Aetiopathogenesis of Bipolar Disorder 13

BD was traditionally conceptualized in the frame of mood (affective) disorders until its separation from unipolar depression by DSM-5. This long history caused much of the research to focus indiscriminately on 'mood disorders' by pooling together bipolar and unipolar patients in study samples. Bipolar depression was not studied separately from unipolar for too long, and mania was not the intensive focus of research.

Therefore, the aetiopathogenesis of BD was considered as related with that of unipolar depression rather than with that of schizophrenia. Most experts agree that mood disorders have both endogenous and exogenous components and in most patients they are both present. This approach is a sharp rejection of the 'historical dualism' suggested by Rene Descartes in the seventeenth century and theoretically has its roots in the 'psychobiology' of Adolf Meyer (1866–1950) which used the term to emphasize that psychological and biological factors interact in the development of mental disorders. The bio-psychosocial model, proposed by George L. Engel (1913–1999) (Engel 1977, 1980), provides a non-specific but inclusive theoretical framework in order to host all variables suggested by various approaches to cause depression.

However, such an approach is obsolete today because the need is for specific and accurate models and predictions and not for general frameworks. It is a problem that in psychiatry such an advanced understanding is lacking not only for BD but for mental disorders in general.

13.1 Social Theories

All the literature on social theories for mood disorders refer essentially to unipolar depression, and much of it is often generalized to include bipolar depression although such an approach is probably mistaken. Social theories are attractive to lay people especially since along with many psychological theories, they attribute mood disorders to adverse life events. However, even in the frame of unipolar

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depression, this assumption is far from being proven (Harkness and Luther 2001; Paykel et al. 1984). But the sensitization of stress-responsive neurobiological systems as a possible consequence of early adverse experience has been more solidly implicated in the pathophysiology of mood and anxiety disorders. A history of childhood abuse per se may be related to increased neuroendocrine stress reactivity, which is further enhanced when additional trauma is experienced in adulthood (Heim et al. 2002).

Depressed patients were reported to have higher perceptions of day-to-day stressors (hassles), reduced perception of uplifting events, excessive reliance on emotion-focused coping strategies and diminished quality of life in comparison to controls, and this can be considered in the frame of an early sensitization procedure. Among depressed patients the hassles, coping styles and some elements of quality of life were related to symptom severity, as well as treatment resistance (Ravindran et al. 2002). However, it is questionable whether this is a true fact or these patients (which have higher personality psychopathology and interpersonal rejection sensitivity) tend to over-report life events (Fountoulakis et al. 2006).

Thus, many authors insist that psychosocial factors are relatively unimportant in the subsequent course of severe and recurrent depressions, in contrast to their contribution to onset of such depressions and subsequent outcome of milder depressions (Paykel et al. 1996; Thomson and Hendrie 1972). This could be especially valid concerning bipolar depression which is longitudinally characterized by more 'endogenous' and psychotic features.

13.2 Psychological Theories

The literature on psychological theories for BD is limited. Most of the researchers had focused so far on the unipolar types depression and mood instability; therefore, there is no clear psychodynamic (or similar) theory concerning mania.

The only available specific theory implies that mania has the same cause with depression and they are both related with the loss of a loved object. The difference is that while depression emerges from the introjection of the lost object, mania is the result of the attempt to avoid depression. Essentially mania constitutes a defence against an underlying depression and utilizes a number of defence mechanisms like omnipotence, denial, idealization and contempt. In this frame, the euphoric state of the patient is understood as a tendency to extinguish any unpleasant aspects of reality and to disregard for the problems of reality, even if the situation is tragic. Thus, mixed episodes are easily psychodynamically understood, since the manic elements seen in depressed patients are considered to be defences. Overall this hypothesis corresponds more to 'elation' but not to mania, and there are no empirical studies to support the suggestion that a stressful event precedes the onset of acute mania.

Some authors stress the repetitive maladaptive patterns in the family, including avoidance of affect, unrealistic standards of conformity and displaced parental low self-esteem (Davenport et al. 1979), but such approaches lack specificity and probably refer to a generic family and personality dysfunction which is more or

less common in most mental disorders (Kutcher et al. 1992). Some reports include problematic methodology and study samples, and the results are difficult to interpret (Loeb and Loeb 1992; Louet et al. 2010) or are based on the study of isolated cases (Steggles 2012).

The psychological theories on the aetiopathogenesis of depression are more elaborated, and they cover a wide variety of concepts and hypotheses. All of them were derived from observations in patients with conditions including reactive and characterological depression, personality disorders and unipolar depression, and they assume that more or less all these conditions emerge from a common or similar background. The most important psychological theories for depression are listed below:

13.2.1 Aggression-Turned-Inward Model

It has been proposed by Sigmund Freud and Karl Abraham on the basis of a 'metaphor' from physics to psychology ('hydraulic mind'). According to this model, during the oral phase (i.e. during the 12th–18th months of life) disturbances in the relationship between the infant and the mother establish a vulnerability to develop depression. Then during the adult life, a real or imaginary loss leads to depression as the result of aggressive impulses turned inward and directed against the ambivalently loved internalized object which had been lost. The aim of that turned-inward aggression was supposed to be the punishment of the love object which fails to fulfil the patient's need to be loved. It is therefore accompanied by guilt which could lead to suicidal behaviour. Later other authors proposed somewhat different versions of this model. The drawbacks of this model include that it represents a relatively closed circuit independent of the outside world, while the clinical fact is that many depressed patients openly express anger and hostility against others which is reduced after treatment and that there is no evidence supporting the concept that expressing anger outwards has a therapeutic effect in the treatment of clinical depression.

13.2.2 Object Loss

The term refers to traumatic separation from significant objects of attachment. However, according to empirical research data, only a minority of no more than 10 % of people experiencing bereavement will eventually manifest clinical depression. Thus, the model includes two steps: an early one which includes the development of vulnerability because of a significant loss during childhood and a second step during which this vulnerability interacts with a significant loss during adult life and eventually leads to clinical depression. This model fits better the data in comparison to the aggression turned inward and has some support from studies on primates although the latter point to a broad psychopathology rather than specifically depression.

13.2.3 Loss of Self-Esteem

Depression is considered to originate from the inability of the ego to give up unattainable goals and ideals resulting in a collapse of self-esteem. This model suggests that the narcissistic injury that destroys the patient's self-esteem comes from the internalized values of the ego rather than the hydraulic pressure deriving from the id as proposed by the aggression-turned-inward model. In this frame the loss of self-esteem has a sociocultural and existential dimension, and thus, this theory is to a significant extent testable. The drawback of this theory is that both persons with low and high self-esteem can develop depression or mania without any significant differences among them.

13.2.4 Cognitive Model

The cognitive model was developed by Aaron Beck and suggests that thinking in a negative way is the core of clinical depression. According to this, depression is conceptualized in the frame of the 'cognitive triad'. This triad proposes that patients conceive the self, the environment and the future in a negative depressive way (helplessness, negativism and hopelessness). In the core there seems to be bias in the way of thinking of the person. This is the cause of an interpretation of any experiences in a profound negative attributional style (mental schemata) which is considered to be global, internal and stable. This bias in the way of thinking is because of overgeneralization, magnification of negative events with a simultaneous minimization of positive events, arbitrary inference and selective abstraction. Systematic errors in thinking allow the persistence of negative schemas despite contradictory evidence. The major drawback of this model is the fact that it is based on retrospective observations of depressed patients; thus, the negative triad could be simply part of the clinical picture or subclinical manifestations of depression and not the cause of it. The major advantage is that it led to the first testable and practical psychotherapeutic approach which seems to be effective in a specific subgroup of patients.

13.2.5 Learned Helplessness Model

This model is based on animal experiments and proposes that the depressive attitude is learned during past situations in which the person was not able to terminate or avoid undesirable or traumatic events. However, it seems that the learned helplessness paradigm is more general and refers to a broader mental condition (e.g. social behaviour, posttraumatic stress disorder, etc.). It seems that past events could shape a personality profile which includes passivity, lack of hostility and self-blame. However, this line of thinking could lead to the notion that depression and the behaviours accompanying it should be considered to be a result of a masochistic lifestyle with manipulative behavioural patterns in order to handle interpersonal issues. Even more, recent animal research has implicated the importance of genetic factors in the vulnerability to learning to behave helplessly.

13.2.6 Depression and Reinforcement

According to the reinforcement model, the behaviours characteristic for depression develop because of a lack of appropriate rewards and with receipt of non-contingent rewards. This theory bridges personality, low self-esteem and learned helplessness with the human social environment; however, it seems more appropriate for the interpretation of social issues than clinical depression. A psychotherapeutic approach aiming to improve the patient's social skills is based on this theory.

13.3 Neurobiology of BD

13.3.1 Neuroanatomy of BD

A first step in understanding the neurobiology of BD would be to adequately explore and understand the neurobiology of emotions. However, in spite of the tremendous development of clinical neurosciences during the last 20 years, emotions and their disorders are still not satisfactorily understood.

There are many brain structures which are supposed to associate with the experience of mood and production of normal affect and emotions. Grossly, they form two complementary neural networks referred to as the ventral and the dorsal systems. The ventral system includes the amygdala, insula, ventral striatum, ventral anterior cingulate cortex (ACC) and the prefrontal cortex (PFC) and subserves the identification of the emotional significance of a stimulus, the production of affective states and also the automatic regulation of emotional responses (Swanda et al. 2000). The dorsal system includes the hippocampus, the dorsal ACC and PFC and subserves the conscious regulation of affective states and subsequent behaviour (Davidson and Irwin 1999). A simplified neurobiological model may propose that 'mood' derives probably from processes largely taking part in the amygdala and the insula, while 'emotion' is generated mainly in the anterior cingulate cortex (ACC) and more specifically in area 25 (Anderson and Phelps 2002). However, its regulation is likely to implicate area 24 and the dorsolateral prefrontal cortex (DLPFC). In between, 'mood' and 'emotion' lies the 'affect' which is at least partially generated in the ACC and partially in other brain areas including the prefrontal cortex (PFC).

Both psychological and biological aetiological factors converge in the diencephalic substrates of pleasure and reward (Akiskal and McKinney 1973), and the corresponding conceptual model (Figs. 13.1 and 13.2) links the central chemistry and physiology of structures that generate mood and reward mechanisms, memory storage and retrieval, as well as motor responses and behavioural disturbances which are characteristic of BD (Fountoulakis et al. 2008a). Among the structures involved in this model, the ACC and amygdala are thought to play a key role in the integration of emotional and cognitive dimensions mainly during the depressive phases of BD. The CC is a heterogeneous structure in terms of cytoarchitecture and function (Fig. 13.2). Its role on the neurophysiological basis of emotional expression and affective regulation is considered of major importance. For instance, damage of this

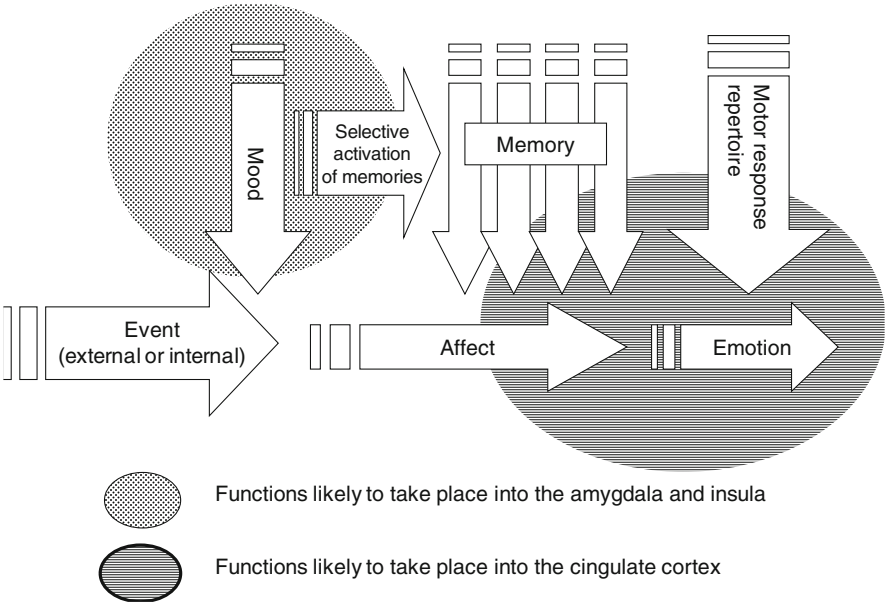

Fig. 13.1 A very simplified model for mood affect and emotion in response to stimuli. The model does not include the plethora of existing feedback (Reprinted with permission from Fountoulakis et al. (2008a))

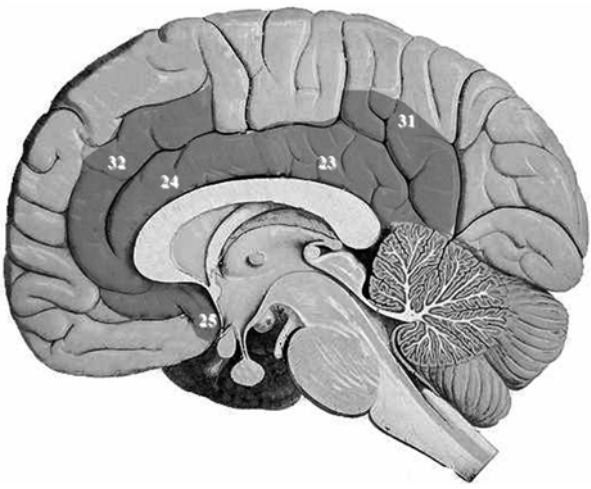

Fig. 13.2 The areas of the cingulate cortex implicated in the production of affect (Reprinted with permission from Fountoulakis et al. (2008a))

area has been associated with impaired pain regulation, akinetic mutism and apathy and indifference to pain (Chow and Cummings 2000).

Mood disorders may involve a dysfunctional coordination of limbic-cortical connections, with dorsal structures being responsible for neurocognitive disorders, ventral structures for somatic symptoms and the rostral ACC for the coordination of

them (Tekin and Cummings 2002). Most of the current neuroanatomical and functional observations in ACC, mostly in its subgenual part (areas 25 and part of 24), argue in favour of a mixed neurodevelopmental and neurodegenerative process contributing in the pathophysiology of mood disorders.

13.3.1.1 Structural Neuroimaging

The presence of volumetric changes in the brains of BD patients is definitely known since approximately 20 years, and they have been interpreted according to two major theories. The first implies the presence of neurodevelopmental abnormalities which are independent of the severity or the long-term course of the disease or the response to treatment. Alternatively, they may reflect neurodegenerative changes related to the chronicity of the disorder. Both conceptions are supported by research data which showed that volume decrease in this area is present as early as the prodromal phase but seems to increase with the duration of illness (Farrow et al. 2005; Hajek et al. 2005; Hirayasu et al. 1999; Kaur et al. 2005; Lyoo et al. 2006; Lagopoulos et al. 2012; Strakowski et al. 2002). Thus, a volumetric decrease seems to be present and it might have some prognostic value.

The literature so far suggests that patients with BD manifest an enlargement of the third and lateral ventricles (Soares et al. 2005), white matter hyperintensities (Moore et al. 2001; Silverstone et al. 2003; Marlinge et al. 2014) and reduced grey matter in the prefrontal cortex, the hippocampus and the cerebellum (Moorhead et al. 2007; Soares et al. 2005; Blumberg et al. 2006) as well as a volume reduction in the left cingulate cortex (CC) (Bruno et al. 2006; Lyoo et al. 2006) or the right CC (McDonald et al. 2004). Some studies suggest the volumetric reduction in the CC is bilateral (Bearden et al. 2007; Coyle et al. 2006; Doris et al. 2004; Lochhead et al. 2004). There is a large body of literature pointing to a specific vulnerability of the left anterior CC (ACC) and in particular its subgenual part (sgACC) (Atmaca et al. 2007; Lyoo et al. 2004; Sassi et al. 2004) or left posterior CC (PCC) (Hirayasu et al. 1999; Houenou et al. 2007; Wilke et al. 2004). However, some studies report a right or bilateral ACC (Bruno et al. 2004; Cannon et al. 2006a) or a left or bilateral PCC volume decrease (Farrow et al. 2005; Kaur et al. 2005; Lim et al. 1999; Lochhead et al. 2004). Although, it should be noted that there is some degree of heterogeneity among studies concerning the specific areas which manifest atrophy or lesions, in general the findings concern the prefrontal, cingulate and subgenual cortices; the fusiform gyrus; and the left hippocampus (Lim et al. 2013; Javadapour et al. 2007; Fountoulakis et al. 2008a).

Histologically, volume loss may reflect grey or white matter changes. There are reports suggesting a grey matter loss in the CC bilaterally (Lim et al. 1999; Doris et al. 2004) or specifically in the left CC (Wilke et al. 2004; Drevets et al. 1997; Lyoo et al. 2004) which could be progressive (Farrow et al. 2005). Loss of macromolecular density was reported for the right sgACC and adjacent white matter in BD patients compared to controls (Bruno et al. 2004), while the use of diffusion tensor imaging tractography (DT-MRI) documented a significantly increased number of reconstructed fibres between the left sgACC and left amygdalo-hippocampal complex in BD patients compared to healthy controls (Houenou et al. 2007). Another DT-MRI study reported significantly shorter white matter tracts in the genu, body and splenium of the corpus callosum compared to healthy controls. Additionally,

BD patients exhibited reduced fibre density in the genu and body of the corpus callosum and in the inferior longitudinal fasciculus bilaterally. In the left uncinate fasciculus, however, BD subjects exhibited significantly greater fibre density than healthy controls (Torgerson et al. 2013).

While in schizophrenia a loss of brain volume is evident already at onset, in BD this happens latter. This is especially true concerning grey matter, while on the contrary, the loss of white mater volume might happen first and be present already at onset (Berk et al. 2010; Vita et al. 2009; Bora et al. 2010; Strakowski et al. 1993). Therefore, it is possible that white matter pathology is the prominent finding during the early stages (Lim et al. 2013; Lin et al. 2013), while grey matter loss follows years later (Arango et al. 2012).

The decrease in volume is generally correlated with the number of episodes (Strakowski et al. 2002), and these findings are considered to be associated with a poor prognosis (Moore et al. 2001; Silverstone et al. 2003).

On the other hand, there are reports suggesting that there was no difference in grey matter loss in BD patients in comparison to controls and there was also no effect of the number of episodes (Brambilla et al. 2002; Lopez-Larson et al. 2002; Zimmerman et al. 2006; Zipursky et al. 1997; Nery et al. 2009). It is interesting that in contrast to the rest of the literature, an increase in the size of the amygdala (Blumberg et al. 2006) and the grey matter density in the ACC of BD patients have been reported (Adler et al. 2007; Bearden et al. 2007) thus raising doubts about the presence of a widely present neurodevelopmental abnormality in BD. Also, in spite of findings concerning specific regions, it seems that the total brain volume remains stable, and this puts forward a number of problems concerning the methods of quantification of brain volume and other methodological issues (Fountoulakis et al. 2008a).

There are evidences that at least three variables might influence the volumetric changes in BD: the presence of cognitive decline (Bruno et al. 2006), response to treatment (Sassi et al. 2004; Cannon et al. 2006a; Atmaca et al. 2007; Bearden et al. 2007) and genetic background (McDonald et al. 2004), but overall the literature on neuroimaging data at different stages of BD is limited and most of the data are cross-sectional (Lim et al. 2013; Balanza-Martinez et al. 2005) which make generalizable conclusions difficult.

13.3.1.2 Neuropathological Data

A significant part of the total contribution on the neuropathology of BD is based on the material provided by the Stanley Neuropathology Consortium (Cotter et al. 2002; Knable 1999; Raedler et al. 1999; Torrey et al. 2005; Webster et al. 2005; Zavitsanou et al. 2004, 2005).

The validity of histological findings depends on the quality of the material available, staining procedures and number of sections within each area. An additional variable to consider is a possible pharmacological effect on brain microstructure (Fountoulakis et al. 2008a). For instance, an early neuropathological study showed a preferential concentration of lithium in the retrosplenial CC (corresponding to BA 23 and 31) and caudate nucleus suggesting a differential regional impact of this molecule in BD (Spirtes 1976). Not surprisingly, to date there are no convincing evidence supporting neuronal or glial loss in BD.

Macroscopically, one study reported a 20 % reduction in the volume of area 24 in BD patients compared to controls. However, because of the small study sample, the difference was not significant. The authors did not find changes in the number or size of neurons in area sg24 in BD cases. The reduction in glial number (41 %) was statistical significant only in the familial BD subgroup (bilaterally) (Ongur et al. 1998). Two other studies reported no differences in the size of cell bodies; however, they also reported a 27 % reduction in the density of non-pyramidal neurons in layer II of the ACC in BD patients. In sporadic cases without chronic drug treatment, it has been reported that the mean total and laminar cortical thicknesses as well as mean pyramidal neuron size were significantly decreased in sg Brodmann area (BA) 24 in BD patients (Bouras et al. 2001). Another study reported a decreased clustering of neurons in the BA 24c bilaterally in BD patients, and the neuronal somal size was reduced in layer V (16 %), and neuronal density was increased in layer VI in (63 %) (Chana et al. 2003). An increase in density of 2,3-dioxygenase-immunoreactive glial cells in both grey and white matter of the ACC was also reported (Miller et al. 2006).

A number of independent studies failed to identify differences in glial density or neuronal size in BD compared to controls (Benes et al. 2000, 2001; Cotter et al. 2001).

A meta-analysis reported a decreased density (31 %) of non-pyramidal neurons bilaterally in layer II of the ACC in BD patients. They reported no differences in glial numbers with 2D cell counting, but significant glial reduction in layers III, V and VI when using 3D cell counting (Todtenkopf et al. 2005). Western blot data did not add further clarity since studies reported decreased levels (32 %) of glial fibrillary acidic protein (GFAP) mRNA in the white but not grey matter of ACC, area 24b (bilaterally) in BD patients (Torrey et al. 2005; Webster et al. 2005).

Interestingly, it has been reported that proteins related to the number and functioning of synapses such as synaptophysin, complexin II and growth-associated protein-43 (GAP-43) may be reduced in the BA 24a and 24b of the ACC of BD patients. On the contrary, there were no differences in complexin I and beta-actin levels between BD and controls (Eastwood and Harrison 2001). Since synaptophysin is a marker of synaptic density and GAP-43 is a marker of insult-induced plasticity, these findings suggest a loss of synapses with impaired remodelling. The reduction of complexin II but not I suggests a progressive destruction of excitatory rather than inhibitory synapses (Auer et al. 2000).

Exploring the hypothesis that glutamatergic inputs onto gamma-aminobutyric acid interneurons via the N-methyl-d-aspartate (NMDA) receptor are altered in the ACC in schizophrenia and BD, Woo et al. reported that the density of all GAD(67) mRNA-containing neurons was decreased by 35 % in layer II of the ACC. This decrease reached 60 % for GAD(67) mRNA-containing neurons that co-expressed NR(2A)mRNA (Woo et al. 2004).

To test the hypothesis that apoptosis could play a role in BD-related neuronal pathology, the Klenow method for in situ end-labelling of single-stranded DNA breaks was applied to the ACC from 18 healthy controls, 18 patients with schizophrenia and 10 with BD. Here again, the results did not reveal any reduction in BD patients (Benes et al. 2003). In contrast, apolipoprotein D protein levels showed

a 57 % increase in BA 24 (Thomas et al. 2003). Moreover, there is evidence indicating that there is more DNA fragmentation in cells showing no detectable GAD67 mRNA in patients with BD than controls. These findings suggest that non-GABAergic cells may be selectively vulnerable to oxidative stress in patients with BD (Buttner et al. 2007).

A recent review focused on the medial prefrontal cortex (mPFC) network and reported the presence of a volume decrease with reductions in neuronal size and/or changes in neuronal density, reductions in glial cell density and changes in gene expression. These findings point to both white and grey matter loss probably on the basis of a reduction in the cell counts of specific subpopulations of GABAergic interneurons (Savitz et al. 2014).

13.3.2 Functional Studies

13.3.2.1 Functional Neuroimaging

Unfortunately the functional neuroimaging studies are usually restricted to the depressive phase of the illness simply because when patients are in an acute manic phase, it is very difficult to provide the level of collaboration needed to apply this kind of examination.

One of the rare studies on mania reported an increased activity in the left dorsal ACC (BA 24 and 32) and postulated the presence of a state-dependent activation of a left fronto-striatal neural system that includes the ACC and the caudate nucleus (Blumberg et al. 2000). Another study was in accord with this observation and also showed a decreased metabolism in the left sgACC (BA 25 and part of 24) during the depressed phase in familial BD (Drevets et al. 1997). This latter finding may partly reflect the concomitant grey matter volume reduction that reached 39 % in this area. In contrast, a PET analysis in 27 medication-free, mildly to severely depressed BD patients revealed that the psychomotor–anhedonia symptom cluster correlated with increased metabolism in the right ACC raising the question of interhemispheric differences in ACC involvement in BD (Dunn et al. 2002). Besides the already mentioned methodological limitations, the impact of psychopharmacological treatment on metabolic values at rest is a key parameter to consider when interpreting these data. For instance, the administration of lithium or valproate is associated with increased metabolism in right pregenual ACC in BD-II patients as compared to controls (Mah et al. 2007).

Activation data in untreated BD patients could be divided into two main categories: those obtained with classical neuropsychological tests and those corresponding to emotionally significant situations. Neuropsychological activation studies mainly included working memory, executive function and attention paradigms. Functional MRI results were quite variable in respect to possible trait- related changes. For instance, while performing a 2-back visuospatial working memory task, children and adolescents with stable BD showed an increased activation of the ACC bilaterally compared to controls (Chang et al. 2004). In contrast, negative or discrepant data were obtained after activation using the Stroop interference task (Gruber et al.

2004). In terms of state-related changes, increased metabolic rates were found in the left dorsal ACC using PET in manic patients during tests involving decision-making and sustained attention (Rubinsztein et al. 2001). In the same line, SPECT data pointed to the relationship between poor executive function performance and increased CC metabolism in unmedicated manic patients (Benabarre et al. 2005). However, most fMRI studies still support the hypofrontality hypothesis in mania (Altshuler et al. 2005; Blumberg et al. 2003; Roth et al. 2006).

Emotional activation in BD led to strikingly discrepant trait- and state-dependent fMRI patterns. During the visualization of positively valenced pictures, familial euthymic BD patients had greater activation in the left ACC, while during the visualization of negatively valenced pictures, they displayed a decreased activation in the right PCC compared to controls (Chang et al. 2004). Euthymic BD patients exhibited an increased activity in the right pregenual ACC in response to both angry and happy faces compared to neutral faces (Pavuluri et al. 2007). Conversely, a fMRI study of ten euthymic patients with BD-I and ten age- and gender-matched healthy subjects during a modified word-based memory task designed to implicitly evoke negative, positive or no affective changes showed a significantly greater ACC and PCC activation by both negative and positive affects in healthy subjects as compared to patients in response (Malhi et al. 2007). During an emotional and nonemotional go/no-go test, euthymic BD patients displayed an increased activity in the left dorsal ACC (BA 24) and right PCC (BA 23) when inhibiting emotional compared to neutral stimuli (Wessa et al. 2007).

Patients with mania had attenuated subjective rating of the intensity of sad facial expressions that was associated with decreased activation in the sgACC and bilateral amygdala and increased activation in the PCC and posterior insula (Lennox et al. 2004). Importantly, the rostral ACC response to emotional faces was decreased in unmedicated, but not in medicated, manic patients compared to controls pointing to the possibility that mood-stabilizing medications may reverse functional abnormalities in BD (Blumberg et al. 2005). This is further supported by recent PET/SPECT studies on the induction of negative emotions in BD. Both at baseline and after transient sadness induction, euthymic BD patients had an increase in dorsal ACC (BA 24a) and a decrease in the left PCC (BA 24 and 31) rCBF compared to controls. Depressed patients showed only a decrease in the right PCC (BA 31) (Kruger et al. 2003). A subsequent PET study utilizing the same method in nine euthymic lithium responders and nine healthy siblings revealed that induced sadness increases rCBF in the ACC in all subjects. The siblings' pattern of rCBF changes was similar to that of the lithium-treated patients and included an increased rCBF in the dorsal and rostral ACC (BA 24a/b) (Kruger et al. 2006).

13.3.2.2 Impact of Pharmacological Treatment on Activation Patterns

It is a very difficult task to isolate the effect of pharmacological treatment on metabolic patterns in BD patients. However, most contributions confirm the well-known confounding influence of most psychotropic agents. Overall, the literature suggests that medicated BD patients exhibit greater activation in the ACC in comparison to drug-free BD patients (Strakowski et al. 2005).

Concerning lithium, the double-blind acute withdrawal of lithium was associated with a marked decrease of perfusion in limbic areas and mainly in the ACC. Interestingly, half of patients developed manic symptoms during the placebo phase, which was accompanied by a relative increase of perfusion in the superior ACC (Goodwin et al. 1997). During treatment, lithium-treated patients displayed an increased activation of BA 24a, whereas valproate treatment seems to decrease the metabolic rates in this area (Kruger et al. 2006). However, proton magnetic resonance spectroscopy (1H MRS) indicated that acute lithium treatment is associated with a significant reduction in the myoinositol/creatine ratio. This decrement was also present in lithium responders when analysed separately from nonresponders (Davanzo et al. 2001).

A PET study on ten depressed BD patients and ten controls suggests that the administration of high-dose levothyroxine treatment adjunctive to ongoing medication (antidepressants and mood stabilizers) reduced the significantly higher activity in the right sgACC (areas 25 and part of 24) measured before treatment in BP depressed patients compared to controls. In contrast to that observed in subcortical structures, this decrease did not correlate with symptom improvement (Bauer et al. 2005).

An MRS study of glutamate+glutamine/creatine ratio (Glx/Cr) in the ACC of ten untreated manic and eight risperidone-treated BD children suggested that untreated children had a lower Glx/Cr (Moore et al. 2007a). Another MRS study evaluated the status of the ACC at baseline and after an open trial of lamotrigine in 23 BD depressed patients and 12 control subjects. It revealed that baseline CSF-corrected absolute concentrations of Glx, glutamate (Glu) and creatine+phosphocreatine (Cr) were significantly higher in BD depressed subjects vs. healthy controls. The non-melancholic subtype had significantly higher baseline Glx and Glu levels than the melancholic subtype. Remission with lamotrigine was associated with a significant decrease in glutamine (Gln) concentrations (Frye et al. 2007). A third MRS study exploring again the Glu and Glx levels in the ACC of 22 (15 medicated and 7 unmedicated) children and adolescents with BD vs. ten healthy controls suggests that untreated BD patients have significantly lower glutamine levels than controls or medicated patients. In the light of the cardinal role of glial cells in glutamate metabolism, these results suggest the presence of an abnormality in ACC glia in untreated children and adolescents with BD (Moore et al. 2007b).

13.3.3 Neurotransmitters and Receptors

Data coming from animal experiments and models implicate the limbic–diencephalic brain in mood disorders and more specifically neurons containing serotonin and noradrenaline. Historically the monoamine deficiency hypothesis is based on data from the study of the cerebrospinal fluid (CSF) metabolites. According to this theory, there is a monoamine deficiency, especially norepinephrine (NE), in depression. Later, studies illustrated that this theory should also include serotonin (5-HT), leading to a broader theory regarding neurotransmission disorder in the central nervous system (CNS) (Schildkraut 1965; Maas 1975; Van Praag and Leijnse 1963).

Later, the cholinergic–noradrenergic imbalance hypothesis (Davidson 1972; Tarsy et al. 1972; Janowsky et al. 1972) included acetylcholine in a broader model for mood disorders. More complex models include state changes (depending on the polarity of the mood episode) in the excitatory amino acid function in specific areas of the cortex (Fountoulakis et al. 2008a).

However, in spite of decades of extensive research, there is no definite proof for either a deficiency or an excess of either the quantity or the overall functioning of biogenic amines in specific brain structures. Even when these abnormalities were documented, it has been shown that they are neither necessary nor sufficient for the occurrence of mood disorders. In contrast, it seems that the neurotransmitter disorders recognized until today refer to a broader behavioural dysfunction which includes behavioural disinhibition, obsessive–compulsive symptoms, anxiety, eating disorders and substance and alcohol abuse as well as personality disorders. This is not peculiar since most classic animal models are in essence post-traumatic stress models and most biological psychoendocrinological markers are markers of stress-related somatic reactions. Recent research explores disturbances at the level of second messengers and close to DNA function with variable success but no definite conclusions.

Using a 5-HT radioligand in 18 depressed, unmedicated BD patients and 37 controls, the same group showed that in BD, the mean 5-HT binding is increased in the dorsal CC. Most importantly, the presence of anxiety symptoms (and mainly obsessions and compulsions) correlated positively with 5-HT binding in the dorsal CC. BD suicide attempters displayed an increased 5-HT binding in ACC compared to both controls and BD non-attempters (Cannon et al. 2006b). A more recent PET study of 11 unmedicated BD patients revealed that they had significantly lower dopamine transporter (DAT) availability relative to healthy controls in the dorsal caudate bilaterally (Anand et al. 2011).

Another PET study assessed the binding potential of muscarinic M2 receptors in 16 unmedicated BD patients in depressive phase vs. 17 unipolar patients and 23 controls. BD patients had a lower mean ACC M2 receptor binding compared to both unipolar depressive patients and controls. The authors suggested that this reduction could be explained by a reduction in M2 receptor density or affinity. Alternatively, it could indicate an elevation in endogenous acetylcholine levels in BD patients compared to the other two groups (Cannon et al. 2006a). Negative autoradiographic data were mainly published for M1 and M4 receptors (Zavitsanou et al. 2004, 2005) with the marked exception of a significant effect of suicide on [(3)H]pirenzepine binding in the ACC in BD (Zavitsanou et al. 2004).

While for unipolar depression the antidepressant effect on serotonin pathways is considered to be both a necessary and a sufficient condition for the achievement of the treatment response, this is not the case with bipolar depression. It is true however that the neurobiology of bipolar depression still remains elusive and the assumption that serotonin has a dominant role comes from the belief that unipolar and bipolar depression share at least some neurobiologic substrates. However, the monoamine hypothesis for unipolar depression is based mainly on treatment data (TCAs and SSRIs), and these treatments have no proven efficacy against bipolar depression.

One of the theories that exist so far suggested that the 5-HT-1A receptor is the most likely target (Yatham et al. 2005). However, the data available today do not support such an assumption, since that receptor is activated by aripiprazole, lamotrigine, ziprasidone and other compounds which are proven not to be efficacious (Fountoulakis et al. 2008a, b; Fountoulakis and Vieta 2008; Fountoulakis et al. 2007; Vieta et al. 2010). A second model reviewed both the clinical treatment data as well as the preclinical properties of those agents with proven efficacy against bipolar depression vs. those with proven non-efficacy (Fountoulakis et al. 2012). The results suggested that the stronger predictors for antidepressant efficacy in bipolar depression were norepinephrine alpha-1, dopamine D1 and histamine antagonism. However, while they seem to be a necessary condition, they don't seem to be sufficient, since they characterize agents without bipolar antidepressant efficacy. The second stronger cluster of predictor activities includes 5-HT2A, muscarinic and dopamine D2 and D3 antagonism, 5-HT-1A agonism and norepinephrine reuptake inhibition. All the above properties characterize both quetiapine and the OFC and seem to be a unique combination not shared by any of the drugs without bipolar antidepressant efficacy.

The importance of the blockade of dopamine receptors is an open question; it could simply be the consequence of the presence of antipsychotic properties in both quetiapine and the OFC. These antipsychotic/antimanic properties could constitute an important element for an agent to succeed in an RCT on bipolar depression, since they might protect from manic switches and subsequently from dropouts (which was largely the cause for the failure of venlafaxine).

Eventually this model suggests that norepinephrine reuptake and 5-HT-1A agonism are at the centre and closer to the core deficit and points out that serotonin reuptake is not a sufficient condition for antidepressant efficacy in bipolar depression, and this is in sharp contrast with unipolar depression. Although 5-HT-1A activation is necessary, it is not sufficient. Another core conclusion is that norepinephrine activity is more important.

A line of research is also in accord with the results and conclusions of the current review. The literature suggests that both serotonin and norepinephrine are lower in the locus ceruleus of bipolar patients who died from suicide (Wiste et al. 2008) and that norepinephrine might play a more important role than serotonin in the pathophysiology of bipolar disorder (Young et al. 1994). It has been proposed that the antidepressant activity of quetiapine is mediated, at least in part, by its metabolite N-desalkylquetiapine through norepinephrine reuptake inhibition and partial 5-HT(1A) agonism (Jensen et al. 2008). Also, chronic administration of olanzapine alone significantly increased firing of locus ceruleus (LC) neurons, while chronic administration of fluoxetine alone significantly reduced firing of LC neurons. It seems that in the combination condition (OFC), olanzapine was able to block the fluoxetine-induced suppression of the LC, and a significant increase in LC activity was observed (Seager et al. 2004, 2005).

Similarly, there are no evidences supporting a significant involvement of the human endogenous cannabinoid system (Burnet and Harrison 2000; Koethe et al. 2007; Peckys and Hurd 2001).

The GABA is considered to be a promising target of research for the elucidation of the pathophysiology of BD but also for the development of novel treatment approaches (Fountoulakis et al. 2012).

A possible deficit in GABA and developmental/synaptic neurochemical systems in BD has been sustained by the detailed analysis of Torrey et al. who assessed up to 100 RNA, protein and other neurochemical markers in a single set of 60 post-mortem brains including 15 from patients with BD (Torrey et al. 2005). Nine post-mortem studies attempted to explore whether changes in receptor densities may influence the expression of key inhibitory or excitatory pathways in BD brains. The density of GABAergic terminals was significantly reduced in all four layers of BA 24 bilaterally. This reduction was most significant in layers II (27.8 %) and III (37.2 %) (Benes et al. 2000, 2001). The study of GABA neurons containing NMDA 2A subunit mRNA in the anterior cingulate cortex (ACC) suggested that their numerical density was decreased by 60 % in layer 2 in patients with BD (Woo et al. 2004). The same researchers reported that in the ACC the subset of GABA interneurons that contained the calcium-binding protein calbindin (with preferential localization to layer 2) was either increased in density or had become more frequently NR2A expressing in patients with schizophrenia compared with the normal control subjects and subjects with BD (Woo et al. 2008b).

The use of calcium-binding proteins (CBPs) parvalbumin (PV), calretinin (CR) and calbindin-D28K (CB) as markers of cortical gamma aminobutyric acid (GABA) neurotransmission in BD did not confirm the involvement of GABA inhibitory circuits in this disorder (Cotter et al. 2002). In the same line, a recent GAD immunocytochemical analysis did not identify differences between BD and controls rendering unlikely a deficit of GABA synthesis in bipolar patients (Bielau et al. 2007).

State-related biochemical changes were also analysed with proton MRS studies. The comparison of ACC choline (Cho) and myoinositol (MI) levels in 9 BD patients taking either lithium or valproate, and 14 controls revealed that BD depression severity correlated positively with Cho/creatine–phosphocreatine (Cr-PCr) in the left CC. No clinical or drug-related changes were observed for the MI/Cr–PCr ratio in this study (Moore et al. 2000) as well as in a similar one (Bertolino et al. 2003). In contrast, significantly higher MI levels and MI/Cr–PCr ratio as well as N-acetyl-L-aspartate (NAA) and glutamate–glutamine metabolite levels were measured in 10 depressed BD patients as compared to 10 patients with intermittent explosive disorder and 13 controls (Davanzo et al. 2003). In line with this observation, mania has been associated with reduced glutamate/glutamine levels in the ACC (Moore et al. 2007a). In terms of trait-related changes, euthymic BD patients receiving lithium treatment for at least 4 weeks showed no significant difference in the ACC NAA/Cr and Cho/Cr ratio compared to controls. However, chronic administration of psychotropic drugs could have had an independent effect on NAA/Cr. In conclusion, these results suggest that NAA, which is a putative marker of neuronal density and a measure of neuronal viability and integrity, could be reduced in the ACC of BD patients, and medication might be able to reverse this deficit. They also suggest that mania may be associated with reduced glutamate/glutamine levels in the ACC. Medication acts here as a confounding factor again.

In the use of in situ radioligand binding and autoradiography to measure neurochemical markers in the prefrontal cortex (PFC) Brodmann area (BA), nine revealed an age-related decrease in NMDA receptor density in control subjects that was absent in schizophrenia and BD (Dean et al. 2001). Two other studies suggested that in the PFC, glutamatergic regulation via the subunit 2A-containing NMDA receptors does not appear to be altered in bipolar disorder in contrast to schizophrenia (Bitanihirwe et al. 2010; Woo et al. 2008a). This was confirmed by a study from another research group, which reported decreased NR1 expression in the dorsolateral prefrontal cortex of bipolar patients and no changes of NR2B or NR2D. Although the NR1 is obligatory, receptor autoradiography revealed no alterations in receptor binding, indicating no change in total receptor number. These authors also measured associated postsynaptic density (PSD) protein (PSD95, neurofilament light (NF-L) and SAP102) transcripts and reported reduced NF-L expression in schizophrenia and reduced SAP102 expression in bipolar disorder restricted to small cells of layer II and large cells of layer III. Taken all together these data suggest abnormal receptor stoichiometry (Beneyto and Meador-Woodruff 2008). The same research group had previously reported the NR3A mRNA was significantly decreased by 12 % in bipolar disorder relative to the comparison group in the dorsolateral prefrontal cortex (Mueller and Meador-Woodruff 2004).

The situ hybridization to assess hippocampal expression of the transcripts encoding NMDA receptor subunits NR1, 2A, 2B, 2C and 2D and the transcripts for the NMDA receptor-associated PSD proteins PSD95, PSD93, NF-L and SAP102 revealed a significant decrease in the expression of transcripts for NR1 and NR2A subunits and SAP102 in BD but no changes in schizophrenia (McCullumsmith et al. 2007). However, peculiarly, the same group reports negative or conflicting results concerning the hippocampus (Beneyto et al. 2007). Another research group did not confirm the reduction in the NR1 specifically in the hippocampal dentate gyrus, but did find a decrease in PSD-95 in the dentate molecular layer (Toro and Deakin 2005). The use of in situ radioligand binding with semiquantitative autoradiography, to measure the density of [3H]MK-801, [3H]CGP39653 (that bind to NMDA receptors), [3H]AMPA and [3H]kainate binding in hippocampi, suggested that in subjects with BD there were significant decreases in the density of [3H]MK-801 binding in the cornu ammonis as well as the pyramidal and polymorphic layers of the subiculum. There were no changes in the densities of [3H]AMPA or [3H]kainate binding in these subjects (Scarr et al. 2003).

In the perirhinal cortex, a decreased expression of NR1 and NR2B is reported (Beneyto et al. 2007); however, another research group did not find any changes in NR1 or PSD-95 in the orbitofrontal cortex (OFC) of bipolar patients (Toro and Deakin 2005).

The investigation of the NR1 subunit in superior temporal cortex (STC) using radioligand binding of [(3)H]L-689,560 to the glycine site and quantitative immunoblotting techniques revealed an increased receptor density in schizophrenia and decrease in bipolar and depressive disorders (Nudmamud-Thanoi and Reynolds 2004).

In the striatum an expression of transcripts encoding PSD-95 and SAP-102 is reported in BD, while no significant changes in NF-L and PSD-93 mRNAs were observed (Kristiansen and Meador-Woodruff 2005). In the thalamus, no changes in

NR1 and NR2A-D were found; however, there was a decreased NF-L, PSD95 and SAP102 transcripts in the thalamus of patients with BD (Clinton and Meador-Woodruff 2004).

Genetic studies suggest a relationship of genes encoding the 1, 2A and 2B subunits of the NMDA receptor with bipolar illness implying a hypoglutamatergic state in bipolar patients. However, the studies are few and have not been replicated. Neuropathological studies suggest a possible decrease in the density of NMDA receptor and more consistently a reduced NMDA-mediated glutamatergic activity in patients with BD. The literature suggests a reduction of NMDA density in the PFC as well as abnormal NMDA composition. In the ACC a reduction of 2A subunit is reported. In the hippocampus data are conflicting concerning the NMDA density, but they confirm a functional hypoactivity specific for this kind of receptors. No changes in density, only functional hypoactivity was reported for the thalamus. Lithium seems to reduce NMDA activity possibly through reduced phosphorylation of this receptor.

Thus, the literature might suggest BD is related with slower NMDA kinetics because of lower contribution of NR2A subunits. This could serve to bridge neurodevelopmental hypotheses for the development of BD and neuropharmacological data. Slower kinetics might make NMDA receptors incapable of dealing with the increased speed of stimuli during manic episodes leading to disorganization (Fountoulakis et al. 2012).

A number of biological markers have been developed so far to assist the diagnosis and assessment of depression, but no one is proved so far strong enough for use in clinical practice. The dexamethasone-suppression test (DST) has been widely used for the study of hypothalamus–pituitary–adrenal (HPA) axis disorders in patients with depression (Green and Kane 1983; Evans and Golden 1987; Stokes et al. 1984). It requires the oral administration of 1 mg dexamethasone (a synthetic glucocorticoid) at 23:00 on day 1 and the assessment of cortisol levels at the same time, at 08:00, at 16:00 and at 23:00 on day 2. A cortisol value of 5 μg/dl, in at least one measurement in day 2, is considered to be the cut-off point between normal (suppressors) and pathological (non-suppressors). Longer protocols requiring higher dosage for dexamethasone and a 24 h long assessment have also been suggested. The test presents a 67 % sensitivity and 96 % specificity in the diagnosis of melancholy in psychiatric inpatients. The results of the up-to-date research efforts report that DST presents results that are probably related with the severity of depression and the patient's family history. Other psychoendocrinological markers are the TRH stimulation test (blunted thyroid-stimulating hormone response to thyrotropin-releasing hormone) (Musselman and Nemeroff 1996; Kendler et al. 2000) and the fluramine and d-fenfluramine challenge tests which (Siever et al. 1984; Fessler et al. 1984; Quattrone et al. 1979; Garattini et al. 1987; Di Renzo et al. 1989; Rowland and Carlton 1986) are supposed to reflect central serotonin activity (administration of 30 mg of the d-fenfluramine orally and measurement of prolactin plasma levels at the baseline and 60′, 120′, 180′, 240′ and 300′ after the administration), blunted growth hormone (GH) response to the a2-adrenergic receptor agonist clonidine (an index of noradrenergic dysregulation) and others. A non-endocrinological marker

is based on EEG and concerns the observation that depressed patients are phase advanced in many biological rhythms, especially concerning the latency to the first rapid eye movement in sleep (shortened REM latency) (Kupfer 1976).

A possible comprehensive model could suggest that mood patients have a deficit in the adequate mobilization of neurotransmitters when facing continued or repeated stress, and as a result, through a 'kindling' effect (Kendler et al. 2000; Post and Silberstein 1994; Post et al. 1984, 1988, 1992; Post and Weiss 1989, 1998) the mood change is intense, prolonged and not self-limited and tends to be triggered by progressively unimportant events and finally automatically.

13.3.4 Genetic Studies

The role of genetics in the development of BD is well known, and there is significant support in the literature from family, twin and adoption studies. It is also known that the mechanisms through witch genetic factors play a role are complex, probably with several of them interacting with the environment.

Not only the genes involved are multiple but also the mode of transmission seems to be complex; thus, BD is not a Mendelian disease (Andreassen et al. 2013). On the contrary it seems that it manifests significant genetic heterogeneity. Methodological issues also exist and perplex the problem but emerging technologies promise to solve at least some of the problems. Research is rapidly moving towards the utilization of genome-wide association scan (GWAS) studies (Segurado et al. 2003).

So far one of the greatest problems is that studies suffer from poor replicability and explain only a small portion of the genetic variance (around 70–80 %). Overall mood disorders have a reduced penetrance (less than 100 %) which increases with age. Little is known about the role of epigenetics and imprinting in BD.

Overall, family studies indicate a morbid risk of BD in first-degree relatives of bipolar probands that ranges between 3 and 8 % that is significantly higher in comparison to the general population. It is interesting to note that unipolar depression is the most common mood disorder in families of bipolar probands, while the reverse does not happen. Patients with BD are more likely to marry a person who also has a mood disorder (assortative mating). This leads to families with higher load than expected. Twin studies often pool together unipolar and bipolar disorders and report a two to four times higher risk for monozygotic twins in comparison to dizygotic. When BD is contrasted with unipolar depression the genetic load appears to be higher for BD. Again, as in family studies, unipolar depression is the most common mood disorder in monozygotic co-twins of bipolar probands. Concerning adoption studies, only a few exist and their results are inconclusive (Kelsoe 2009).

The analysis of genetic data to elucidate the mechanism of genetic transmission has not given robust results yet probably because the data are inconsistent. Most findings so far have not been replicated. Essentially all models of transmission that have been tested were rejected. The presence of multiple genes and simultaneously of multiple modes of transmission is the probable answer. It is fortunate that genetic

research is one of the hottest and fastest developing areas of research on BD. On the other hand it is unfortunate that the fruits are yet to come. Often weak findings are reported (Badner et al. 2012). A meta-analysis reported that six pathways (corticotropin-releasing hormone signalling, cardiac beta-adrenergic signalling, phospholipase C signalling, glutamate receptor signalling, endothelin 1 signalling and cardiac hypertrophy signalling) and nine genes (CACNA1C, DTNA, FOXP1, GNG2, ITPR2, LSAMP, NPAS3, NCOA2 and NTRK3) were found to relate with BD (Nurnberger et al. 2014). Another review concluded that the expression profiles of BD-associated genes do not explain the majority of structural abnormalities observed in BD (McCarthy et al. 2014).

A GWAS study in 1461 BD patients reported that after genotyping for 372,193 single nucleotide polymorphisms (SNPs), the strongest results concerned myosin5B (MYO5B) and tetraspanin-8 (TSPAN8) and possibly the epidermal growth factor receptor (EGFR), but the results failed to replicate. Further analysis with the use of controls from the Wellcome Trust Case Control study reported that the results pointed to SNPs related with the voltage-dependent calcium channel, L-type, alpha 1C subunit (CACNA1C) gene (Sklar et al. 2008; Wellcome Trust Case Control 2007). Another GWAS confirmed the involvement of ion channel structural and regulatory genes, including voltage-gated ion channels and the broader ion channel group that comprises both voltage- and ligand-gated channels in the pathogenesis of BD (Askland et al. 2009).

In accord with the above are a number of studies concerning the genes related with NMDA receptors (Mundo et al. 2003; Itokawa et al. 2003; Avramopoulos et al. 2007; Martucci et al. 2006; Fountoulakis et al. 2012). These studies suggested that BD is associated with an abnormal structure of the NMDA receptor because of lower contribution of NR2A subunits, with predominance of more immature forms resulting in disordered receptor properties and slower kinetics. These slower kinetics might make NMDA receptors incapable of dealing with the increased speed of stimuli during manic episodes leading to disorganization (Fountoulakis et al. 2012).

A number of special issues have also been the focus of genetic research. It has been suggested that some genes are less specific and contribute to multiple phenotypes giving rise to the bipolar spectrum (Kelsoe 2003). There are data suggesting that the hyperthymic temperament relates to chromosomes 1q44, 2p16, 6q16 and 14q23; the dysthymic to chromosomes 3p21 and 13q34; and the irritable to chromosome 6q24 (Greenwood et al. 2013a). Also it has been reported that irritable mania results from a distinct set of genes in comparison to euphoric mania, including a region on chromosome 13q31 (Greenwood et al. 2013b). Comorbidity is another issue with migraine being at the centre (Oedegaard et al. 2010). The genetic distinction between BD and other disorders was also the focus of research. It seems that BD and unipolar depression share some common genetic substrate, while at the same time BD-I and BD-II are not genetically identical. There is also a genetic overlap between BD and schizophrenia (Fountoulakis et al. 2012; Cross-Disorder Group of the Psychiatric Genomics et al. 2013; Andreassen et al. 2013).

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