation is a core feature and is associated with large emotional and cognitive changes (Versijpt et al. 2003). In psychotic disorders, an increase in microglia activation was demonstrated after a first psychotic episode (van Berckel et al. 2008). During a psychotic episode, this inflammation was found to predominate in the hippocampus (Doorduin et al. 2009). Finally, microglia express all neurotransmitter receptors (Pocock and Kettenmann 2007) and are also important in the reuptake of these neurotransmitters, especially the potentially toxic glutamate. Glutamate is an important mediator in MDD and is involved in aberrant prefrontal functioning in emotion regulation (Muller and Schwarz 2007; Walter et al. 2009).

In the first published TSPO study concerning MDD, [^{11}C]-PBR28 did not demonstrate an increase in binding in ten MDD patients compared to ten healthy controls (Hannestad et al. 2013), but not all MDD patients were currently depressed. In an earlier conference paper, van Otterloo et al. (2005) also did not find increased density of activated microglia in the white matter of the orbitofrontal region in ten MDD subjects. A larger, subsequent study including 20 MDD patients and 20 healthy controls using [^{18}F]-FEPPA demonstrated increased binding in the prefrontal cortex, anterior cingulate cortex, and insula of patients (Setiawan et al. 2015). In a third study, using [^{11}C]PK11195, binding was increased in the subgenual anterior cingulate cortex of 5 elderly patients with MDD, compared to 13 healthy controls, showing that microglia activation is also present in elderly patients (Su et al. 2016). A fourth study, also using [^{11}C]PK11195, again demonstrated increased binding in the anterior cingulate cortex of 14 medication-free patients with MDD, compared to 13 healthy controls. In a post hoc analysis, TSPO binding was found to be specifically increased in patients having suicidal thoughts, compared to patients that did not have such thoughts (Holmes et al. 2018). Cognitive functioning was found to be related to [^{18}F]-FEPPA binding in 50 medication-free MDD patients (Li et al. 2018a).

In a relatively large-scale PET study, including 51 patients, [^{18}F]-FEPPA binding was found to be greater in patients with chronologically advanced major depressive disorder and long periods of no antidepressant treatment than in patients with major depressive disorder and short periods of no antidepressant treatment (Setiawan et al. 2018). A yearly increase in microglial activation was not evident when antidepressant treatment was given. A similar relationship of [^{11}C]-PBR28 binding with duration of illness was found in another study in 28 MDD patients but not in medicated patients (Richards et al. 2018). Cognitive behavioral therapy, but not supportive psychotherapy, was found to reduce [^{18}F]-FEPPA binding in 20 patients with MDD (Li et al. 2018b).

Thus far, in BD increased [^{11}C]PK11195 binding has been demonstrated in the hippocampus of 14 euthymic type I patients, compared to 11 healthy controls (Haarman et al. 2014).

In summary, microglia activation has been demonstrated quite robustly in MDD patients with varying duration of illness and age. Both treatment with antidepressants and cognitive behavioral therapy seem to have an ameliorating effect on this activation.

Recently, Meyer (2017) proposed that microglia activation in MDD is associated with reduced astroglia availability (Rajkowska and Stockmeier 2013) and increased activity of MAO-A (see above), which could be resulting in increased extracellular glutamate levels. These abnormalities might be contributing to a pathological reorganization of the nervous system ("neuroprogression") along the course of MDD. For further clarification, additional studies are needed, which may also investigate the possibility to use these different markers for treatment stratification (Meyer 2017).

Patients with recurrent and/or persistent unipolar mood disorders have demonstrated alterations in the innate immune system and inflammatory responses, including increased concentrations of circulating cytokines such as IL-1β. The P2X7 receptor (P2X7R) is one of seven subtypes of adenosine triphosphate (ATP)-gated P2X ion channels present on various human cells. Peripherally, P2X7R is expressed mainly by monocytes, while in the central nervous system (CNS), the receptor is mostly expressed by microglia (Romagnoli et al. 2008). P2X7R activation by ATP may arise from diverse stimuli such as oxidative stress, hypoglycemia, ischemia, inflammation, cellular injury, or chronic stress. During such conditions, ATP activates the P2X7R which leads to inflammatory-like activation and subsequent production of pro-inflammatory cytokines including interleukin (IL)-1β in both the CNS and the periphery. Because of the well-recognized role of the P2X7R in IL-1β release, it is hypothesized that antagonists might have beneficial effects in the treatment of mood disorders. A number of CNS-penetrant high-affinity and selective P2X7R antagonists such as JNJ-54175446 and JNJ-55308942 are currently in development (Bhattacharya 2018; Timmers et al. 2018). A PET tracer ([^{18}F]-JNJ-64413739) has been developed for the P2X7R and has been evaluated preclinically in rhesus monkeys, demonstrating reproducible and dose-dependent receptor occupancy of P2X7R antagonists, making it suitable for P2X7R imaging studies in humans (Kolb et al. 2019).

Substance P acts both as a neurotransmitter and neuromodulator and has pro-inflammatory properties by binding neurokinin-1 receptors (NK1Rs). Previous failure of the NK1R antagonist aprepitant to separate from placebo in severe MDD trials was ascribed to inadequate central NK1R occupancy. This has led to renewed interest in the NK1R antagonists casopitant and orvepitant (GW823296) for the treatment of MDD, for which several PET tracers such as 2-[^{18}F]fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]([2*S*,3*S*]2-phenyl-piperidin-3-yl)-amine ([^{18}F]SPA-RQ), (2*S*,3*S*)-*N*-[[2-[^{11}C]methoxy-5-[5-(trifluoromethyl) tetrazol-1-yl]phenyl]methyl]-2-phenyl-piperidin-3-amine ([^{11}C]GR205171), and N1-(2,6-dimethylphenyl)-2-(4-(2R,4S)-2-benzyl-1-[3,5-di(trifluoromethyl) [carbonyl-^{11}C]benzoyl]hexahydro-4-pyridinyl(piperazino)acetamide ([^{11}C]R116301) are available to quantify NK1R occupancy in humans (Masdeu 2011; Majkowska-Pilip et al. 2019).

4.4.6 Imaging of Other Neurotransmitter Systems and Neuropeptides

Although the majority of research in MDD has addressed monoamine systems, glutamate, inflammatory pathways, other neurotransmitter systems that are potentially less well-known and/or less implicated in mood disorders, and neuropeptides are currently subject of investigation.

Cannon et al. reported a reduction of muscarinic receptor binding of [^{18}F]FP-TZTP in the ACC in bipolar, but not unipolar, depression. Until now, it remains unknown whether this finding represents a reduction in M_2 receptor density or affinity or an elevation in endogenous acetylcholine levels (Cannon et al. 2006a). Nevertheless, this system merits further research as muscarinic receptor agonists, genetic polymorphisms of the M_2 receptor, or acetylcholinesterase inhibitors are associated with depressive symptoms (Comings et al. 2002; Dilsaver 1986).

Scopolamine is a selective muscarinic-1 receptor (M_1R) antagonist that has been shown to reduce symptoms of depression and anxiety following intravenous administration in MDD patients (Furey and Drevets 2006; Drevets and Furey 2010). 8-((1S,2S)-2-Hydroxycyclohexyl)-5-((6-(methyl-t3)pyridin-3-yl)methyl)-8,9-dihydro-7H-pyrrolo[3,4-h]quinolin-7-one ([^{3}H]PT-1284) is currently under development as radioligand to investigate the effect of positive allosteric modulators (PAMs) that target M_1R (Smith et al. 2016). CP-601-927 is a α4β2 nicotinic acetylcholine (nACh) receptor partial agonist which demonstrated no efficacy as an augmentation agent in TRD (Fava et al. 2015). [^{18}F]Flubatine displayed favorably kinetics and imaging properties, suggesting it to be a suitable and clinically applicable PET tracer for in vivo imaging of α4β2 nAChRs (Sabri et al. 2015). Current nAChR radiotracer development focuses on improving specificity for the α7 subtype while maintaining or improving brain uptake over known tracers (Kassenbrock et al. 2016).

The orexins/hypocretins have been shown to regulate the sleep–wake cycle and vigilance in numerous preclinical and clinical studies (Yamanaka 2013). Orexin nuclei are primarily located in the lateral and posterior hypothalamus, from where efferent axons project to the cerebral cortex and structures involving the limbic system such as the nucleus accumbens (NA), mesocorticolimbic VTA, and the histaminergic tuberomammillary nucleus (TMN). In addition, neuronal projections to brain stem nuclei such as the locus coeruleus and raphe nuclei are involved in modulating noradrenergic and serotonergic neurotransmission, which are implicated in the regulation of arousal (Inutsuka and Yamanaka 2013). Interestingly, the absence of orexin-producing cells in the lateral hypothalamus results in narcolepsy with cataplexy (narcolepsy type I) in humans. Overactivity of the orexin system has therefore been related to MDD symptoms related to hyperarousal such as insomnia, anxiety, and/or anhedonia. Orexinergic effects are mediated by the excitatory neuropeptides orexin A (OX-A) and orexin B (OX-B) that function as endogenous ligands for the G-protein-coupled orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R). The affinity of OX-A for OX1R is roughly 100 times higher compared to OX-B, whereas for OX2R, the affinity is similar for both endogenous ligands.

Suvorexant is a nonselective dual OX1R/OX2R antagonist (DORA) which is currently registered in Japan, the USA, and Australia for the treatment of insomnia. However, selective OX2R antagonists such as seltorexant (JNJ-54717793/MIN-202) may have broader applications since they promote a more balanced sleep in preclinical models and display a lower narcoleptic/cataplectic potential compared to DORAs. Pharmacological manipulation of OX2R is of particular interest to treat insomnia as they are primarily expressed in histaminergic neurons in the TMN. Studies with the selective OX2R antagonist seltorexant (JNJ-54717793/MIN-202) have indeed shown beneficial effects on sleep (de Boer et al. 2018; Brooks et al. 2019). Also, antidepressant effects, albeit limited, were demonstrated in a proof-of-concept study in MDD although mood improvement could have been secondary to improved sleep (Recourt et al. 2019). The ligand [^{11}C]CW4 has been synthesized and investigated in rats and nonhuman primates using PET-MR imaging and displayed rapid kinetics and high nonspecific binding, indicating excellent brain penetrance and possible future application as a lead compound for developing new CNS-penetrant PET imaging probes of orexin receptors (Wang et al. 2013). In addition, [N-methyl-(11)C](S)-N-([1,1′-biphenyl]-2-yl)-1-(2-((1-methyl-1H-benzo[d]imidazol-2-yl)thio) acetyl)pyrrolidine-2-carboxamide ([^{11}C]BBAC) and [N-methyl-(11)C](S)-N-([1,1′-biphenyl]-2-yl)-1-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)propanoyl)pyrrolidine-2-carboxamide ([^{11}C]BBPC) have been synthesized successfully, but limited brain uptake has thwarted their continued development (Liu et al. 2012).

4.4.7 Imaging the Blood–Brain Barrier

It has been proposed that dysfunction of the blood–brain barrier (BBB) contributes to the pathophysiology of MDD. Influx of proteins or other molecules across the barrier is tightly regulated; however, small, lipophilic, and uncharged molecules can pass the BBB and are expelled by the P-glycoprotein pump (P-gp). It has been hypothesized that hyperactivity of the P-gp, which also expels lipophilic drugs like antidepressants, contributes to MDD and/or treatment-resistant depression (TRD). One study investigated P-gp activity in 13 MDD patients (of whom 7 had TRD) with [^{11}C]verapamil (de Klerk et al. 2009). Relative to controls, MDD patients showed decreased [^{11}C]verapamil uptake in the DLPFC, temporal lobe, ACC, and amygdala. This is indeed indicative of increased P-gp activity in MDD patients, which might preclude appropriate levels of antidepressants in the brain. Since all patients used antidepressants, it cannot be ruled out that these drugs influenced the study outcomes by P-gp induction or by affecting the pharmacokinetics of the tracer. This is of relevance as it was shown that P-gp expression may affect the binding of different radioligands (e.g., [^{18}F]MPPF and [^{11}C]flumazenil (Ishiwata et al. 2007)). In the future, this involvement of the P-gp in MDD or BD merits further investigation, especially in the context of TRD (Smith and Jakobsen, 2013).

4.4.8 Imaging Synaptic Density

Synaptic dysfunction appears to be involved in the pathophysiology of depression, which is supported by reduction of dendritic spine number and function of neurons in the prefrontal cortex (PFC) in animal models of depression (Liu and Aghajanian 2008). Symptoms of MDD include cognitive impairment and loss of memory (Rock et al. 2014; Ahern and Semkovska 2017; De Winter et al. 2017) even when patients are in remission (Smith et al. 2018), and the severity of cognitive deficits appears to increase with each depressive episode and may be a risk factor for AD (Gorwood et al. 2014). Until recently, it has not been possible to image synaptic density in vivo. Now, novel radioligands have been established for clinical PET studies. The ^{11}C-UCB-J PET radioligand for the synaptic vesicle glycoprotein 2A (SV2A) can be used to assess the number of nerve terminals, representing an indirect estimate of synaptic density (Mendoza-Torreblanca et al. 2013; Koole et al. 2019). In MDD, only one study (n = 26 mixed MDD or PTSD patients vs. 21 controls) has been published. Here, MDD severity was inversely correlated to synaptic density, and severely affected MDD patients had lower SV2A binding than healthy controls (Holmes et al. 2019).

4.4.9 Multimodal (Molecular) Imaging

From the abovementioned studies, it is clear that the brain is a complex system in which many neurotransmitters and brain functions interact. With the enormous amount of single modality studies that have emerged since the 1990s, much information about separate systems has been gathered. However, this information often led to slightly different or even conflicting results, which can often be understood in the perspective of system interactions (e.g., 5-HT$_{1A}$ receptor and SERT). Indeed these systems have been started to be investigated in conjunction (Frey et al. 2008; Takano et al. 2011a, b). We expect that in the (near) future different techniques will be combined in larger groups of MDD patients to study the interactions of these systems. This could be either dual isotope tracer studies (Frey et al. 2008; Hsieh et al. 2010; Takano et al. 2011a, b; Yang et al. 2008), preferably with short half-life isotopes like [^{11}C] to avoid changes over time, or the combination of MRI and molecular imaging (Paillere Martinot et al. 2010) or magnetic resonance spectroscopy combined with fMRI (Horn et al. 2010; Walter et al. 2009).

4.5 Discussion and Conclusions

This chapter summarizes findings of a large number of molecular imaging studies in the field of unipolar and bipolar depression. Brain function/metabolism in depressed unipolar and bipolar patients is generally hypoactive in the bilateral middle frontal gyri, pgACC, posterior ACC, left superior temporal gyrus, insula, and cerebellum, while a hyperactivity exists in subcortical (caudate, thalamus), limbic

(amygdala, anterior hippocampus), and medial and inferior frontal regions. A review based on fMRI studies has reached similar conclusions (Phillips et al. 2003a, b, 2008). In addition, monoamine depletion studies showed that after depletion of serotonin or noradrenalin/dopamine in vulnerable (recovered) MDD patients, a similar response pattern in metabolism occurs, especially when subjects show a recurrence of depressive symptoms.

Findings on the pre- and postsynaptic dopaminergic system are not yet conclusive, although there are indications that at least in subgroups of retarded MDD patients, presynaptic dopaminergic markers may be decreased, while postsynaptic markers may be increased. The observed abnormalities may be interpreted as a result of reduced extracellular dopamine concentrations in the synaptic cleft. Although not new in the perspective of the monoamine hypothesis, recent reviews resulted in increased attention for dopaminergic dysfunction in MDD and especially in TRD (Dunlop and Nemeroff 2007).

Despite contradictory results, the findings regarding 5-HT synthesis, pre- and postsynaptic imaging, can be synthesized to a loss of 5-HT in MDD, while this remains unclear in BD. A reduction of 5-HT (and dopamine) was proposed in a revised version of the monoamine hypothesis (Meyer 2012), which focused more on the abnormalities found at the level of the MAO enzyme. As shown, MAO-A density may be increased dramatically in several brain areas, and enzyme levels remain elevated after treatment and even during remission. Increased density and activity of MAO-A result in increased breakdown of 5-HT. This decrease in 5-HT might become problematic and lead to a depressive episode when subjects have increased SERT availability and/or fail to downregulate their SERT. Increased SERT will then remove the remaining 5-HT from the synaptic cleft, reducing serotonergic neurotransmission. As a result of this low 5-HT state, compensatory increases in postsynaptic 5-HT_{2A} receptors occur, while it has been suggested that a decrease of 5-HT_2 might be a better compensatory response, at least in ATD studies (Yatham et al. 2012). For the dopaminergic system, less research has been done and only in patients with retardation of movement, but comparable effects could occur after increased breakdown of dopamine (unaltered DAT, but increased D_2 receptors). This might suggest that in these patients the MAO-B enzyme might be involved, which has partly been corroborated by one study (Moriguchi et al. 2019).

Future research should clarify whether changes in MAO-A density are a trait marker of disease in euthymic or at-risk (yet healthy) states. It may further be hypothesized that MAO-A abnormalities might only exist in subgroups of patients, and if such subgroups exist, it would be of interest to evaluate whether these patients should be treated differently (more quickly) with, for example, MAO inhibitors.

Finally, reduced or unchanged SERT and postsynaptic serotonergic receptors (as reviewed in this chapter) and vulnerability findings especially for the low-SERT-expressing S/S polymorphism (Caspi et al. 2003; Willeit and Praschak-Rieder 2010) do not corroborate or at least challenge this revised monoamine hypothesis. Also, the dopaminergic system must be investigated more in depth in MDD and TRD, and it may become possible to study norepinephrine, glutamate, opioid, and inflammatory pathways in relation to MDD.

Finally, because of a lack of longitudinal molecular imaging studies at different clinical mood states in the same subjects, it remains unclear whether the changes of SERT and DAT, or the increases in 5-HT_{2A} or D_2 receptors, are compensatory responses to reduced levels of serotonin or dopamine or reflect different, potentially causal mechanisms. Also, as outlined in this chapter, measurements in this field are still hindered by suboptimal methodology, tracers, and reference standards, thus needing further standardization (Innis et al. 2007). We expect that these challenges will be solved in the future.

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