Chapter 14

Neurocognitive endophenotypes in bipolar disorders

Alexandre Paim Diaz[1,2], João Quevedo[1,2,3,4], Marsal Sanches[1] and Jair C. Soares[5]

[1]Center of Excellence on Mood Disorders, Faillace Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, United States, [2]Translational Psychiatry Program, Faillace Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, United States, [3]Neuroscience Graduate Program, The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, TX, United States, [4]Translational Psychiatry Laboratory, Graduate Program in Health Sciences, University of Southern Santa Catarina (UNESC), Criciúma, Brazil, [5]UT Center of Excellence on Mood Disorders, Louis Faillace, M.D Department of Psychiatry and Behavioral Sciences, McGovern Medical School, UTHealth Science Center, Houston, TX, United States

14.1 Cognitive dysfunctions in bipolar disorders

Cognitive impairment is highly prevalent in individuals with bipolar disorders (BD) (Vieta et al., 2018), with some studies showing that more the 50% of the euthymic BD patients present cognitive dysfunction (Jensen, Knorr, Vinberg, Kessing, & Miskowiak, 2016; Sole et al., 2016). Elias et al. analyzed 24 studies that investigated the cognitive performance of euthymic pediatric patients with BD compared with healthy controls (HC) (510 and 636 participants, respectively) (Elias et al., 2017). In seven studies, the results showed that youths with BD presented significant impairment in global cognition. Verbal learning and memory, and working memory were also significantly impaired. The impairment in visual learning and memory in youths with BD presented a moderate to large effect size. There were no differences regarding age and intelligence quotient (IQ) scores. Attention and vigilance, reasoning and problem solving, and speed of processing were not different between the groups (Elias et al., 2017). Robinson et al. (2006) reviewed studies investigating cognitive impairment in euthymic BD patients

Biomarkers in Bipolar Disorders. DOI: https://doi.org/10.1016/B978-0-12-821398-8.00022-9

compared with HC. The authors found that patients with BD presented a worse cognitive performance in all domains investigated, but IQ. As found by Elias et al., the deficits were also more pronounced in verbal learning, in addition to executive function, despite a different degree of impairment for executive measures (Robinson et al., 2006). Sole et al. reviewed studies that compared patients with BD type I, type II, and HC. Like Robinson et al. findings, most of the studies did not find differences in IQ (Sole et al., 2011). The results also showed that patients with BD type II may present subtle different cognitive profiles compared with patients with BD type I, and that the cognitive impairment of patients with BD type II was mainly in verbal memory, inhibitory control, and working memory functions (Sole et al., 2011). The cognitive dysfunction in patients with BD can be evident in the early stages of the disease. Bora et al. reviewed studies that compared cognitive function in first-episode BD (within a maximum of 2 years), HC, and first-episode schizophrenia. Fifteen studies compared first-episode BD and HC (533 and 1417 individuals, respectively). The results showed that first-episode euthymic BD individuals performed worse in all cognitive domains compared to HC ($d = 0.22-0.66$), independently of age, gender, education, and drug use (Bora & Pantelis, 2015). Despite first-episode BD outperformed those individuals with first-episode schizophrenia, the differences were modest (Bora & Pantelis, 2015). The neuronal underpinnings of cognitive dysfunction in BD may be associated with a failure to recruit regions as the left dorsolateral prefrontal cortex and frontal and parietal regions (hypoactivity), in addition to hyperactivity in the default mode network compared to HC (Zarp Petersen et al., 2021).

14.2 Impact of cognitive dysfunctions in bipolar disorders

The highly prevalent and broad cognitive impairment seen in individuals with BD is associated with poorer outcomes. Depp et al. (2012) reported that cognitive function is significantly related to everyday functioning in patients with BD, suggesting it is a potential target for functional rehabilitation. Worse executive function was significantly associated with poorer functioning among patients with BD even after accounting for the length of illness, exposure to antipsychotics, and years of education (Lomastro, Valerio, Szmulewicz, & Martino, 2021). In a 1-year follow-up study, Martino et al. investigated the relationship between cognitive impairment and functional outcome in patients with BD. The authors followed 35 outpatients in an euthymic state and found a statistically significant association between impairment in measures of attention and verbal memory, independently of depression, and manic/hypomanic symptoms (Lomastro et al., 2021). Cognitive impairment in patients with BD is also associated with high consumption of mental healthcare resources, including hospital admissions and the number of scheduled clinical appointments (Ribera et al., 2021). In addition, cognitive dysfunctions in patients with BD have been associated with lower treatment

adherence. Fuentes et al. compared the cognitive function of patients with BD and low treatment compliance with patients with BD and high treatment compliance. The authors found that low compliance was associated with worse performance in verbal memory (immediate free recall, immediate cued recall, delayed free recall, and delayed cued recall) compared to BD patients with high treatment compliance (Fuentes, Rizo-Mendez, & Jarne-Esparcia, 2016). Luo et al. reported that subjective cognitive functioning could negatively predict psychosocial functioning and positively predict suicidal ideation in patients with BD (Luo, Zhu, Lu, Zong, & Lin, 2020). Regarding cognitive impairment and suicidal behavior, Malloy-Diniz et al. compared neuropsychological characteristics of patients with BD with and without a lifetime history of a suicide attempt. The authors found a statistically significant negative correlation between measures of decision-making and the number of suicide attempts. In addition, patients with a lifetime history of suicide attempts presented worse decision-making results compared to BD patients with no history of suicide attempts (Malloy-Diniz, Neves, Abrantes, Fuentes, & Correa, 2009).

14.3 Concept of endophenotypes

McGuffin, Farmer, and Gottesman (1987) referred to endophenotypes in a meaning similar to a biological marker, which could help to classify patients with a psychiatric illness according to a biological criteria rather than based on clinical signs and symptoms (McGuffin et al., 1987). Other terms that have been used as a synonymous of endophenotype are "vulnerability marker," "subclinical trait," and "intermediate phenotype" (Gottesman & Gould, 2003). However, Gottesman and Gould make distinctions between a biological marker from endophenotypes by considering the former as those differences not genetically related and the latter when there is evidence of certain heritability (Gottesman & Gould, 2003). However, while a biological marker links the phenotype with an underlying biological mechanism, endophenotypes require evidence of heritability and state independence; that is, it would manifest regardless of whether the disease is active or not (Roffman, 2019). Leboyer et al. defined endophenotypes as traits – for instance, biochemical, neurophysiological, brain structural, or neurocognitive—found in nonaffected relatives of affected individuals (subclinical) and the "endophenotype approach" as the process of identifying these subclinical traits (Leboyer et al., 1998; Leboyer et al., 1999). More precisely, Leboyer et al. define endophenotype as "traits that are associated with the expression of an illness and are believed to represent the genetic liability of the disorder among nonaffected subjects" (Leboyer et al., 1998). The authors consider that to be considered an endophenotype, the trait should be present before the disease onset and must be heritable (Leboyer et al., 1998). In addition, Gottesman and Gould state that an endophenotype should be associated with a candidate gene or gene region and with parameters of the disease

(Gottesman & Gould, 2003). According to Lenzenweger (1999), endophenotypes are assessed by valid objective indicators of latent liability. Thus, while phenotypes are related to the clinical manifestation of a disease, and genotypes reflect the genetic substrate (Leboyer et al., 1998), endophenotypes refer to traits present in nonaffected individuals that can be interpreted as a marker of disease vulnerability, which genetic substrate is potentially linked to the genetic disease substrate. In other words, the phenotype is related to observable manifestations of the disease ("exophenotypes," more apparent), resulted from an interaction between genotype and environmental influences (Bernardi & Kanan, 2015; Gottesman & Gould, 2003). In its turn, endophenotype is a characteristic that would be present in the path between the phenotype and the genotype (Gottesman & Gould, 2003). However, this understanding of endophenotype assumes, as Kendler and Neale pointed out, a mediational model. Nevertheless, the endophenotype could also represent a characteristic that shares a similar genetic basis with the psychiatric diagnosis despite not be in the path between them (liability-index model) (Kendler & Neale, 2010). In summary, to be considered an endophenotype, it is required evidence of (1) association with illness in the population; (2) heritability; (3) manifestation independently of whether or not the disease is active; (4) cosegregation with illness within families; and (5) higher frequency among nonaffected family member compared to the general population (Gottesman & Gould, 2003).

The heterogeneity of psychiatric disorders according to the current diagnostic classifications and the complexity of behavior manifestations regarding its biological underpinnings difficult the identification of genetic determinants in psychiatry (Gottesman & Gould, 2003). Kendler and Neale highlight the importance of endophenotypes in genetic studies to characterize the etiology of psychiatric disorders (Kendler & Neale, 2010). Therefore, the study of endophenotypes could help in the identification of genes that suggests susceptibility to disease. Thus, if an endophenotype is a marker of vulnerability for a disease, the genes that are related to the endophenotype could help to identify genes that suggest increased disease susceptibility (Leboyer et al., 1998). As an example, Leboyer et al. cite the juvenile myoclonic epilepsy, in which a genetic susceptibility factor was found by the study of an endophenotype of the disease, in this case, an abnormal electroencephalography measure (Leboyer et al., 1998). Thus, endophenotypes can help to reduce the clinical heterogeneity in psychiatry, "reducing the noise" when searching for a biological pathway associated with a disorder and facilitating the identification of the genes associated with BD (Lenzenweger, 1999; Merikangas et al., 2002). Therefore, identifying endophenotypes would help in the genetic study of complex diseases as mental illness (Gottesman & Gould, 2003). According to Greenwood et al. (2019), endophenotypes can help parse the heterogeneity of psychiatric disorders, and "refining the genetic signal." Endophenotypes are also usually quantitative, providing

more information than the categorical diagnosis provided by current diagnosis classification systems (Kendler & Neale, 2010). Another advantage of studying endophenotypes is their potential for early detection of the disease (Lenzenweger, 1999). Considering the two models described by Kendler and Neale, the mediational model and liability-index, in both the endophenotype could help identify genes associated with the psychiatric disorder, but only in the mediational model we could potentially assume that interference in the endophenotype would also reflect modifications in the clinical presentation of the psychiatric disorder (Kendler & Neale, 2010), which would have important clinical implications.

14.4 Neurocognitive endophenotypes in bipolar disorders

Several studies have investigated neurocognitive endophenotypes of BD, mainly by evaluating individuals with genetic vulnerability for the disease as first-degree relatives of BD patients. Given the relationship between the serotoninergic system and cognitive functioning, Sobczak et al. (2002) investigated the effect of acute tryptophan depletion on cognition of first-degree relatives of individuals with BD types I and II compared with HC. The groups did not differ significantly regarding age, IQ, and cognitive performance at baseline, which included focused attention and divided attention, working memory retrieval, measuring planning, and concept shifting. Despite acute tryptophan depletion not being associated with impairment in short-term memory and attention (focused and divided), the intervention was related to impaired speed of information processing on the planning task and long-term memory performance. The findings suggest a serotonergic vulnerability in frontal lobe regions in first-degree relatives of individuals with BD, in addition to impaired planning and memory tasks as potential endophenotypes of BD (Sobczak et al., 2002). Frangou et al. evaluated executive function dimensions related to ventral prefrontal cortex (VPFC) and dorsal PFC (DPFC) integrity in 15 unaffected offspring compared to their probands (10 individuals with BD) and 43 HC (Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2008). The authors hypothesized that deficits in VPFC-related executive functions would be an endophenotype of BD based on previous studies that found abnormalities in this region in individuals with BD (Frangou, Haldane, Roddy, & Kumari, 2005). Response inhibition, cognitive set-shifting, and rule discovery were the three dimensions of executive function investigated through the Wisconsin Card Sorting Test and the Hayling Sentence Completion Task (HSCT), which are related to DPFC and VPFC function, respectively. The results showed that patients and offspring performed worse in the HSCT compared to HC, suggesting deficient VPFC-related inhibition as a potential endophenotype of BD type I (Frangou et al., 2005). Cognitive flexibility and verbal learning were investigated as endophenotypes of BD in the study of Clark et al. The authors evaluated 15

patients with recurrent depression in a euthymic state, 27 first-degree relatives of patients with BD type I, and 47 HC (Clark, Sarna, & Goodwin, 2005). Cognitive flexibility was assessed with the intradimensional/extradimensional shift task and verbal learning with the California Verbal Learning Test. The results showed that euthymic participants with a history of recurrent unipolar depression and BD type I first-degree relatives presented worse extradimensional shift, suggesting that attentional set-shifting may be considered an endophenotype of mood disorders potentially associated with lateral PFC impairment (Clark et al., 2005).

The neuropsychological function of healthy first-degree relatives of individuals with BD was compared to HC in the study of Ferrier et al. with the Cambridge Neuropsychological Test Automated Battery, which assesses declarative memory, attention and executive function, and psychomotor function (Sahakian & Owen, 1992). The groups did not present significant differences in age, gender, IQ, years of education, depressive or manic/hypomanic symptoms (Ferrier, Chowdhury, Thompson, Watson, & Young, 2004). The results showed a worse cognitive performance in executive control and declarative memory (limited to the visuospatial domain) tasks in the first-degree relatives group, suggesting that these deficits may indicate endophenotypes of BD (Ferrier et al., 2004). Antila et al. applied a neuropsychological test battery in individuals with BD type I, their unaffected first-degree relatives, and HC. The authors hypothesized that the second group would present an intermediate pattern of cognitive performance compared to the other two groups (Antila et al., 2007). The neuropsychological assessment included tasks that measure attention, working memory, verbal learning, and executive functions. The groups were similar in terms of gender, age, and the number of years of education. Patients and first-degree relatives presented worse psychomotor performance speed compared to HC. First-degree relatives also performed worse in the executive task, although the difference was not statistically significant. The results thus suggest psychomotor performance speed and potentially executive functioning, as endophenotypes of BD (Antila et al., 2007).

Glahn, Bearden, Niendam, and Escamilla (2004) reviewed neuropsychological endophenotypes of BD and found that only executive function, working memory, verbal learning, and memory were the neurocognitive domains that satisfied all criteria considered for a valid endophenotype (highly heritable, associated with the illness, independent of clinical state, and cosegregate within family) (Glahn et al., 2004). In a systematic review, Arts et al. evaluated cognitive functioning in first-degree relatives of individuals with BD compared to HC. Fourteen studies were included. Metaanalysis of the neurocognitive functions showed that first-degree relatives performed worse than HC in all cognitive domains studied, despite the smaller effect sizes related to the BD−HC comparison. For executive functioning and verbal memory, although small effect sizes, the differences were statistically significant

(Arts, Jabben, Krabbendam, & van Os, 2008). To address the distinct stages that potentially precede the incidence of BD, Lin et al. compared high-risk and ultrahigh-risk offspring of patients with BD, individuals with subthreshold symptoms and no family history of BD, and HC. The high-risk group encompassed offspring of BD patients with no symptoms. The ultrahigh-risk group included offspring of BD patients with evidence of subthreshold manic/hypomanic, depressive, psychotic, or hyperactivity and impulsivity symptoms (Lin et al., 2017). The neuropsychological battery involved cognitive domains as attention/vigilance, verbal learning, reasoning and problem solving, working memory, processing speed, visual learning, and planning. The results showed that high-risk offspring presented a significantly worse performance in verbal learning and memory than HC after controlling for age, sex, years of education, and clinical symptoms. In addition, ultrahigh-risk offspring of patients with BD presented a significantly worse performance than HC regarding visual learning and memory, working memory, and visual-spatial planning, differences that were not observed in the comparison between individuals with subthreshold symptoms and no family history of BD and HC. The findings may suggest that, on the one hand, while verbal learning and memory may represent an endophenotype of BD, deficits in visual learning and memory, working memory, and visual-spatial learning may represent dysfunctions in a critical stage, probably close to BD onset (Lin et al., 2017).

In the systematic review of Balanza-Martinez et al., the authors included studies with discordant twins, genetic high-risk subjects (offspring of parents with BD), and studies of first- and second-degree relatives of patients with BD. The results showed a high frequency of deficits in verbal memory and learning, with three of the four twin studies showing impaired verbal declarative memory in non-BD cotwins (Balanza-Martinez et al., 2008). Impaired working memory, more precisely verbal working memory, was also reported in three of six studies. The authors also found that impairment in some cognitive domains as sustained and selective attention, alternating attention, cognitive flexibility, abstraction, psychomotor speed, and visual-spatial learning was less described, suggesting preservation of these cognitive functions in BD unaffected relatives (Balanza-Martinez et al., 2008). Bora et al. conducted a metaanalysis with studies comparing the neuropsychological performance of euthymic patients with BD and their first-degree relatives. The findings showed that the impairment in response inhibition, executive function, set-shifting, sustained attention, and verbal memory in BD relatives were similar to that found in BD patients, with the former presenting small to medium effect sizes (Bora, Yucel, & Pantelis, 2009). Chandrasekaran et al. compared cognitive performance of unaffected siblings of patients with BD type I with HC matched for sex, age, and education (Chandrasekaran, Kattimani, Subramanian, Penchilaiya, & Karunanithi, 2020). Among the cognitive functions evaluated, unaffected siblings presented lower scores in tests

of memory, but similar scores in attention, processing speed, visuospatial, and executive functioning domains, suggesting memory domain as a potential neurocognitive endophenotype (Chandrasekaran et al., 2020).

Few studies have examined endophenotypes in BD with a longitudinal design. In a 5-year longitudinal study, Correa-Ghisays et al. (2019) investigated if visual memory would represent an endophenotype of BD. The study included 140 individuals with BD, 60 of their unaffected first-degree relatives, and 117 HC. Assessments were performed at baseline (T1), 1−2 years after the baseline (T2), and after 5 years of the baseline (T3), despite data from first-degree relatives were obtained only at baseline and T2. First-degree relatives of patients with BD presented a statistically worse and a trend for worse measures of visual memory at T1 and T2, respectively, compared to HC. Also, BD relatives presented statistically significant better visual memory measures than BD patients at baseline and T2, despite the differences not being statistically significant at the last assessment. Together, these longitudinal findings suggest visual memory as a putative endophenotype of BD (Correa-Ghisays et al., 2019).

14.4.1 Affective cognition

Miskowiak et al. (2017) investigated nonemotional ("cold") and emotion-laden ("hot") cognitive functions in unaffected first-degree relatives of individuals with BD in a systematic review with 19 studies. The results showed cognitive impairment in executive function, sustained attention, and verbal learning and memory, with dysfunctions in executive function and sustained attention associated with aberrant neural activity in striatal, parietal, limbic, and prefrontal regions. In addition, unaffected first-degree relatives of individuals with BD presented consistent impairment of facial expression recognition, emotion regulation, and increased reactivity to emotional stimuli and interference of attentional resources by emotional stimuli (Miskowiak et al., 2017). Facial emotion recognition was also compared between 23 euthymic BD type I patients, 22 of their first-degree relatives, and HC in the study of de Brito Ferreira Fernandes et al. (2016). The three groups were similar regarding sex, age, IQ, and years of education. First-degree relatives of patients with BD presented a higher number of correct responses for fear than BD patients and lower than HC, despite the differences being statistically significant only between BD patients and HC. A similar pattern was seen for time to response for recognition of happy faces and very happy faces, with BD relatives presenting intermediate values between BD patients (longer response) and HC (de Brito Ferreira Fernandes et al., 2016). Kjaerstad et al. investigated whether unaffected relatives of patients with BD would present an intermediate cognitive performance regarding nonaffective and affective cognition (Kjaerstad, Eikeseth, Vinberg, Kessing, & Miskowiak, 2021). The authors evaluated 158 individuals with BD, 52 of their unaffected first-degree relatives, and 110 HC. Measures of affective cognition included

evaluating emotion regulation and reactivity to social scenarios, processing of emotional faces, and attentional vigilance toward emotional faces. Related to facial expression recognition, results showed that unaffected first-degree relatives of cognitively impaired BD patients presented significative lower discrimination accuracy compared to HC. In addition, there was a trend for association toward worse discrimination accuracy in first-degree relatives of cognitively impaired BD patients compared to first-degree relatives of cognitively intact BD patients. Thus, according to the authors, facial expression recognition is a potential endophenotype that may be more specific for BD than nonaffective cognition (Kjaerstad et al., 2021). Figure 14.1 provides a summary of the main information discussed in this book chapter.

14.4.2 Limitations of neurocognitive endophenotypes in bipolar disorders

In a review, Savitz et al. discussed whether neurocognitive dysfunctions would be a viable endophenotype of BD for genetic investigation (Savitz, Solms, & Ramesar, 2005). The authors took into account Gottesman and Gould (2003) criteria for a trait to be considered an endophenotype and pointed out some limitations of the endophenotype approach with neurocognitive function (Gottesman & Gould, 2003). For instance, given the heterogeneity of BD in terms of clinical presentation and neurobiology, the neurocognitive impairment can be different for distinct subtypes of the disease. Also, the heterogeneity of the studies in terms of cognitive assessment and multiple testing can result in a considerable rate of false positives. In addition, the transdiagnostic characteristic of several neurocognitive impairments may reflect the low specificity of some findings for BD diagnosis. Thus, their presence may reflect a vulnerability to psychiatric illness in general rather than related to a specific diagnosis. The limited heritability of neurocognitive function can also limit its use in the endophenotype approach. Finally, it is difficult to prove that neurocognitive dysfunction and BD cosegregate in families (Savitz et al., 2005). Considering all these factors, the authors suggest that researchers should be cautious when using neurocognitive endophenotypes to unveil the genetic basis of BD. Another potential limitation is the questionable longitudinal stability of neurocognitive performance in individuals with BD. Burdick et al. evaluated the cognitive function of individuals with BD and schizophrenia in two moments, 5 years apart. The results showed that attentional measures were stable over time, but there was greater variability in memory and executive function domains, despite Mur et al. reported stability of executive function and processing speed impairment over a 2-year follow-up (Burdick, Goldberg, Harrow, Faull, & Malhotra, 2006; Mur et al., 2008). In a perspective paper, Kessing and Miskowiak also discussed whether cognitive dysfunction in BD would qualify as an endophenotype in BD. The authors conclude that, considering the clinical characterization of endophenotypes, the association between endophenotype and

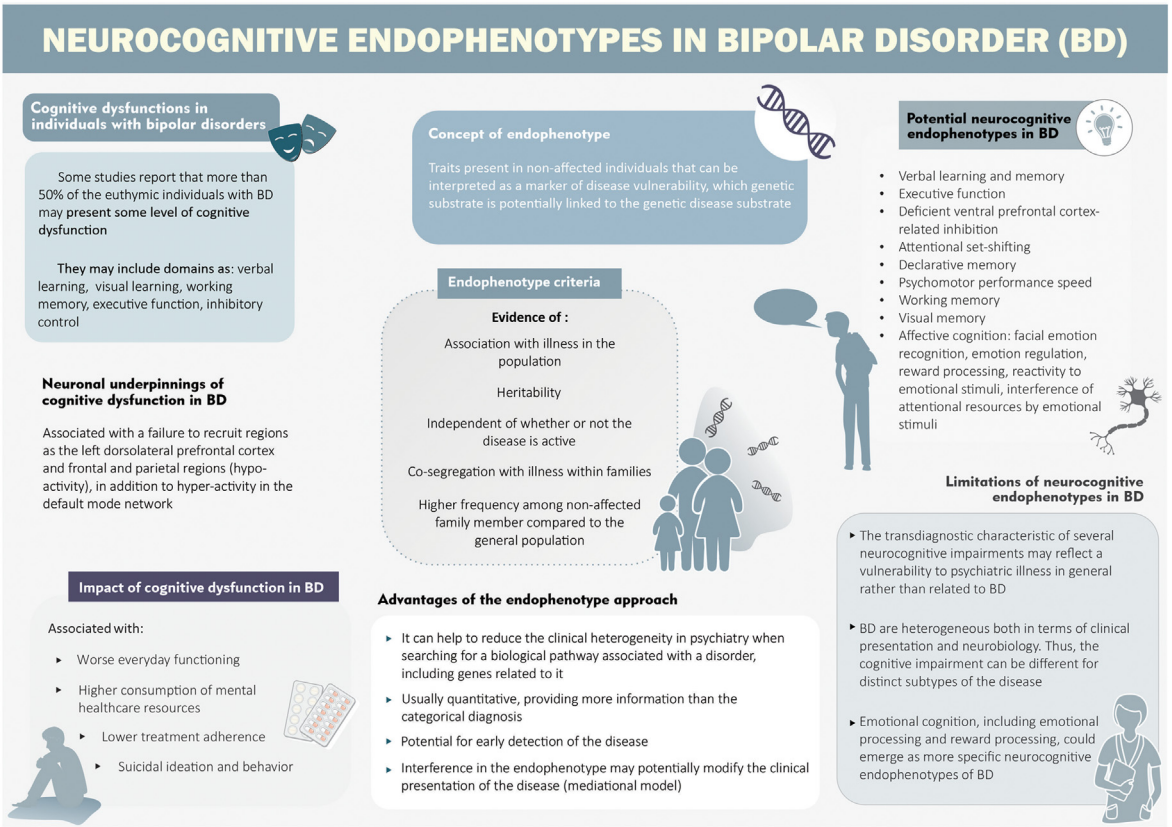

FIGURE 14.1 Neurocognitive endophenotypes in bipolar disorders—summary of concepts and main findings.

biological data as brain imaging and blood markers, family history and genetics, long-term stability, and effects of treatment, cognition does not qualify as an endophenotype for BD, especially because the literature so far shows shared cognitive characteristics between BD and other diagnosis, that is, there is no specific neuropsychological signature for BD (Kessing & Miskowiak, 2018). However, according to the authors, there is evidence supporting "hot" (emotional) cognition, including emotional processing and reward processing, as potential endophenotypes for BD (Kessing & Miskowiak, 2018).

14.5 Conclusion

Cognitive impairment is highly prevalent in individuals with BD. The endophenotype approach of neurocognitive function could help to unveil genetic basis of BD and in the identification of cognitive targets which therapeutic interventions could help to improve patients' functioning. Verbal memory and learning, attention, executive dysfunctions, and impaired response inhibition may be the most useful cognitive endophenotypes for BD (Balanza-Martinez et al., 2008; Bora et al., 2009; Guglielmo, Miskowiak, & Hasler, 2021). There is no evidence for impairment in general intellectual functioning in first-degree relatives of individuals with BD, indicating that it is not associated with BD's genetic liability (Miskowiak et al., 2017). The studies also suggest that the cognitive endophenotype of BD appears to be related to frontotemporal and frontolimbic related cognitive impairments (Bora et al., 2009). However, deficits in verbal learning and memory are most probably related to a genetic vulnerability to psychiatric illness in general than specifically to BD (Miskowiak et al., 2017). Some authors argue that "hot" (emotional) cognition, including emotional processing and reward processing, could emerge as more specific neurocognitive endophenotypes of BD.

References

Antila, M., Tuulio-Henriksson, A., Kieseppa, T., Eerola, M., Partonen, T., & Lonnqvist, J. (2007). Cognitive functioning in patients with familial bipolar I disorder and their unaffected relatives. *Psychological Medicine*, *37*(5), 679–687.

Arts, B., Jabben, N., Krabbendam, L., & van Os, J. (2008). *Meta*-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychological Medicine*, *38*(6), 771–785.

Balanza-Martinez, V., Rubio, C., Selva-Vera, G., Martinez-Aran, A., Sanchez-Moreno, J., Salazar-Fraile, J., … Tabares-Seisdedos, R. (2008). Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar disorder subjects: A systematic review. *Neuroscience and Biobehavioral Reviews*, *32*(8), 1426–1438.

Bernardi, A. B., & Kanan, L. A. (2015). Características dos serviços públicos de saúde mental (Capsi, Capsad, Caps III) do Estado de Santa Catarina. *Saúde em Debate*, *39*(107), 12.

Bora, E., & Pantelis, C. (2015). *Meta*-analysis of cognitive impairment in first-episode bipolar disorder: Comparison with first-episode schizophrenia and healthy controls. *Schizophrenia Bulletin*, *41*(5), 1095−1104.

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: A *meta*-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of Affective Disorders*, *113*(1−2), 1−20.

Burdick, K. E., Goldberg, J. F., Harrow, M., Faull, R. N., & Malhotra, A. K. (2006). Neurocognition as a stable endophenotype in bipolar disorder and schizophrenia. *The Journal of Nervous and Mental Disease*, *194*(4), 255−260.

Chandrasekaran, V., Kattimani, S., Subramanian, K., Penchilaiya, V., & Karunanithi, A. (2020). Cognitive performance and psychosocial functioning in unaffected siblings of bipolar disorder patients in comparison with healthy controls. *Asian Journal of Psychiatry*, *54*, 102246.

Clark, L., Sarna, A., & Goodwin, G. M. (2005). Impairment of executive function but not memory in first-degree relatives of patients with bipolar I disorder and in euthymic patients with unipolar depression. *The American Journal of Psychiatry*, *162*(10), 1980−1982.

Correa-Ghisays, P., Sanchez-Orti, J. V., Ayesa-Arriola, R., Setien-Suero, E., Balanza-Martinez, V., Selva-Vera, G., … Tabares-Seisdedos, R. (2019). Visual memory dysfunction as a neurocognitive endophenotype in bipolar disorder patients and their unaffected relatives. Evidence from a 5-year follow-up Valencia study. *Journal of Affective Disorders*, *257*, 31−37.

de Brito Ferreira Fernandes, F., Gigante, A. D., Berutti, M., Amaral, J. A., de Almeida, K. M., de Almeida Rocca, C. C., … Nery, F. G. (2016). Facial emotion recognition in euthymic patients with bipolar disorder and their unaffected first-degree relatives. *Comprehensive Psychiatry*, *68*, 18−23.

Depp, C. A., Mausbach, B. T., Harmell, A. L., Savla, G. N., Bowie, C. R., Harvey, P. D., … Patterson, T. L. (2012). *Meta*-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disorders*, *14*(3), 217−226.

Elias, L. R., Miskowiak, K. W., Vale, A. M., Kohler, C. A., Kjaerstad, H. L., Stubbs, B., … Carvalho, A. F. (2017). Cognitive impairment in euthymic pediatric bipolar disorder: A systematic review and *meta*-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(4), 286−296.

Ferrier, I. N., Chowdhury, R., Thompson, J. M., Watson, S., & Young, A. H. (2004). Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: A preliminary report. *Bipolar Disorders*, *6*(4), 319−322.

Frangou, S., Haldane, M., Roddy, D., & Kumari, V. (2005). Evidence for deficit in tasks of ventral, but not dorsal, prefrontal executive function as an endophenotypic marker for bipolar disorder. *Biological Psychiatry*, *58*(10), 838−839.

Fuentes, I., Rizo-Mendez, A., & Jarne-Esparcia, A. (2016). Low compliance to pharmacological treatment is linked to cognitive impairment in euthymic phase of bipolar disorder. *Journal of Affective Disorders*, *195*, 215−220.

Glahn, D. C., Bearden, C. E., Niendam, T. A., & Escamilla, M. A. (2004). The feasibility of neuropsychological endophenotypes in the search for genes associated with bipolar affective disorder. *Bipolar Disorders*, *6*(3), 171−182.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *The American Journal of Psychiatry*, *160*(4), 636−645.

Greenwood, T. A., Lazzeroni, L. C., Maihofer, A. X., Swerdlow, N. R., Calkins, M. E., Freedman, R., … Braff, D. L. (2019). Genome-wide association of endophenotypes for

schizophrenia from the Consortium on the Genetics of Schizophrenia (COGS) Study. *JAMA Psychiatry*, *76*(12), 1274–1284.

Guglielmo, R., Miskowiak, K. W., & Hasler, G. (2021). Evaluating endophenotypes for bipolar disorder. *International Journal of Bipolar Disorders*, *9*(1), 17.

Jensen, J. H., Knorr, U., Vinberg, M., Kessing, L. V., & Miskowiak, K. W. (2016). Discrete neurocognitive subgroups in fully or partially remitted bipolar disorder: Associations with functional abilities. *Journal of Affective Disorders*, *205*, 378–386.

Kendler, K. S., & Neale, M. C. (2010). Endophenotype: A conceptual analysis. *Molecular Psychiatry*, *15*(8), 789–797.

Kessing, L. V., & Miskowiak, K. (2018). Does cognitive dysfunction in bipolar disorder qualify as a diagnostic intermediate phenotype?-A perspective paper. *Front Psychiatry*, *9*, 490.

Kjaerstad, H. L., Eikeseth, F. F., Vinberg, M., Kessing, L. V., & Miskowiak, K. (2021). Neurocognitive heterogeneity in patients with bipolar disorder and their unaffected relatives: Associations with emotional cognition. *Psychological Medicine*, *51*(4), 668–679.

Leboyer, M., Bellivier, F., Nosten-Bertrand, M., Jouvent, R., Pauls, D., & Mallet, J. (1998). Psychiatric genetics: Search for phenotypes. *Trends in Neurosciences*, *21*(3), 102–105.

Leboyer, M., Quintin, P., Manivet, P., Varoquaux, O., Allilaire, J. F., & Launay, J. M. (1999). Decreased serotonin transporter binding in unaffected relatives of manic depressive patients. *Biological Psychiatry*, *46*(12), 1703–1706.

Lenzenweger, M. F. (1999). Schizophrenia: Refining the phenotype, resolving endophenotypes. *Behaviour Research and Therapy*, *37*(3), 281–295.

Lin, K., Lu, R., Chen, K., Li, T., Lu, W., Kong, J., & Xu, G. (2017). Differences in cognitive deficits in individuals with subthreshold syndromes with and without family history of bipolar disorder. *Journal of Psychiatric Research*, *91*, 177–183.

Lomastro, M. J., Valerio, M. P., Szmulewicz, A. G., & Martino, D. J. (2021). Manic morbidity and executive function impairment as determinants of long-term psychosocial dysfunction in bipolar disorder. *Acta Psychiatrica Scandinavica*, *144*, 72–81.

Luo, X., Zhu, Y., Lu, D., Zong, K., & Lin, X. (2020). Subjective cognitive dysfunction in patients with bipolar disorder: The prevalence, related factors and effects on predicting psychosocial functioning and suicidal ideation. *Psychiatry Research*, *284*, 112669.

Malloy-Diniz, L. F., Neves, F. S., Abrantes, S. S., Fuentes, D., & Correa, H. (2009). Suicide behavior and neuropsychological assessment of type I bipolar patients. *Journal of Affective Disorders*, *112*(1–3), 231–236.

McGuffin, P., Farmer, A., & Gottesman, I. I. (1987). Is there really a split in schizophrenia? The genetic evidence. *The British Journal of Psychiatry: The Journal of Mental Science*, *150*, 581–592.

Merikangas, K. R., Chakravarti, A., Moldin, S. O., Araj, H., Blangero, J. C., Burmeister, M., ... Takahashi, S. (2002). Future of genetics of mood disorders research. *Biological Psychiatry*, *52*(6), 457–477.

Miskowiak, K. W., Kjaerstad, H. L., Meluken, I., Petersen, J. Z., Maciel, B. R., Kohler, C. A., ... Carvalho, A. F. (2017). The search for neuroimaging and cognitive endophenotypes: A critical systematic review of studies involving unaffected first-degree relatives of individuals with bipolar disorder. *Neuroscience and Biobehavioral Reviews*, *73*, 1–22.

Mur, M., Portella, M. J., Martinez-Aran, A., Pifarre, J., & Vieta, E. (2008). Long-term stability of cognitive impairment in bipolar disorder: A 2-year follow-up study of lithium-treated euthymic bipolar patients. *The Journal of Clinical Psychiatry*, *69*(5), 712–719.

Ribera, C., Vidal-Rubio, S. L., Romeu-Climent, J. E., Vila-Frances, J., Van Rheenen, T. E., & Balanza-Martinez, V. (2021). Cognitive impairment and consumption of mental healthcare resources in outpatients with bipolar disorder. *Journal of Psychiatric Research*, *138*, 535−540.

Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., … Moore, P. B. (2006). A *meta*-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of Affective Disorders*, *93*(1−3), 105−115.

Roffman, J. L. (2019). Endophenotype research in psychiatry-The grasshopper grows up. *JAMA Psychiatry*, *76*(12), 1230−1231.

Sahakian, B. J., & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: Discussion paper. *Journal of the Royal Society of Medicine*, *85*, 399−402.

Savitz, J. B., Solms, M., & Ramesar, R. S. (2005). Neurocognitive function as an endophenotype for genetic studies of bipolar affective disorder. *Neuromolecular Medicine*, *7*(4), 275−286.

Sobczak, S., Riedel, W. J., Booij, I., Aan Het Rot, M., Deutz, N. E., & Honig, A. (2002). Cognition following acute tryptophan depletion: Difference between first-degree relatives of bipolar disorder patients and matched healthy control volunteers. *Psychological Medicine*, *32*(3), 503−515.

Sole, B., Jimenez, E., Torrent, C., Del Mar Bonnin, C., Torres, I., Reinares, M., … Martinez-Aran, A. (2016). Cognitive variability in bipolar II disorder: Who is cognitively impaired and who is preserved. *Bipolar Disorders*, *18*(3), 288−299.

Sole, B., Martinez-Aran, A., Torrent, C., Bonnin, C. M., Reinares, M., Popovic, D., … Vieta, E. (2011). Are bipolar II patients cognitively impaired? A systematic review. *Psychological Medicine*, *41*(9), 1791−1803.

Vieta, E., Berk, M., Schulze, T. G., Carvalho, A. F., Suppes, T., Calabrese, J. R., … Grande, I. (2018). Bipolar disorders. *Nature Reviews Disease Primers*, *4*, 18008.

Zarp Petersen, J., Varo, C., Skovsen, C.F., Ott, C.V., Kjaerstad, H.L., Vieta, E., … Miskowiak, K.W. (2021). Neuronal underpinnings of cognitive impairment in bipolar disorder: A large data-driven functional magnetic resonance imaging study. Bipolar Disorders.