Bipolar disorders

Haarman, Bartholomeus Benno C.M.; Riemersma-Van der Lek, Rixt F.; Ruhé, Henricus Eric G.; de Groot, Jan Cees; Nolen, Willem A.; Doorduin, Janine

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Bartholomeus (Benno) C. M. Haarman, Rixt F. Riemersma-Van der Lek, Henricus (Eric) G. Ruhé, Jan Cees de Groot, Willem A. Nolen, and Janine Doorduin

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B. (B.) C. M. Haarman (✉) · R. F. Riemersma-Van der Lek · W. A. Nolen
Department of Psychiatry, CC44, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
e-mail: b.c.m.haarman@umcg.nl; h.g.ruhe@umcg.nl; w.a.nolen@umcg.nl

H. (E.) G. Ruhé
Department of Psychiatry, Radboud UMC, Radboud University, Nijmegen, The Netherlands

Donders Institute for Brain, Cognition and Behavior, Radboud University, Nijmegen, The Netherlands
e-mail: eric.ruhe@radboudumc.nl

J. C. de Groot
Department of Radiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
e-mail: j.c.de.groot@umcg.nl

J. Doorduin
Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
e-mail: j.doorduin@umcg.nl

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Abstract

Bipolar disorder is characterized by (hypo)manic episodes and depressive episodes which alternate with euthymic periods. It causes serious disability with poor outcome, increased suicidality risk, and significant societal costs. This chapter describes the findings of the PET/SPECT research efforts and the current ideas on the pathophysiology of bipolar disorder.

First, the cerebral blood flow and cerebral metabolism findings in the prefrontal cortex, limbic system, subcortical structures, and other brain regions are discussed, followed by an overview of the corticolimbic theory of mood disorders that explains these observations.

Second, the neurotransmitter studies are discussed. The serotonin transporter alterations are described, and the variation in study results is explained, followed by an overview of the results of the various dopamine receptor and transporter molecules studies, taking into account also the relation to psychosis.

Third, a concise overview is given of dominant bipolar disorder pathophysiological models, proposing starting points for future molecular imaging studies.

Finally, the most important conclusions are summarized, followed by remarks about the observed molecular imaging study designs specific for bipolar disorder.

Abbreviations

ACC	Anterior cingulate cortex
BA	Brodmann areas
BD	Bipolar disorder
BD-I	Bipolar I disorder
BD-II	Bipolar II disorder
CBF	Cerebral blood flow
CFT	[O-methyl-^{11}C]-carbomethoxy-3β-(4-fluorophenyl)tropane
CMR	Cerebral metabolic rate
DASB	3-^{11}C-amino-4-(2-dimethylaminomethylphenylsulfanyl)benzonitrile
DAT	Dopamine transporter
DTBZ	(+)-α-^{11}C-dihydrotetrabenazine
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FDG	^{18}F-labeled fluorodeoxyglucose
fMRI	Functional magnetic resonance imaging
HMPAO	Hexamethylpropylene amine oxime
IDO	Indoleamine 2,3 dioxygenase
IMP	Iodoamphetamine
LCSPT	Limbic-cortical-striatal-pallidal-thalamic
McNeil 5652	Trans-1,2,3,5,6,10-hexahydro-6-[4-(methylthio)phenyl] pyrrolo-[2,1-a] isoquinoline
MD	Mean diffusivity
MDD	Major depressive disorder

MRS	Magnetic resonance spectroscopy
NAA	N-acetylaspartate
PBR	Peripheral benzodiazepine receptor
PET	Positron-emission tomography
PFC	Prefrontal cortex
SPECT	Single-photon emission computed tomography
TZTP	3-(3-(3-[^{18}F]Flouropropyl)thio)-1,2, 5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine
VMAT2	Vesicular monoamine transporter 2

7.1 Introduction

Bipolar disorder (BD) (American Psychiatric Association 2013) is a mood disorder characterized by episodic pathologic disturbances in mood: (hypo)manic episodes and depressive episodes which alternate with euthymic periods, i.e., with normal mood. BD has to be distinguished from (unipolar) major depressive disorder (MDD), which is characterized by only depressive episodes. The main criterion of a (hypo) manic episode is the occurrence of pathologic elated (euphoria), expansive, or irritable mood. DSM-5 added increased energy or activity to this list. In addition there are other symptoms such as inflated self-esteem or grandiosity, decreased need for sleep, being more talkative than usual, flight of ideas, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in pleasurable activities that have a high potential for painful consequences. A depressive episode consists of at least one of the core symptoms depressed mood and loss of interest or pleasure, completed with symptoms such as sleep problems, psychomotor changes, fatigue or loss of energy, feelings of worthlessness or excessive feelings of guilt, difficulty concentrating, or making decisions and recurrent thoughts of death (American Psychiatric Association 2013). Two types of BD are recognized: bipolar I disorder (BD-I) and bipolar II disorder (BD-II), characterized by the occurrence of manic episode(s) or by only hypomanic episode(s), respectively. The difference between manic and hypomanic episodes (and thus between BD-I and BD-II) is that manic episodes are associated with marked impairment in occupational, relational, or social functioning, which can lead to hospitalization, while hypomanic episodes do not have this marked impairment and do not lead to hospitalization. When manic and depressive symptoms co-occur (or alternate very quickly) in the same episode, in DSM-IV it is labeled as a mixed episode and in DSM-5 as a bipolar disorder, manic or depressive episode with mixed features. Manic, depressive, and mixed episodes can be complicated by the presence of concurrent psychotic symptoms. Besides the mood symptoms, many patients with BD also show cognitive dysfunctions which may persist during euthymic periods, and which involve disturbances in various domains such as attention, verbal memory, and executive functioning (Arts et al. 2008; Bora et al. 2009).

The lifetime prevalence of BD-Is about 2% across different countries, women being affected as frequently as men (Pini et al. 2005; Merikangas et al. 2011). Across the world, the disorder is sixth among all health conditions in terms of causing disability (World Health Organization 2001) with poor clinical and functional

outcome (Goodwin 2007), increased risk for suicidality (Baldessarini and Tondo 2003), and significant societal costs (Begley et al. 2001).

Although the clinical picture seems clear at first glance, making the diagnosis is more complicated in practice. On average, there is a lag time of about 6 years between the first episode and the making of the right diagnosis and another 6 years before the start of adequate treatment. This is in most cases in part impeded by the precedence of depressive episodes without obvious (hypo)manic symptoms in the beginning of the disease (Suppes et al. 2001). Because antidepressants appear less effective in the treatment of bipolar depressive episodes (Sachs et al. 2007), delayed diagnosis often leads to prolonged illness and dysfunction.

It is generally accepted that the cause of BD-Is multifactorial, with multiple genes making someone vulnerable, and with psychological and social factors causing the genes to be expressed. Moreover, somatic factors are supposed to play a role. To unravel the complex interplay between genotype and phenotype researchers are trying to find intermediary processes, so called endophenotypes. These are more related to the underlying genotype than the ultimate phenotype. Endophenotypes should be consistently associated with the illness and represent persistent "trait" rather than episodic or "state" features. By definition, they also should be found in high-risk individuals such as non-affected first-degree family members at a higher rate than in the general population (Gottesman and Gould 2003). Over the last three decades, many molecular neuroimaging studies have been performed in BD. Alterations of function assessed by molecular neuroimaging may be regarded as important endophenotypes.

Probably the best approach in neuroimaging of bipolar disorder is to study patients during their depressive and manic episodes as well as during the euthymic phase with different (functional) neuroimaging techniques. However, these are very complicated patients, both technically and practically (e.g., one can never be sure that the same patient will develop both manic and depressive episodes within a certain time frame).

In this chapter, we will describe the findings of various PET/SPECT studies, sometimes performed in combination with other imaging techniques, as well as current ideas on the BD pathophysiology.

7.2 PET/SPECT

7.2.1 General Information

Positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) are imaging techniques that use radiolabeled, biological active compounds (PET or SPECT tracers) to gain information on specific functions of the brain, by measuring brain metabolism or blood flow, or functions of individual cells, such as transporter mechanisms or receptors.

The tracers involved are administered in such small doses that pharmacological activity or chemical toxicity is practically absent and due to the usual short half-life of the radionuclides total radiation remains within generally accepted safety levels.

Where PET uses positron-emitting radionuclides, that give rise to two oppositely directed 511 kV gamma rays after annihilation of positrons with electrons, the radionuclides in SPECT directly emit gamma rays. Because the gamma rays are emitted in 180° opposite directions, PET does not need a collimator for position information and is able to achieve higher spatial resolutions (about 4 mm) than SPECT (7–12 mm). SPECT is more widely accessible due to the lower maintenance costs and generally easier tracer handling.

7.2.2 Cerebral Blood Flow and Cerebral Metabolism

Accumulating scientific evidence supports the theory of metabolic alterations in specific parts of the brain in patients with mood disorders: the prefrontal cortex, the limbic system, and subcortical regions (Fig. 7.1). With molecular imaging techniques, the metabolic activity in the brain (cerebral metabolic rate (CMR)) as well as the blood flow in specific regions (cerebral blood flow (CBF)) can be measured (Table 7.1). It is generally accepted that CMR and CBF are physiologically coupled,

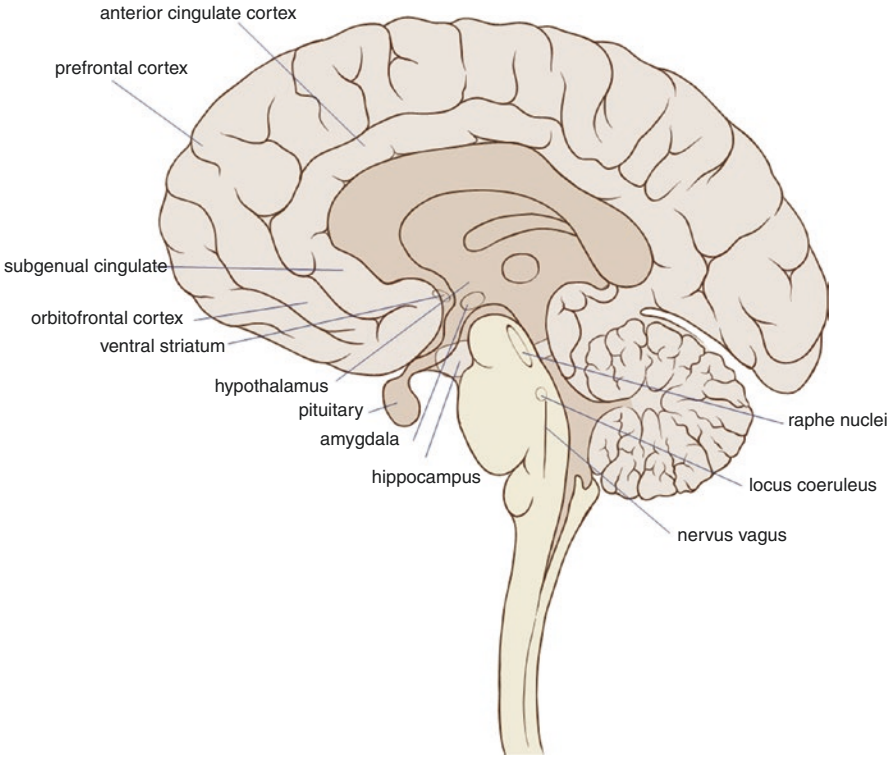

Fig. 7.1 Neuroanatomic regions important in mood disorders. Adapted from Patrick J. Lynch, medical illustrator, and C. Carl Jaffe, MD, cardiologist, under the Creative Commons Attribution 2.5 Generic license (CC BY 2.5))

Table 7.1 Overview of PET/SPECT studies on cerebral blood flow and cerebral metabolism in BD patients

Study (author (year))	Subjects	Medication	Method	Main findings
al-Mousawi et al. (1996)	15 BD-I (15 M) 14 SZ 10 MDD 10 HC	+	^{18}FDG PET Resting state	Decreased left dorsolateral prefrontal cortex and left amygdala in the manic BD patients compared to HC
Altamura et al. (2013)	26 BD 26 SCZ	+	^{18}FDG PET Resting state	White matter metabolic rates significantly differed between schizophrenia and bipolar disorder, whereas no differences were shown for cortical activity
Altamura et al. (2017)	27 BD (10 +SUD) 16 SIP 54 HC	+	^{18}FDG PET Resting state	A unique pattern of GM volumes reduction, with concomitant increased of striatal metabolism, was observed in SIP patients compared to BD and HC
Bauer et al. (2005)	9 BD-I (9 D) 1 BD-II (1 D)	+	^{18}FDG PET Treatment with levothyroxine CPT	Before levothyroxine treatment, BD patients exhibited significantly higher activity in the right subgenual cingulate cortex, left thalamus, medial temporal lobe (right amygdala, right hippocampus), right ventral striatum, and cerebellar vermis and had lower relative activity in the middle frontal gyri bilaterally. Levothyroxine decreased relative activity in the right subgenual cingulate cortex, left thalamus, right amygdala, right hippocampus, right dorsal and ventral striatum, and cerebellar vermis
Bauer et al. (2010)	10 BD (10 D)	+	^{18}FDG PET Treatment with levothyroxine	New analysis on Bauer et al. (2005). After treatment anxiety was improved significantly. Change in trait anxiety covaried positively with changes in relative activity in right amygdala and hippocampus. Change in state anxiety covaried positively with changes in relative activity in the hippocampus bilaterally and left thalamus and negatively with changes in left middle frontal gyrus and right dorsal anterior cingulate

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Bauer et al. (2016)	25 BD (25 E)	+	^{18}FDG PET RCT treatment with levothyroxine	A significant decrease in regional activity was demonstrated in the left thalamus, right amygdala, right hippocampus, left ventral striatum, and the right dorsal striatum. Decreases in the left thalamus, left dorsal striatum, and the subgenual cingulate were correlated with a reduction in depression scores
Baxter et al. (1985)	5 BD (5 M, 2 Mi, 5 D) 11 MDD HC	+	^{18}FDG PET Resting state	The whole-brain CMR for patients with bipolar depression increased going from depression or a mixed episode to a euthymic state or manic episode
Baxter et al. (1989)	15 BD (10 D, 5 M) 10 MDD 10 OCD w/o D 14 OCD w/ D 12 HC	+	^{18}FDG PET Resting state	The results in CMR of the dorsal anterolateral PFC for MDD and BD D were the same, but lower than in controls
Benabarre et al. (2005)	43 BD (12 D, 3 E, 8 HM, 7 M) 6 HC	+/–	^{99m}Tc-HMPAO SPECT Resting state	Several corrected correlations between neuropsychological function and CBF were identified
Blumberg et al. (1999)	11 BD-I (6 E, 5 M) 5 HC	+	$H_2{}^{15}O$ PET Word generation, letter repetition, resting state	Decreased right rostral and orbital prefrontal cortex activation during word generation and decreased orbitofrontal activity during rest were associated with mania
Blumberg et al. (2000)	11 BD-I (6 E, 5 M) 5 HC	+	$H_2{}^{15}O$ PET Resting state	The principal findings were an increased activity in left dorsal anterior cingulate and left head of caudate during manic episodes
Bøen et al. (2019)	22 BD-II 22 BPD 21 HC	+	^{18}FDG PET Resting state	Reduced metabolism in the insula regions was shown in both disorders
Bonne et al. (1996)	9 BD (9 D) 11 MDD 21 HC	+	^{99m}Tc-HMPAO SPECT Resting state	Examining individual regions of interest significantly lower perfusion in the left superior temporal, right parietal, and bilateral occipital regions in the patient group was found

(continued)

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Brooks et al. (2006)	8 BD (8 D) 27 HC	–	^{18}FDG PET CPT	No statistically significant differences in performance in CMR between the two groups was found
Brooks et al. (2010)	10 BD-I 6 BD-II 11 HC	+	^{18}FDG PET Resting state	Relative to HC, in BD commission errors were more strongly related to inferior frontal gyrus hypometabolism and paralimbic hypermetabolism. Relative to HC, in BD omission errors were more strongly related to dorsolateral prefrontal hypometabolism and greater paralimbic, insula, and cingulate hypermetabolism
Buchsbaum et al. (1986)	16 BD (16 D) 4 MDD 24 HC	–	^{18}FDG PET Electrical stimulation to the forearm	Global cerebral metabolism was found to be significantly higher in subjects with affective ness (both unipolar and bipolar depressed) compared to normal controls
Caletti et al. (2017)	36 BD-I 27 PD	+	^{18}FDG PET Resting state	Patients with low insight, compared to those with high insight, showed decreased metabolism in the right fusiform gyrus, left precuneus, superior temporal gyrus, and insula bilaterally, as well as increased metabolism in the left orbitofrontal gyrus
Culha et al. (2008)	16 BD (16 E) 10 HC	+	^{99m}Tc-HMPAO SPECT Resting state	The mean regional cerebral blood flow values of the euthymic BD patients were significantly lower than those of the controls in the bilateral medial-basal temporal, occipital; medial frontal; parietal regions and in the cingulate gyrus
Drevets et al. (1997)	21 BD (9 D, 8 E, 4 M) 17 MDD 51 HC	+	^{18}FDG and $H_2{}^{15}O$ PET Resting state	An area of abnormally increased activity in the prefrontal cortex ventral to the genu of the corpus callosum in both familial bipolar depressives and familial unipolar depressives has been found after correction for grey matter volume
Drevets et al. (2002)	15 BD (7 D, 9 E) 21 MDD 12 HC	–	^{18}FDG PET Resting state	Amygdala activity, which was correlated with stress plasma cortisol levels, was increased in depressed BD patients. Mood stabilizers normalize the amygdala activity in remitted BD

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Dunn et al. (2002)	27 BD (27 D) 31 MDD	–	^{18}FDG PET Auditory CPT	In both MDD and BD, the psychomotor-anhedonia symptom cluster correlated with lower absolute metabolism in right insula, claustrum, anteroventral caudate/putamen, and temporal cortex, and with higher normalized CMR in anterior cingulate
Forlenza et al. (2014)	19 BD (12 Li, 7 non-Li)	+	^{18}FDG PET Resting state	Chronic lithium treatment was not associated with any significant increase in brain glucose metabolism in the studied areas. A significant reduction in glucose uptake in several clusters of the cerebellum and in both hippocampi was demonstrated
Goodwin et al. (1997)	14 BD (14 E)	+	^{99m}Tc-EMZ SPECT Lithium withdrawal	Lithium withdrawal was associated with an important redistribution of brain perfusion, with increases in inferior posterior regions and decreases in limbic areas, particularly ACC
Gyulai et al. (1997)	13 BD (7 HM, 2 M)	+	^{123}I-IMP SPECT Resting state	The CBF distribution in the anterior part of the temporal lobes was asymmetric in both depressive and manic but not in euthymic state. Images taken sequentially on the same patient showed temporal lobe asymmetry in the pathological mood states that diminished or disappeared in the euthymic state
Ito et al. (1996)	6 BD (6 D) 11 MDD 9 HC	+	^{99m}Tc-HMPAO SPECT Resting state	Significant decreases in CBF in the prefrontal cortices, limbic systems, and paralimbic areas were observed in both depression groups compared with the healthy control group
Ketter et al. (2001)	14 BD-I (11 D, 4 E) 29 BD-II (22 D, 7 E) 43 HC	–	^{18}FDG PET CPT	In bipolar depression a pattern of prefrontal hypometabolism was observed additionally a cerebello-posterior cortical normalized hypermetabolism was seen in all bipolar subgroups

(continued)

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Krüger et al. (2006)	9 BD-I (9 E) 9 HS	+	$H_2{}^{15}O$ PET Transient sadness induction	Common to all three groups with induced sadness were CBF increases in the dorsal/rostral anterior cingulate and anterior insula and decreases in the orbitofrontal and inferior temporal cortices. Distinguishing the groups were decreases in the medial frontal cortex in the patients but an increase in this region in the siblings
Li et al. (2012)	17 BD-I (17 E) 17 BD-II (17 E) 17 HC	+	^{18}FDG PET Resting state	No difference in attention and memory tests was found among these three groups. Brain PET analysis showed that BD-I patients (compared to BD-II patients) had significantly lower glucose uptake in the bilateral anterior cingulum, insula, striatum, and part of the prefrontal cortex, and higher glucose uptake in the left parahippocampus
Li et al. (2015)	20 BD (20 E) 20 HS 20 HC	+	^{18}FDG PET Resting state	A dysfunctional connection with intact glucose uptake was demonstrated in the dlPFC-amygdala circuit of the HS, which highlights a vulnerability in families with BD
Mah et al. (2007)	13 BD-II (13 D) 18 HC	+	^{18}FDG PET Resting state	CMR was increased in the bilateral amygdala, accumbens area, and anteroventral putamen, left orbitofrontal cortex, and right pregenual ACC in depressive patients versus healthy control subjects. Post hoc exploratory analysis additionally revealed increased metabolism in left parahippocampal, posterior cingulate, and right anterior insular cortices in depressive patients versus healthy control subjects
Nugent (2014)	21 BD (21 D)	+	^{18}FDG PET Ketamine or placebo	Subjects had significantly lower glucose metabolism in the left hippocampus following the ketamine infusion than following the placebo infusion

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Rubin et al. (1995)	11 BD-I (11 M) 11 MDD 11 HC	+	^{133}Xe SPECT Resting state	The three groups were equivalent in global CBF. Both patient groups showed significant reductions of CBF in anterior cortical areas and reduction of the normal anteroposterior gradient
Rubinsztein et al. (2001)	6 BD (6 M) 6 MDD 10 HC	+	$H_2{}^{15}O$ PET Probability-based decision-making task	Task-related activation was increased in the manic patients compared with the control patients in the left dorsal ACC but decreased in the right frontal polar region
Rush et al. (1982)	12 BD 16 HC		^{133}Xe SPECT Resting state	During manic episode global CBF was increased compared to HC
Silfverskiöld and Risberg (1989)	40 BD (10 D, 30 M) 22 MDD 61 HC	+/–	^{133}Xe SPECT Resting state	Both patient groups showed a normal cerebral blood flow level and regional distribution compared with age- and sex-matched normal controls
Tutus et al. (1998)	7 BD (7 D) 10 MDD 9 HC	+/–	^{133}Xe SPECT Between groups and before/after medication Resting state	No significant differences in CBF emerged between the BD patients and the healthy control subjects
Zhang et al. (2011)	20 BD-I 20 BD-II 20 HC	+	^{18}FDG PET	PBMC p11 mRNA expression is associated with CMR in the mPFC, aCC, left insula, bilateral orbitofrontal cortex (OFC), and left middle, inferior, and superior temporal gyri of BD patients

HS Healthy sibling, *D* Depressive episode, *E* Euthymic episode, *M* Manic episode, *HM* Hypomanic episode, *Mi* Mixed episode, *CPT* Continuous performance test, *ADT* Auditory discrimination task, *SUD* Substance use disorder, *SIP* Substance-induced psychosis, *PD* Psychotic disorder

and both are indeed closely correlated in healthy controls (Drevets 2000). This appeared also to be the case in BD. Dunn et al. (Dunn et al. 2005) demonstrated that CMR and CBF were coupled globally and in most regions in BD, except the left pregenual anterior cingulate cortex.

CMR can be investigated with an ^{18}F-labeled fluorodeoxyglucose (FDG) PET scan. CBF is measured in PET by ^{15}O-labeled water. The most common SPECT tracers to measure CBF are ^{133}Xe, ^{123}I-labeled iodoamphetamine (IMP) and ^{99m}Tc-labeled hexamethylpropylene amine oxime (HMPAO). CMR and CBF can be measured in resting state or during various tasks.

Across the whole-brain level, it remains unclear whether there is an overall global CMR and CBF change in BD when compared to healthy controls. When investigated across mood states, some studies found reduced global CMR (Baxter et al. 1985, 1989; Ketter et al. 2001), while in other studies, no alterations were found in CMR (Bauer et al. 2005; Brooks et al. 2006).

In depressed patients CMR was found to be reduced when compared to controls and manic patients in some studies (Baxter et al. 1985, 1989) but increased in another study (Buchsbaum et al. 1986). One study investigating CBF found an increased perfusion in manic patients compared to controls (Rush et al. 1982), but others did not find any difference between the different mood states (Silfverskiöld and Risberg 1989; Tutus et al. 1998).

7.2.2.1 Prefrontal Cortex

The prefrontal cortex (PFC) is the area of the frontal lobes of the cerebral cortex that is located before the motor and premotor areas. It plays an important role in executive functioning such as planning complex behavior, personality expression, decision-making, and moderating social behavior (Miller et al. 2002). Regions of the brain are defined as Brodmann areas (BA) based on their cytoarchitectonic structure.

In general, BD patients in a depressive or manic episode have a decreased prefrontal cortex CMR and CBF, compared to euthymic patients or healthy controls. Blumberg et al. found a reduced CBF in the right orbital PFC (BA 11) and medial frontal gyrus (BA 10) in manic patients when compared to euthymic patients (Blumberg et al. 1999). Euthymic patients demonstrated orbitofrontal CBF decrease (Culha et al. 2008). The healthy siblings of BD patients demonstrated a comparable CBF decrease in the orbitofrontal PFC during induced sadness (Krüger et al. 2006).

In manic patients, a decrease in dorsolateral PFC (BA 8, 9, 46) CBF has been demonstrated (Rubin et al. 1995; al-Mousawi et al. 1996). Manic patients also showed a decrease of CMR during a decision-making task in the ventrolateral PFC (BA 47) when compared to controls (Rubinsztein et al. 2001). Furthermore, euthymic older BD patients (50–65 years) had a lower CMR in this region than controls of the same age (Brooks et al. 2006).

7.2.2.2 Limbic System and Subcortical Structures

The limbic system is a combination of in origin different brain structures that are involved in visceral behavioral patterns (related to survival: eating, drinking, sexual activity), emotions, and memory. Some structures, such as the hippocampus, amygdala, and anterior thalamic nuclei, are phylogenetically rather old structures (hence the other name paleomammalian brain), while the septum, fornix and limbic cortex are more recently developed structures.

The limbic cortex consists of the parahippocampal gyrus (BA 34–36), the cingulate gyrus (BA 23–26; 29–33), the insula (BA 13), and the dentate gyrus, which are parts of the frontal, parietal. and temporal cortical lobes on the medial surfaces of both hemispheres, surrounding the corpus callosum. The anterior part of the cingulate gyrus, the anterior cingulate cortex (ACC, BA 24, 25, 32, 33), plays a role in

autonomic functions (regulating blood pressure, heart rate), rational cognitive functions (reward anticipation, decision-making, empathy), pain perception, and emotion (Luu and Posner 2003).

In BD patients with depressive or manic episodes, an increased CMR and CBF were demonstrated in various parts of the limbic system. In depressed BD patients, Drevets et al. found an increased CMR in the subgenual portion of the ACC (BA 25) when compared to controls, after correction for grey matter volume (Drevets et al. 1997). This finding was repeated both in treated (Bauer et al. 2005) and in untreated depressed patients (Dunn et al. 2002). Dunn reported an association between this CMR increase and the presence of psychomotor and anhedonia symptoms. A similar increase in CMR was demonstrated in the pregenual and ventral area (BA 33, 24) of the ACC (Mah et al. 2007), whereas a decreased CMR was demonstrated in the insula (Bøen et al. 2019). Decreased CMR in the right fusiform gyrus, the left precuneus, superior temporal gyrus, and the insula bilaterally was associated with low insight (Caletti et al. 2017).

In manic patients, an increase in CBF, in the subgenual portion of the ACC (BA 25), was described compared to controls (Drevets et al. 1997). This increase was also found in the left dorsal ACC (BA 32) when compared to euthymic patients (Blumberg et al. 2000). In the manic patients, CMR during a decision-making task was increased in the left dorsal ACC, when compared with controls (Rubinsztein et al. 2001). In untreated manic patients, a SPECT study showed that increased cingulate cortex CBF is associated with poor executive functioning (Benabarre et al. 2005).

Goodwin et al. (Goodwin et al. 1997) examined 14 euthymic patients on lithium with SPECT before and after acute double-blind withdrawal of lithium. As often seen clinically, rapid withdrawal was associated with an increase of manic symptoms. The increase of manic symptoms correlated with a CBF decrease in the limbic areas, particularly the ACC.

Euthymic patients also demonstrated ACC CBF aberrations (Culha et al. 2008). The healthy siblings of BD patients demonstrated an comparable CBF increase in the ACC during induced sadness (Krüger et al. 2006). In another study in euthymic BD patients, p11 expression in peripheral blood mononuclear cells associated with CMR in the mPFC, aCC, left insula, bilateral orbitofrontal cortex (OFC), and left middle, inferior, and superior temporal gyri (Zhang et al. 2011). p11, also known as S100A10, is protein that belongs to a family of proteins that regulate a number of cellular processes such as cell cycle progression and differentiation. It is linked with the transport of neurotransmitters and found in the brain of humans and other mammals; it has been implicated in the regulation of mood (Hedhli et al. 2012).

The amygdala, part of the limbic system, is one of the subcortical areas that is known to be involved in BD. Others are the nucleus accumbens, globus pallidus, and striatum (including nucleus caudatus), all part of the basal ganglia of the brain that play a role in higher-order motor control. Individually they are involved in different functions, the nucleus accumbens in the reward circuitry, nucleus caudatus in learning and memory, particularly regarding feedback processing, and the globus pallidus in visceral regulation such as fever induction and emotion-induced tachycardia (Packard and Knowlton 2002).

Initially, studies of depressed BD patients versus controls described a reduced CMR in the amygdala (al-Mousawi et al. 1996) as well as the striatum (Baxter et al. 1985; Bonne et al. 1996; Ito et al. 1996). However, thereafter, various PET studies in depressed patients showed increased activity in the striatum, together with increased activity in limbic structures including the amygdala, hippocampus, and parahippocampal regions (Ketter et al. 2001; Drevets et al. 2002; Bauer et al. 2005; Mah et al. 2007; Brooks et al. 2009; Altamura et al. 2017). Additionally, amygdala and ventral striatal CMR correlated positively with depression severity and with cortisol levels (Ketter et al. 2001; Drevets et al. 2002). The difference between these initial and later studies is most probably explained by a higher signal quality and more careful patient selection in the later studies (Gonul et al. 2009).

Bipolar depression-related anxiety was found to respond to levothyroxine (Bauer et al. 2010, 2016). Change in anxiety covaried positively with changes in relative CMR in right amygdala and hippocampus. Change in state anxiety covaried positively with changes in relative CMR in the hippocampus bilaterally and left thalamus and negatively with changes in left middle frontal gyrus and right dorsal anterior cingulate (Bauer et al. 2010).

High CMR or CBF was also observed in the nucleus caudatus in manic patients (Blumberg et al. 2000) and nucleus accumbens in depressed patients (Benabarre et al. 2005).

7.2.2.3 Other Cortical Regions

An asymmetric CBF was found in the anterior temporal cortex in manic and depressed patients but not when the patients were euthymic (Gyulai et al. 1997). In a more recent study, it was demonstrated that euthymic older BD patients (50–65 years) have a higher CMR in this region than controls of the same age (Brooks et al. 2009). Furthermore, CBF in the temporal cortex of BD patients was positively associated with executive functions but negatively with attention and memory (Benabarre et al. 2005).

7.2.2.4 Corticolimbic Theory of Mood Disorders

Partly based on the above mentioned molecular imaging results, complemented with functional MRI (fMRI) research, a meta-analysis displays an overall hyperactivation of limbic brain regions in BD patients relative to controls, along with an overall hypoactivation of frontal regions (Kupferschmidt and Zakzanis 2011). This corresponds to findings in other mood disorders, especially MDD, which is known as the corticolimbic theory of depression (Mayberg 1997). Hypo- and hyperactivity in frontal and limbic regions, respectively, was most pronounced in manic patients, although also present in depressed and euthymic ones. Depressed patients exhibit more pronounced hypoactivation of frontal regions than euthymic patients, whereas euthymic patients display, surprisingly, more hyperactivity in limbic regions than their depressed counterparts.

CMR activation related to a decision-making task was decreased in manic patients in the PFC (Rubinsztein et al. 2001). Corticolimbic metabolic disbalance

was found to be negatively associated with cognitive functioning, including executive functioning and attention in two other studies (Brooks et al. 2010; Li et al. 2012).

The corticolimbic theory has some overlap with several neurological networks that have been described and are thought to lay at the basis of physiological emotional processing. These networks can be divided into circuits that lay within the cerebral cortex and those that exceed to other parts of the brain (Price and Drevets 2010).

The limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit connects the PFC to the limbic and subcortical areas of the brain (al-Mousawi et al. 1996). This LCSPT circuit is thought to be particularly important to mediate emotional expression, because of its relation to visceral control structures (Drevets et al. 2008).

The mood-related cortico-cortical networks interact with and extend to the LCSPT (Ongür et al. 2003) via top-down inhibitory control (Savitz and Drevets 2009). The orbital prefrontal network consists of the central and caudal part of the orbital cortex and the ventrolateral PFC, and it includes sensory association areas such as the visual-associated areas in the inferior temporal cortex and somatic sensory-associated areas in the insula and frontal operculum, as well as olfactory and taste cortex. In addition to sensory integration, this system codes for affective characteristics of stimuli such as reward, aversion, and relative value (salience) (Drevets et al. 2008).

The medial prefrontal network of cortical areas includes the ventromedial PFC, the dorsolateral PFC, the anterior and posterior cingulate cortex, anterior temporal cortex, and the entorhinal and posterior parahippocampal cortex. This system does not have substantial sensory connections, but is a visceromotor system that is particularly involved in introspective functions such as mood and emotion and visceral reactions to emotional stimuli (Price and Drevets 2010). It is widely known as the "default system," because it appeared activated as a network of areas that become inactive in most tasks that involve external attention in fMRI imaging (Gusnard et al. 2001). It has been proposed that the "ventral" orbital prefrontal network and the "dorsal" medial prefrontal network are reciprocally connected and that the orbital PFC may mediate connections between higher-order dorsolateral prefrontal regions and subcortical limbic regions such as the amygdala during emotion regulation (Phillips et al. 2008).

Corticolimbic functional disconnection has been demonstrated in both patients with BD and their healthy siblings. But only in patients, not in healthy siblings, was this associated with CMR aberrations (Li et al. 2015).

7.2.3 Neurotransmitter Studies

Departing from the neurotransmitter theory of affective disorders (Schildkraut 1965). PET/SPECT radioligand studies have focused on the serotonergic, dopaminergic, and cholinergic systems (Table 7.2).

Table 7.2 Overview of PET/SPECT studies on neurotransmitter systems in BD patients

Neurotransmitter	Study (author (year))	Subjects	Medication	Target	Method	Main findings
Serotonin	Yatham et al. (2005b)	7 BD (7 M)	+	5-HT_2	^{18}F-setoperone PET Valproate treatment	Treatment with valproate had no significant effect on brain 5-HT_{2A} receptor binding in manic patients
	Yatham et al. (2010)	10 BD (10 M) 10 HC	+	5-HT_2	^{18}F-setoperone PET	Brain 5-HT2 receptors are decreased in patients with acute mania
	Lan et al. (2013)	41 BD (41 D)	–	5-HT_{1A}	[^{11}C]WAY-100635 PET	Higher pretreatment brain 5-HT_{1A} receptor binding was associated with remission after 3 months of pharmacological treatment in bipolar depression
	Sargent et al. (2010)	8 BD (8 E) 8 HC	+	5-HT_{1A}	[^{11}C]WAY-100635 PET	No difference in 5-HT_{1A} receptor binding between medicated euthymic bipolar patients and healthy controls
	Nugent et al. (2013a)	10 BD (10 D)	+	5-HT_{1A}	[^{18}F]FCWAY PET valproate treatment, lithium treatment	Mean 5-HT_{1A} binding potential increased following mood stabilizer treatment, most prominently in the hippocampus and amygdala
	Nugent et al. (2013b)	26 BD 37 HC	–	5-HT_{1A}	[^{18}F]FCWAY PET	5-HT_{1A} receptor binding potential was lower in BD subjects compared to HC in cortical regions where 5-HT_{1A} receptors are expressed postsynaptically, most prominently in the mesiotemporal cortex. Across subjects the BPP in the mesiotemporal cortex was inversely correlated with plasma cortisol levels
	Ichimiya et al. (2002)	6 BD (1 D, 5 E) 7 MDD 21 HC	–	SERT	^{11}C(+)-McNeil 5652 PET	Binding potential in the thalamus was significantly increased in patients with mood disorders as compared to control subjects, whereas binding potential in the midbrain did not differ between the groups
	Oquendo et al. (2007)	18 BD (18 D) 41 HC	–	SERT	^{11}C(+)-McNeil 5652 PET	BD patients had 16–26% lower SERT density in the midbrain, amygdala, hippocampus, thalamus, putamen, and ACC

	Chou et al. (2010)	10 BD-I 14 BD-II 28 HC	–	SERT	^{123}I-ADAM SPECT	A lower SERT density was found in de midbrain of euthymic BD-I patients when compared to euthymic BD-II patients and healthy controls
	Chou et al. (2012)	23 BD-I (23 E) 23 HC	–	SERT	^{123}I-ADAM SPECT	A lower SERT density was found in de midbrain of euthymic BD-I patients when compared healthy controls. No correlation with BDNF was found
	Chou et al. (2015)	28 BD 28 HC	–	SERT	^{123}I-ADAM SPECT	Cortisol was associated with SERT availability in the midbrain in the HCs, but not in BD
	Hsu et al. (2014)	20 BD (20 E) 20 HC	–	SERT	^{123}I-ADAM SPECT	SERT availability was significantly lower in the midbrain and caudate of patients with BD compared with HC, but not in the thalamus and putamen. There was a significant association of SERT availability and IL-10 in the thalamus, but not in the midbrain, caudate, or putamen
	Cannon et al. (2006b)	18 BD (18 D) 37 HC	–	SERT	^{11}C-DASB PET	In BD, the mean SERT BP was increased in thalamus, dorsal cingulate cortex (DCC), medial prefrontal cortex, and insula and decreased in the brain stem at the level of the pontine raphe nuclei when compared to controls
	Cannon et al. (2007)	18 BD (18 D) 18 MDD 34 HC	–	SERT	^{11}C-DASB PET	Relative to the healthy group both MDD and BD groups showed significantly increased 5-HTT BP in the thalamus (24%, 14%, respectively), insula (15%), and striatum (12%). The bipolar depressives had reduced 5-HTT BP relative to both HC and MDD groups in the vicinity of the pontine raphe nuclei
	Miller et al. (2016)	17 BD (17 D) 31 HC	–	SERT	^{11}C-DASB PET	No abnormal SERT binding in bipolar depression using V_T/f_P
Dopamine	Pearlson et al. (1995)	14 BD (3 D, 11 M) 10 SZ 12 HC	–	D_2	^{11}C-3-N-methylspiperone PET	No statistical difference in D_2-binding was found between nonpsychotic BD patients and controls. Post hoc tests showed higher binding for psychotic patients with BD and SZ compared with controls and for SZ and psychotic BD patients compared to nonpsychotic BD patients

(continued)

Table 7.2 (continued)

Neurotransmitter	Study (author (year))	Subjects	Medication	Target	Method	Main findings
	Anand et al. (2000)	13 BD (13 E) 13 HC	+	D_2	^{123}I-IZBM SPECT Baseline, after amphetamine induction	BD patients and healthy subjects did not differ in terms of mood state or striatal D_2-receptor binding at baseline. Amphetamine challenge led to a significantly greater behavioral response in BD patients than in healthy subjects. However, there was no significant difference between the two groups in the amphetamine-induced decrease in striatal binding
	Jauhar et al. (2017)	22 BD 16 SZ 22 HC	+	DOPA uptake	^{18}F-DOPA PET	Dopamine synthesis capacity in the striatum was elevated in the psychotic BD and the SCZ group, compared with HC
	Yatham et al. (2002b)	13 BD-I (13 M) 14 HC	–	DOPA uptake	^{18}F-DOPA PET Baseline, after valproate treatment	No significant differences in ^{18}F-DOPA uptake rate constants in the striatum were found between the manic patients and the comparison subjects. After treatment with valproate, ^{18}F-DOPA rate constants were significantly reduced in the patients and were lower in the patients than in the comparison subjects
	Suhara et al. (1992)	10 BD (3 D, 6 E, 1 M) 21 HC	+	D_1	^{11}C-SCH23390	The binding potentials for the frontal cortex for the patients were significantly lower than those for normal controls, whereas those for striatum were not significantly different
	Yatham et al. (2002a)	13 BD-I (13 M) 14 HC	–	D_2	^{11}C-raclopide PET Baseline, after valproate treatment	The D_2 binding potential was not significantly different in manic patients than in the comparison subjects in the striatum. Treatment with valproate had no significant effect on the D2 binding potential in manic patients
	Amsterdam and Newberg (2007)	5 BD-II (5 D) 10 MD 46 HC	–	DAT	^{99m}Tc-TRODAT-1 SPECT	BD patients had greater binding compared to controls in the right posterior putamen and in the left caudate region. BD patients had modestly lower binding in all brain regions examined and a significantly lower binding in the right caudate region compared to MDD patients

	Chang et al. (2010)	17 BD (17 E) 17 HC	–	DAT	^{99m}Tc-TRODAT-1 SPECT	Compared to the controls, the euthymic BD patients had significantly higher availability of striatal DAT
	Anand et al. (2011)	11 BD-I (6 D; 5 E) 13 HC	–	DAT	^{11}C-CFT PET	BPD subjects had significantly lower DAT availability relative to controls in bilateral dorsal caudate
	Zubieta et al. (2001)	15 BD-I (15 E) 12 SZ 15 HC	+	VMAT	^{11}C-DTBZ PET	Binding of VMAT2 in the thalamus was higher in BD patients than in control subjects and SZ patients. Conversely, ventral brain stem binding was nearly identical between BD and SZ patients and was higher than in the control group
Norepinephrine	Yatham et al. (2018)	5 BD (5D) 5 MDD (5D) 9 HC	+	NET	(S,S)-[^{11}C]O-methyl reboxetine PET	NET density was significantly lower in locus ceruleus in MDD and BD patients compared with HC
Choline	Cannon et al. (2006a)	16 BD (16 D) 17 MDD 23 HC	–	mAChR M_2	^{18}F-FP-TZTP PET	Receptor binding was found to be decreased in the ACC of BD patients when compared to MDD patients and controls
	Cannon et al. (2011)	16 BD (16 D) 24 MDD 25 HC	–	mAChR M_2	^{18}F-FP-TZTP PET	Decreased receptor binding in BD-Is associated with genetic variation within CHRM2
	Hannestad et al. (2013)	25 BD (15 D, 10 E) 25 HC	+	nAChR β2	[^{123}I]5IA-85,380 PET	Lower receptor availability in subjects with bipolar depression compared with euthymic and control subjects across frontal, parietal, temporal, and anterior cingulate cortex, hippocampus, amygdala, thalamus, and striatum

HS Healthy sibling, *D* Depressive episode, *E* Euthymic episode, *M* Manic episode, *HM* Hypomanic episode, *Mi* Mixed episode, *CPT* Continuous performance test, *ADT* Auditory discrimination task

7.2.3.1 Serotonin

Serotonin (5-hydroxytryptamine) is a monoamine neurotransmitter that is formed out of the amino acid tryptophan. It is mainly found in the gastrointestinal tract, where its secreting cells regulate intestinal movement, in platelets, where it is released during aggregation, and in the central nervous system. Serotonin has a regulatory effect with regard to mood, sleep, sexual activity, and appetite.

The neurons located in the raphe nuclei, a cluster of nuclei in the brain stem, are the main source of serotonin in the brain. The axons from the raphe nuclei neurons project to nearly every part of the central nervous system. After serotonin is released in the synaptic cleft, it can bind to one of the various receptors, or it can be removed for reuse by the presynaptic neuron via the serotonin transporter.

As the primary site of serotonergic antidepressant activity, the serotonin transporter (SERT) is the part of the serotonin neurotransmitter system that has received the most attention in molecular imaging. Among the various ligands that are available, the PET ligands *trans*-1,2,3,5,6,10- -hexahydro-6-[4-(methylthio) phenyl] pyrrolo-[2,1-a] isoquinoline (^{11}C(+)-McNeil 5652), 3-^{11}C-amino-4-(2-dimethylam inomethylphenylsulfanyl)benzonitrile (^{11}C-DASB), and the SPECT ligand 2-([2-([dimethylamino]methyl)phenyl]thio)-5-^{123}I-iodophenylamine (^{123}I-ADAM) are used in BD research. An increase of SERT density was found in the thalamus using ^{11}C(+)-McNeil 5652 in a combined group of euthymic or mildly depressed patients (Ichimiya et al. 2002) and a reduction in the midbrain, hippocampus, thalamus, putamen, and ACC in a group of untreated depressed patients (Oquendo et al. 2007). With the use of ^{123}I-ADAM SPECT, a lower SERT density was found in de midbrain of euthymic BD-I patients when compared to euthymic BD-II patients and healthy controls (Chou et al. 2010, 2012, 2016; Hsu et al. 2014). This lower SERT density was not associated with changes of brain-derived neurotrophic factor (BDNF) (Chou et al. 2012). Using the more stable and selective ^{11}C-DASB ligand, an increased SERT density was found in the thalamus, dorsal cingulate cortex, medial prefrontal cortex, and insula of depressed untreated BD patients in some studies (Cannon et al. 2006b, 2007), but not all (Miller et al. 2016).

Although the results are inconsistent, it can be concluded that serotonin transporter alterations occur in BD, especially in parts of the limbic system. Taking the regulatory function and the observed metabolic changes into account, the SERT density alterations may be interpreted as an exponent of a dysfunctional frontolimbic network. It furthermore suggests that there might be (yet to be identified) modulators of gene expression or that other effects, such as serotonin transporter internalization, occur during different mood states.

At the level of the postsynaptic receptors a study using ^{18}F-setoperone demonstrated 5-HT$_2$ receptors to be decreased in patients with acute mania (Yatham et al. 2010). In another study investigating the treatment effect of valproate on the 5-HT$_2$-receptor binding, no difference before or after treatment in manic patients was found (Yatham et al. 2005b). 5-HT$_{1A}$ receptor binding potential was lower in BD subjects compared to healthy controls in mesiotemporal cortical regions (Nugent et al. 2013a, b). This binding potential correlated inversely with plasma cortisol levels (Nugent et al. 2013a) and increased with mood stabilizer treatment (Nugent

et al. 2013b). Also higher pretreatment 5-HT_{1A} receptor binding was associated with remission after 3 months of pharmacological treatment in bipolar depression (Lan et al. 2013). However, in another study no difference in 5-HT_{1A} receptor binding between medicated euthymic bipolar patients and healthy controls could be found (Sargent et al. 2010).

7.2.3.2 Dopamine

Dopamine is a catecholamine neurotransmitter that is formed out of L-DOPA, which in turn is made out of the amino acid tyrosine, while dopamine itself is the precursor of norepinephrine and epinephrine. A dopaminergic imbalance plays an important role in Parkinson's disease and psychotic symptomatology (psychotic symptoms during mood episodes and schizophrenia (SZ) (Beaulieu and Gainetdinov 2011). Additionally it is thought to be of importance in mania because of the antimanic effect of dopamine receptor blockers (antipsychotics) and the mania producing effect of dopamine-inducing substances, such as amphetamines (Cousins et al. 2009).

Five subtypes of dopamine receptors are known. The D_1-like family consists of D_1 and D_5 receptors, which lead to the stimulation of intracellular adenylate cyclase upon activation, causing cAMP to rise. The D_2-like family consists of D_2, D_3, and D_4 receptors, which lead to the inhibition of intracellular adenylate cyclase upon activation, causing cAMP to decrease. Overall, the D_1-receptor and D_2-receptor are the most abundant dopamine receptor subtypes in the brain, with particularly high expression in the striatum and nucleus accumbens and lower levels in the olfactory tubercle. The D_2-receptor is the prominent receptor in the substantia nigra, a region where the D_1-receptor is absent (Hartman and Civelli 1996).

After release into the synaptic cleft and having its neurotransmitting effect via the receptors, dopamine is pumped back into the cytosol of the presynaptic neuron by the dopamine transporter (DAT) from where it can be broken down by enzymes or be reused in synaptic vessels via the vesicular monoamine transporter 2(VMAT2) (Little et al. 2003).

Parts of the dopaminergic neurotransmission than can be examined with molecular imaging are the various dopamine receptors, dopamine release, and the dopamine transporter. These in turn can be investigated during resting state or after an amphetamine challenge (stimulating dopamine release).

The D_2-receptor is an obvious research target because of the known effectiveness of D_2-receptor blocking antipsychotic medication on manic and psychotic symptoms (Yildiz et al. 2011). Radioligands targeting this receptor are benzamides, such as raclopride and iodobenzamide, and butyrophenones, such as methylspiperone. The binding potential of the benzamides is known to fluctuate with changing endogenous dopamine concentrations, e.g., after amphetamine challenge. It is proposed that benzamides and butyrophenones do not bind to the same configuration of theD_2-receptor. Butyrophenones may bind primarily to the monomer form, whereas benzamides may bind to both the monomer and dimer forms of the receptor (Ginovart 2005).

In untreated nonpsychotic manic patients studies with the butyrophenone methylspiperone (Wong et al. 1985; Pearlson et al. 1995) and the benzamides

iodobenzamide and raclopride (Anand et al. 2000; Yatham et al. 2002) did not find striatal D_2-density difference compared to controls. Pearlson et al. however, did find a higher D_2-recepter density in the caudate nucleus of BD patients with psychotic features during their depressive or manic episodes when compared to BD patients during episodes without psychotic features (Pearlson et al. 1995). Within the group with psychotic features, the severity of the psychotic symptoms correlated with the receptor density, which was not the case with severity of mood symptoms. This suggests that the D_2-receptor density is specifically related to psychosis but not to mood symptoms. This theory is further supported by the finding that D_2-receptor density in the striatum was elevated in both psychotic BD and SZ patients, compared to HC (Jauhar et al. 2017), and the observation that the mood stabilizing anti-epileptic valproate sodium did not alter the D_2-receptor density in nonpsychotic manic patients (Yatham et al. 2002).

Concerning the D_1-recepter, Suhara et al. (Suhara et al. 1992) found the binding potential of SCH23390 to be decreased in the frontal cortex of BD patients with various mood states when compared to controls. In the striatum, results were comparable among patients and controls.

Dopamine synthesis can be investigated by measuring the striatal uptake of ^{18}F-labeled 6-fluoro-L-DOPA, which is a precursor to dopamine, as described above. Dopamine synthesis was found to be comparable among untreated nonpsychotic manic patients and controls. In view of the finding that valproate did not change D_2-receptor density, it is interesting that valproate was able to reduce dopamine synthesis in effectively treated manic patients (Yatham et al. 2002a, b). Perhaps the valproate-induced reduction of dopamine synthesis might be explained by an improved function of the PFC and fronto-limbic network resulting in an enhanced regulation of dopamine in the striatum.

Endogenous dopamine release can be measured with an amphetamine challenge, in which dopamine release is stimulated by blocking sequestering via DAT and VMAT2 and inhibiting the breakdown enzyme monoamine oxidase (MOA). In BD amphetamine challenge elicited a greater behavioral response, as measured with the Brief Psychiatric Rating Scale (BPRS) and the Young Mania Rating Scale (YMRS) in BD patients compared to controls. However, a difference between D_2-receptor binding potential of ^{123}I-iodobenzamide between these groups was not found (Anand et al. 2000). Because it is known that benzamide binding can fluctuate during amphetamine-induced endogenous dopamine binding, it cannot be ruled out that BD patients may have a more sensitive dopamine system to challenges with stimulants and treatment with mood stabilizers (Gonul et al. 2009).

In recent years the DAT gained scientific attention because it is hypothesized that some of the efficacy of mood stabilizing medication may be due to their action on DAT (Yatham et al. 2005a). In SPECT studies using ^{99m}Tc TRODAT-1 DAT density was increased in the right posterior putamen and in the left caudate in depressive BD-II patients (Amsterdam and Newberg 2007) and in the striatum of euthymic BD-I and BD-II patients (Chang et al. 2010). However, in untreated BD-I patients, a study using [O-methyl-^{11}C]β-CFT (^{11}C-CFT) PET showed decreased DAT density in the bilateral dorsal caudate. These contradictive results may be explained by

differences in patient groups (BD-I versus BD-II) and the difference in spatial resolution between SPECT and PET (Anand et al. 2011).

Using the (+)-α-^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) ligand, an elevated VMAT2 density was found in the thalamus and ventral striatum in euthymic BD patients with a history of psychotic symptoms, which was comparable to SZ patients, but differed from controls (Zubieta et al. 2001), This would suggest a relation with psychotic symptoms in BD; however, in the absence of research describing the VMAT2 density in BD patients without psychosis, a relation with affective symptoms cannot be ruled out.

Overall, it can be assumed that altered dopamine neurotransmission plays a disease modifying role, especially in BD patients that experience psychotic symptoms in addition to affective symptomatology. However, dopamine neurotransmission as a pathophysiological mechanism in nonpsychotic BD patients needs further research.

7.2.3.3 Norepinephrine

Norepinephrine, also called noradrenaline or noradrenalin, is an organic chemical in the catecholamine family that is formed out of dopamine and functions in the brain and body as a hormone and neurotransmitter. Norepinephrine is the main neurotransmitter used by the sympathetic nervous system, which consists of about two dozen sympathetic chain ganglia located next to the spinal cord, plus a set of prevertebral ganglia located in the chest and abdomen. It is a neuromodulator of the peripheral sympathetic nervous system but is also present in the blood, mostly through "spillover" from the synapses of the sympathetic system. The noradrenergic neurons in the brain form a neurotransmitter system, that, when activated, exerts effects on large areas of the brain. The effects are manifested in alertness, arousal, and readiness for action.

In BD, quetiapine is effective in treating depressive symptoms, and although the underlying mechanisms are not yet completely understood, norquetiapine has high affinity for the norepinephrine transporter. Using (S,S)-[^{11}C]O-methylreboxetine, the norepinephrine transporter occupancy was found to be decreased in BD and MDD patients, compared to healthy controls, providing support for the hypothesis that norepinephrine transporter occupancy by norquetiapine may play a role in the antidepressant effect of quetiapine (Yatham et al. 2018).

7.2.3.4 Choline

Acetylcholine is a neurotransmitter in both the peripheral nervous system and central nervous system. In the central nervous system, it has a variety of effects as a neuromodulator upon plasticity (specifically in learning and memory), salience of sensory stimuli, arousal, and reward.

Interestingly, cholinesterase inhibitors were found to increase depressive symptoms in BD and MDD patients (Dilsaver 1986).

Muscarinic type 2 receptor binding was decreased in the ACC of depressed BD patients when compared to MDD patients and controls, using 3-(3-(3-[^{18}F]flouropropyl)thio)-1,2, 5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine (^{18}F-FP-TZTP)

(Cannon et al. 2006a). This decrease in muscarinic type 2 receptor binding in BD patients was associated with a genetic variation in cholinergic muscarinic-2 receptor gene (Cannon et al. 2011). Furthermore, the depression and anxiety severity in BD patients were negatively correlated with the binding potentials, emphasizing a contribution of the cholinergic neurotransmitter system in BD pathophysiology.

Lower nicotinic β2 receptor availability was demonstrated using [^{123}I]5IA-85380 PET in subjects with bipolar depression compared to euthymic and control subjects across frontal, parietal, temporal, and anterior cingulate cortex, hippocampus, amygdala, thalamus, and striatum (Hannestad et al. 2013).

7.3 Other Pathophysiological Models

Besides the abovementioned corticolimbic theory and the neurotransmitter theory, several other pathophysiological theories have been proposed for BD. Of these, we will address the neuroinflammation theory, the white matter tract integrity disruption theory, and the mitochondrial dysfunction theory to illustrate the even broader neuroimaging field in this type of BD research. These theories provide starting points for future molecular imaging research.

7.3.1 Neuroinflammation

The "macrophage theory of depression" postulates an aberrant pro-inflammatory state of monocytes/macrophages in patients with mood disorder and considers this aberrant state of the cells as a driving force behind the illness (Smith 1991). The theory is based on a higher frequency of autoimmune diseases in mood disorders, aberrant pro-inflammatory cytokines, and elevated pro-inflammatory gene expression in monocytes.

Autoimmune thyroiditis is considered to be an endophenotype of BD (Vonk et al. 2007). Patients with BD and MDD have a raised prevalence of autoimmune thyroiditis (Carta et al. 2004; Bunevicius et al. 2007). Not only BD patients but also their offspring (affected as well as non-affected) and their monozygotic (affected and non-affected) and dizygotic (affected, but not as much unaffected) co-twins have a raised prevalence of autoimmune thyroiditis (Hillegers et al. 2005; Vonk et al. 2007). It was hypothesized that an activated inflammatory response system in monocytes constitutes the shared genetic susceptibility factor for both BD and thyroid autoimmunity, leading to the extensive investigations of neopterin, IL-1β, IL-6, and TNF-α in mood disorders. With regard to the serum concentration of these compounds, increased levels were also described in BD when compared to controls, and concentrations of individual compounds were found to be associated with mood state (Rowland et al. 2018). To investigate the pro-inflammatory state of monocytes in a more precise and robust manner, a Q-PCR analyses of CD14+ purified monocytes were performed in which 22 mRNAs for inflammatory, chemokinesis/motility, cell survival/apoptosis, and MAP kinases pathway molecules were found to

have an increased expression in BD patients compared to controls (Padmos et al. 2008).

Interactions between the immune system and the HPA-axis, as well as interactions between the immune system and the neuronal system via indoleamine 2,3 dioxygenase (IDO) pathways, have been suggested to result in mood disorder symptomatology. The HPA-axis is a complex set of direct influences and feedback interactions among the hypothalamus, the pituitary gland, and the adrenal glands that controls reactions to stress and regulates many body processes. The adrenal glands produce cortisol, which is a major stress hormone and has effects on many tissues in the body, including the brain where it binds to glucocorticoid receptors in the PFC, the amygdala, and the hippocampus (Spijker and van Rossum 2012). Moreover, glucocorticoid insensitivity has been associated with a higher risk on developing an depressive episode (Spijker and van Rossum 2012). In various in vivo and ex vivo studies, a strong association between the activation of the inflammatory response system and glucocorticoid insensitivity has been demonstrated, linking at least in part the overproduction of pro-inflammatory cytokines to the HPA-axis disturbances in major mood disorders (Almawi et al. 1991; Pariante et al. 1999; Ito et al. 2006).

Molecular imaging techniques are of added importance in investigating the neuroinflammation theory. Microglia are the central cells involved in immune regulation in the brain. These cells present the peripheral benzodiazepine receptor (PBR) on their mitochondrial membrane, when activated (Doorduin et al. 2008). Using translocator protein (TSPO) targeting PET ligands, such as ^{11}C-PK11195 and ^{11}C-PRB28, areas of microglia activation in the brain can be visualized. Using [^{11}C]-(R)- PK11195, in BD we demonstrated a statistically significant increased binding potential in the right hippocampus and a, similar but trend level, increased binding potential in the left hippocampus of BD-I patients as compared to healthy controls. This is indicative of microglial activation (Haarman et al. 2014). In the subsequent explorative analyses, we identified a positive association between microglial activation and the NAA + NAAG concentration in the left hippocampus, indicating a positive relation between microglial activation and neuronal integrity in vivo (Haarman et al. 2015). In another study, using ^{123}I-ADAM SPECT, a significant association of SERT availability and peripheral blood IL-10, an anti-inflammatory cytokine, was demonstrated in the thalamus (Hsu et al. 2014).

7.3.2 White Matter Tract Integrity Disruption

Interest in the white matter tracts in BD started with the observation of diffuse cortical and callosal white matter pathology in structural MRI studies in BD patients (Kempton et al. 2008; Vita et al. 2009). With the development of diffusion tensor imaging (DTI), a MRI technique allowing for the investigation of the preferred direction and rate of water diffusion, the integrity of the white matter tracts can be investigated in more detail, because in the physiological situation water diffusion is restricted by the axonal structures (Le Bihan 1996). The main parameters derived

from DTI are the fractional anisotropy (FA) and mean diffusivity (MD). MD measures the magnitude of water molecule diffusion and FA is an index of the degree of directionality of water diffusivity. FA is reduced in diseased states known to be associated with axonal loss and destruction of myelin sheaths in several diseases, e.g., multiple sclerosis, leukoencephalopathies and Alzheimer's disease (Le Bihan 2003).

In BD most studies reported reduced FA and/or elevated MD compared to controls involving the prefrontal lobe frontal lobe, corpus callosum, internal capsule, uncinate fasciculus, and superior and inferior longitudinal fasciculi and suggesting a role for white matter integrity disruption in BD pathophysiology (Heng et al. 2010).

The studies focusing on the specific mood states of BD patients revealed FA to be altered in the different mood states (Zanetti et al. 2009). In the euthymic state, FA was usually found to be increased in the genu of corpus callosum, internal capsule, anterior thalamic radiation, and uncinate fasciculus compared to controls, whereas during depressive episodes, a lower FA has been shown in the genu of the corpus callosum and in corona radiate compared to controls. In mixed samples higher and lower FA values were found in different brain regions (Bellani and Brambilla 2011).

The place of white matter integrity disruption with regard to other disease mechanisms in the pathophysiology is a matter of ongoing investigation. It has been suggested that FA changes, in analogy to multiple sclerosis (Zanetti et al. 2009), could be related to inflammation-related processes in BD or metabolic dysregulation (Altamura et al. 2013).

7.3.3 Mitochondrial Dysfunction

Using various different techniques, scientific evidence for a cellular energy metabolism disturbance has been presented. When observed in cell biological research, abnormal mitochondrial morphology is often linked to altered energy metabolism. In BD patients mitochondria were smaller and concentrated proportionately more within the perinuclear region than in distal processes of the cells, when compared to controls (Cataldo et al. 2010). Conversely, patients with mitochondrial diseases have a higher lifetime prevalence of MDD (54%) or BD (17%) than the average population (Fattal et al. 2007).

Magnetic resonance spectroscopy (MRS) is a neuroimaging technique that allows the investigation of the metabolism on a cellular level. It is a MRI technique that provides additional biochemical information of a selected voxel compared to a regular T1 or T2 image. The cellular metabolites are presumed to represent different cell functions: N-acetyl-aspartate (NAA) relates to cell viability, choline to cell membrane phospholipids integrity and creatine is a measure of cellular metabolism (Gillard et al. 2004). Creatine plays an important role as a cell energy buffer, especially in high-energy consuming cells such as muscular and brain cells. Using the creatine energy buffer reaction (Fig. 7.2), cells with an abundance of ATP can store

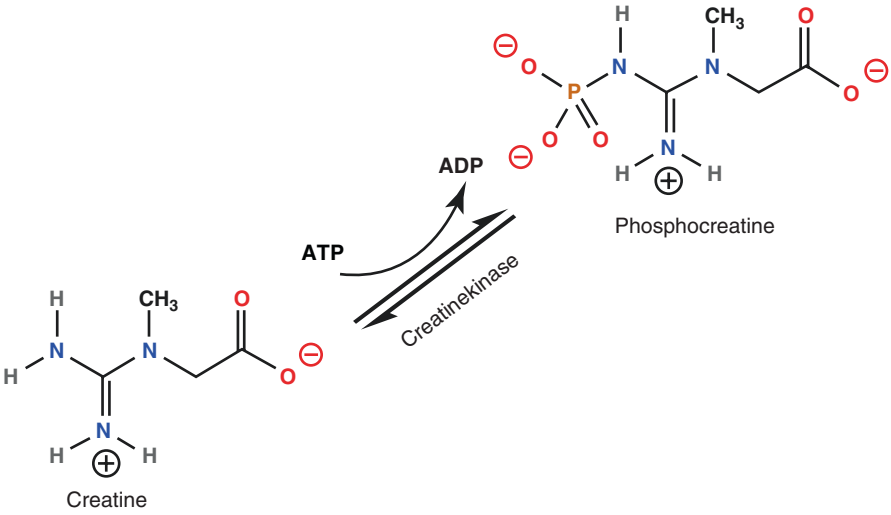

Fig. 7.2 Creatine energy buffer reaction

the energy by converting creatine to phosphocreatine. When in energy demanding circumstances, the ATP stock becomes depleted, ATP can temporarily be supplied by reconverting phosphocreatine to creatine until the phosphocreatine stock is also depleted or energy is resupplied via other routes such as the oxidative phosphorylation.

With ^{31}P-MRS creatine and phosphocreatine concentrations can be measured separately as well as the total concentration of both metabolites. The total concentration can also be measured with ^{1}H-MRS, the separate concentrations to a lesser degree when advanced quantification tools are being used. In BD patients a decreased phosphocreatine (Kato et al. 1993) and reduced total creatine (Frey et al. 2007; Port et al. 2008) was described, when compared to controls, supporting the mitochondrial dysfunction theory. Findings in other MRS metabolites such as a reduced pH and increased lactate, exponents of cell metabolism exhaustion, add indirectly to this theory (Kato et al. 1993; Dager et al. 2004).

A study concerning the nature of the metabolic dysfunction revealed a paradoxical downregulation of mitochondria-related genes to glucose deprivation in fresh lymphocytes derived from BD patients, whereas cells from control subjects showed an upregulation. This finding would suggest that patients with BD might have impairment in molecular adaptation to energy stress (Naydenov et al. 2007). However there is still debate whether this dysregulation is based on mitochondrial DNA disturbances or mitochondria-related nuclear DNA disturbances or due to other mechanisms (Kato 2008). Furthermore, it is not known if this dysregulation occurs in all brain regions and whether there is an association with neuroinflammation or neurotransmitter disturbances. Combined PET-MRI study efforts may help to answer this question.

7.4 Conclusion

Since the beginning of the earliest PET and SPECT studies in patients with BD in the 1980s, this field of research gave rise to many new insights in the pathophysiology of BD. The first, mainly metabolism and blood flow-oriented studies aided to the study of various aspects of the metabolism based disease model in which PFC hypoactivity is accompanied by limbic hyperactivity. This model in its comprehensive form is however probably not precise enough to account for most of the specific mood and cognitive disease features, and efforts are being made to provide more detail. The role of molecular imaging as the main imaging technique in metabolism studies has been taken over by fMRI, but molecular imaging is still used to answer specific questions in which fMRI falls short. Molecular imaging demonstrated the importance of serotonin transporter alterations in parts of the limbic system in BD and underscored the role of dopamine and cholinergic neurotransmission.

Apart from serotonergic/dopaminergic dysfunction, and the corticolimbic theory of mood disorders, the neuroinflammation theory is of particular interest because it endeavors to incorporate the complex interactions between the neurologic, immunologic, and endocrine systems into one model. In addition, the white matter tract integrity disruption and mitochondrial dysfunction models provide other invigorating viewpoints to the BD disease mechanism.

Most molecular imaging studies in BD have unique designs, extending the knowledge on the pathophysiological mechanisms but also complicating comparisons between studies. The earlier studies with selection of heterogeneous patient groups, including both BD-I and BD-II patients and being in different mood states (manic, depressed, and euthymic) led to results that were difficult to interpret. Moreover, use of medication can affect study outcomes, while studies with only medication-naïve patients, studies with washout periods and naturalistic studies, all have their specific advantages but also disadvantages. Naturalistic study designs have the advantage that they are generally easier to perform and less burdensome for patients with this serious psychiatric disorder, but the effect of medication use can never be evaluated in a valid way. The obvious advantage of studies in medication-naïve subjects is the exclusion of these medication effects. The question arises however in how far the uniqueness of these patients in that they are able to function without medication, interferes with the investigated mechanism (i.e., the internal validity), and limits the generalizability (i.e., the external validity). In washout studies one could argue that drug withdrawal interferes with the investigated mechanism.

Another complicating factor is that the molecular imaging studies are limited in patient number because of careful ethical considerations due to the ionizing nature of the technique, which complicates comparisons between subgroups. Finally, some ligands are generally expected to measure the same biological property but are later on found to differ in some specific aspects of the measurement complicating comparison between studies. Nevertheless, because of its unique selectivity emanating from a large and continuously extending range of ligands, molecular imaging remains an important tool in BD research.

The important challenge for the next years will be to position and interconnect the individual models and observations into a more comprehensive model, explaining not only the specific mood characteristics of the disorder but also other aspects like, e.g., vulnerability for relapses, the variability in cognitive disturbances associated with BD, although not in all patients. Furthermore, genetic, epigenetic, and developmental vulnerabilities need to be more incorporated into these models. Finally, BD and its pathophysiology do not stand on its own, but there is overlap with other psychiatric disorders, which also makes it important to study proposed mechanisms not only in BD but also in the other disorders, in order to further understand the similarities as well as the difference between the various disorders.

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