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Does Cognitive Dysfunction in Bipolar Disorder Qualify as a Diagnostic Intermediate Phenotype?—A Perspective Paper

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The present perspective paper addresses and discusses whether cognitive dysfunction in bipolar disorder qualifies as a diagnostic intermediate phenotype using the Robin and Guze criteria of diagnostic validity. The paper reviews current data within (1) delineation of the clinical intermediate phenotype, (2) associations of the intermediate phenotype with para-clinical data such as brain imaging and blood-based data, (3) associations to family history / genetics, (4) characteristics during long-term follow-up, and (5) treatment effects on cognition. In this way, the paper identifies knowledge gaps and suggests recommendations for future research within each of the five areas. Based on the current state of knowledge, we conclude that cognitive dysfunction does not qualify as a diagnostic intermediate phenotype or endophenotype for bipolar disorder, although promising new evidence points to emotion and reward processing abnormalities as possible putative endophenotypes.

Keywords: cognition, cognitive dysfunction, bipolar disorder, unipolar disorder, schizophrenia, intermediate phenotype, endophenotype

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Cognitive dysfunction in bipolar disorder is a core illness symptom that has received intensive research interest over the past decade because of its negative impact on socio-occupational outcome, quality of life and illness prognosis (1–3). However, it is unclear whether patients' cognitive deficits comprise a diagnostic intermediate phenotype that may aid diagnostic accuracy and represent a key treatment target. The present perspective paper evaluates the present evidence and discusses whether cognitive dysfunction in bipolar disorder qualifies as a diagnostic intermediate phenotype using the Robin and Guze criteria of diagnostic validity (4) also concurrent with the later endophenotype concept (5) and extended criteria suggestions (6). The rationale for the Robin and Guze criteria was to develop criteria distinguishing between various psychiatric disorders and aiming for a valid psychiatric classification system (4). An intermediate phenotype was later defined as a measurable component along the pathway between disease and distal genotype, and have emerged as an important concept in the study of complex neuropsychiatric diseases (5). An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature (5). The paper will review current data on cognitive dysfunction within (1) delineation of the clinical intermediate phenotype, (2) associations of the intermediate phenotype with para-clinical data such as brain imaging and blood-based data, (3) associations to family history / genetics, (4) characteristics during long-term

follow-up, and (5) treatment effects on cognition. Within each of these five points, the specificity of the findings in relation to bipolar disorder compared with schizophrenia and unipolar disorder will be summarized. The paper will identify knowledge gaps and suggest recommendations for future research within each of the five areas.

DELINEATION AND CHARACTERIZATION OF THE CLINICAL INTERMEDIATE PHENOTYPE

This area concerns whether cognitive dysfunction in bipolar disorder in remission is circumscribed clinically as a separate diagnostic intermediate phenotype of bipolar disorder and whether such an intermediate phenotype differs from similar intermediate phenotypes within related disorders such as schizophrenia and unipolar disorder.

Meta-analyses have consistently shown disturbances in executive function, verbal learning and memory, visual memory and attention in bipolar disorder compared with healthy control individuals (7–10). Cognitive impairment in the remitted phase of bipolar disorder is on average of a moderate effect size (7), however, with a substantial cognitive heterogeneity: 12–40% of patients present global cognitive impairments across several domains, 29–40% show selective deficits in attention and psychomotor speed, and 32–48% are relatively "cognitively intact" in comparison with norms (11). Subgroups with neurocognitive impairments present reduced functional capacity, more stress and poorer quality of life than patients who are cognitively intact, despite similar degrees of subsyndromal mood symptoms (2, 11, 12). Compared with bipolar disorder type II (hypomanic and depressive episodes; no manic episodes), bipolar disorder type I (manic and/or depressive episodes) seems to be associated with modestly more pronounced global cognitive impairment as well as increased disturbances in verbal memory, processing speed, executive function speed, and executive function accuracy (13).

On the other hand, cognitive deviances are not specific for bipolar disorder. Cognitive impairment is also prevalent in schizophrenia (14) and unipolar disorder (15), and there is no specific neuropsychological signature that can facilitate the diagnostic differentiation between bipolar disorder, schizophrenia, and unipolar disorder (16), notwithstanding, neuropsychological deficits appear more severe in schizophrenia (14, 17) and bipolar disorder (15). In schizophrenia and bipolar disorder, cognitive impairments have been found to correlate with socio-demographic (lower education and work capacity), clinical (more hospitalizations, longer duration of illness, negative psychotic symptoms, and non-remission status), treatment (antipsychotics, anti-cholinergics) variables and lower psychosocial functioning (1, 3, 18). Similar predictors of cognitive dysfunction are found in unipolar disorder but with more variable evidence, possibly because of the generally milder cognitive impairments in this patient group (19, 20).

Emotion dysregulation may be another cognitive feature of bipolar disorder that persists into periods of remission. Such deficits in "hot" (emotional) cognition are closely linked to emotional disturbances (21) and difficulties in socio-emotional behavior and interpersonal relations in bipolar disorder (22). Hot cognition abnormalities in bipolar disorder have been observed within three domains; emotional processing, reward processing, and emotion regulation [reviews in (23, 24)].

Emerging evidence points to partial persistence of such hot cognition dysfunction during remission in unipolar disorder, particularly within negative affect processing, (25) and the presence of similar abnormalities in healthy relatives of patients with unipolar disorder, at least at a neural level (25, 26). Hot cognition has not been systematically investigated across mood disorders and schizophrenia although some data point toward somewhat dissociable deficits in primary reward processing in unipolar disorder and schizophrenia (27). A key question remains whether deficits in experiencing rewards are independent of anhedonia in schizophrenia and whether level of observed reward disruption across unipolar disorder and schizophrenia a is a matter of severity rather than reflecting a qualitatively distinct mechanism (27). In contrast, a few studies of patients with bipolar disorder found evidence for a distinct positive bias in emotion processing and elevated reward responsiveness (28)—cognitive features that may in the future aid diagnostic discrimination between the disorders.

ASSOCIATIONS OF THE INTERMEDIATE PHENOTYPE WITH PARA-CLINICAL DATA SUCH AS BRAIN IMAGING AND BLOOD-BASED DATA

It is unknown whether shared manifestations of cognitive dysfunction across diagnostic categories also reflect shared neurobiological mechanisms or whether the sources of impairment differ. A recent study investigated the associations between general cognitive deficits (non-emotional or so called "cold") and functional network integrity measures including global and local efficiency of the whole brain, cingulo-opercular network (CON), frontoparietal network, and auditory network (29). Patients with schizophrenia and psychotic bipolar disorder had significantly reduced CON global efficiency compared with healthy controls (29). All patients with psychotic disorders had significantly reduced CON local efficiency, but the clinical groups did not differ from one another. The CON global efficiency was significantly associated with general cognitive ability across all groups and significantly mediated the association between psychotic disorder status and general cognition. It was concluded that these findings provide evidence that "reduced CON and subcortical network efficiency may play a role in the general cognitive deficit observed across the psychosis" (29).

Another common neural underpinning of cognitive deficits across bipolar disorder, unipolar disorder, and schizophrenia is aberrant task-related activity in the dorsal prefrontal cortex (PFC), although findings regarding the direction of the aberrant activity vary between studies with most evidence for *hypo*-activity in schizophrenia and bipolar disorder while the findings in unipolar disorder are more variable. In particular, we found

in a systematic review of >100 neuroimaging studies across bipolar disorder and unipolar disorder consistent evidence for abnormal (predominantly hypo-) activity in dorsal and lateral PFC cognitive control regions during performance on working memory, executive skills, memory encoding, and sustained attention (Miskowiak and Petersen, in press). Notably, the *direction* of this dorsal PFC activity depended on patients' performance levels. Dorsal PFC *hypo*-activity is consistently linked to impaired task performance; that is *reduced cognitive capacity*. In contrast, dorsal PFC *hyper*-activity is generally accompanied by normal performance levels and thus seems to reflect *reduced cortical efficiency*; that is, a need to recruit more neural resources to maintain normal performance. These associations are likely to explain the more consistent evidence for dorsal PFC hypo-activity in the generally more severely cognitively impaired patients groups (i.e., schizophrenia and bipolar disorder).

Another consistent finding in the review was reduced deactivation of the default mode network (DMN) and limbic structures during active task performance across bipolar disorder and unipolar disorder (ibid). This suggests that cognitive impairments across mood disorders are exacerbated by a failure to suppress task-irrelevant neural activity associated with emotional reactivity, self-focus and rumination (ibid).

Emerging neuroimaging evidence points to deficits in emotion dysregulation being a prominent feature of bipolar disorder, while unipolar disorder seems to be more consistently associated with negative processing biases (30). Emotion dysregulation in bipolar disorder seems associated with increased activity in limbic regions implicated in emotion-generation paired with deficient lateral prefrontal top-down control of emotional responses (31). However, this finding is not specific to bipolar disorder; indeed neuroimaging studies of social cognition in patients with mood disorders have generally revealed enhanced activation in limbic and emotion-related structures and attenuated activity within frontal regions associated with emotion regulation and higher cognitive functions. These results reveal an "overall lack of inhibition by higher-order cognitive structures on limbic and emotion-related structures during social cognitive processing in patients with mood disorders" (32). Critically, key variables, including illness burden, symptom severity, comorbidity, medication status, and cognitive load may moderate this pattern of neural activation (32).

Peripheral inflammation might be related to cognitive deficits in schizophrenia and bipolar disorder. Single studies suggest the role of C-reactive protein (CRP), interleukin (IL)-1 receptor antagonist, IL-6, and tumor necrosis factor-α (TNF-α) with its receptors in the development of cognitive impairment in bipolar disorder as summarized in reviews (33, 34). Due to low number of studies, it is difficult to draw conclusions on the involvement of CRP and cytokine alterations in the development of cognitive deficits in bipolar disorder. More consistent results indicate worse cognitive performance in schizophrenia patients with higher CRP levels (33). Evidence for the involvement of other cytokines in cognitive impairment in patients with schizophrenia is less convincing due to discordant results and scarcity of studies (33). Nevertheless, a larger study found that general cognitive abilities may be associated with IL-1Ra and sTNF-R1 in schizophrenia and with soluble CD40 ligand (sCD40L) and IL-1Ra in bipolar disorder patients (35).

ASSOCIATIONS TO FAMILY HISTORY / GENETICS

A recent meta-analysis of cognitive functions in first-degree relatives of probands with bipolar disorder and schizophrenia showed that probands with schizophrenia displayed cognitive deficits in all domains (d = 0.20–0.58) whereas probands with bipolar disorder underperformed healthy controls in processing speed, verbal fluency and speed based executive function tests (36). It was concluded that "inefficiency in processing information and impaired processing speed might be common vulnerability factors for major psychoses." On the other hand, "low performance in accuracy based tasks and deficits in general intellectual ability, verbal learning, planning, and working memory might be more specifically associated with risk for schizophrenia" (36). Further, we found in a systematic review of neuroimaging studies of healthy first-degree relatives of patients with bipolar disorder emerging evidence for abnormalities in emotional processing—and regulation and reward processing being candidate endophenotypes (37). We investigated this notion in a cohort of monozygotic twins at risk of either unipolar or bipolar disorder (reflected by a co-twin history of that disorder) (38). Interestingly, we found that twins at risk of bipolar disorder showed increased sensitivity and reactivity to positive social stimuli in comparison with individuals at risk of unipolar disorder and low-risk control twins. Together, these findings provide emerging evidence for positive bias being a putative neurocognitive endophenotype that is specific for bipolar disorder.

In terms of neurocognitive-genetic investigations, catechol-O-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) are the two most studied candidate genes especially in patients with schizophrenia (39). Whereas BDNF Val66Met carriers seem to perform worse on verbal working memory, problem solving, and visuo-spatial abilities, COMT Val158Met carriers may perform better in working memory, attention, executive functioning with evidence of genotype by diagnosis interactions including high-risk individuals (39), although findings are not uniform (40, 41). In terms of genetic-structural MRI studies, "patients with schizophrenia are found to have reductions in the frontal, temporal, parietal cortices, and limbic regions, which are associated with BDNF, COMT, and neuregulin-1 (NRG1) genes" (39). Genetic-functional MRI studies in bipolar disorder are sparse and results conflicting (39, 42).

CHARACTERISTICS OF COGNITION DURING LONG-TERM FOLLOW-UP

Cognitive deficits in bipolar disorder in remission seem to persist over time or even progress supporting the view that these deficits qualify for an intermediary phenotype. Using

a 5 years longitudinal cohort, 91 individuals with bipolar disorder and 17 healthy controls were administered a battery of neuropsychological tests that captured four main areas of executive functioning that were found to persist over time (43).

Based on cross-sectional studies, cognitive deficits seem to deteriorate during late stages of the disorder (44). In contrast, there is a lack of longitudinal studies on cognition in bipolar disorder (45, 46) with the largest study being the study by Ryan et al. (43, 47). A new meta-analysis comparing short-term (mean of 1.5 years) and long-term (mean of 5.5 years) neurocognitive changes in 643 euthymic patients with bipolar disorder, 367 healthy controls and 168 patients with schizophrenia found no cognitive changes over time in any of the three cohorts (46). Besides the small sample sizes in each study, limitations included short follow-up (mean follow-up period of 4.6 years) specifically for studies of bipolar disorder, high attrition rates (up to 45%) among all participants and strict euthymia criteria for bipolar patients included in the analyses, which may have introduced a selection bias (including only the high functioning patients), as also concluded in a prior similar meta-analysis of bipolar disorder (48).

Regarding cognitive functioning in unipolar disorder, some cross-sectional studies suggest that cognitive function in the euthymic phase is associated with the duration or number of prior episodes [(49–54), for a review see: (19)].

Studies on the risk of developing dementia in unipolar disorder and bipolar disorder have recently been summarized (55). It was concluded that a meta-analysis including 44 studies on depression and six on bipolar disorder (56) as well as *all* subsequent studies have confirmed that unipolar disorder (56–60) and bipolar disorder (56–58, 60, 61) are associated with increased risks of developing dementia long-term (as a clinical diagnosis). It was further concluded that longitudinal studies of bipolar disorder may have had to short follow-up time (mean follow-up period of 4.62 years) to reveal a decrease in *neuropsychological* functioning over time in contrast to the much longer follow-up time in studies with dementia as the outcome measure (55).

TREATMENT EFFECTS ON COGNITION

A recent systematic review on novel pharmacological (N-acetyl cysteine, pregnolone, ketamine and pramipexole, mifepristone, galantamine, insulin, erytrophoietin, withania somnifera, and citicoline) and psychological treatments (cognitive remediation and cognitive training) on cognition in bipolar disorder identified 19 studies of which 13 were RCTs and six were open-label or non-randomized studies (62). The efficacy on cognition was overall disappointing or preliminary, possibly due to several methodological challenges. Similarly, a later controlled trial found no effect of methylene blue on cognition in bipolar disorder (63). Among the most promising pharmacological treatments for cognitive dysfunction across bipolar disorder and unipolar disorder is erythropoietin, but the evidence is still preliminary (62, 64). These findings are partly in accordance with findings within unipolar disorder and schizophrenia with only a few studies have shown benefit for pharmacological treatments (64–66) and with a lack of successful replication of these data (64, 66, 67). However, psychological treatment programs involving intensive cognitive remediation have revealed more consistent positive effects on cognition in schizophrenia (68, 69) and emerging evidence in mood disorders (64, 70).

CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH

It is clear from the present summary of studies on cognition in bipolar disorder that at the current state of knowledge cognition in bipolar disorder does not qualify as a diagnostic intermediate phenotype using the Robin and Guze criteria of diagnostic validity (4) or the later endophenotype concept (5, 6), although emerging evidence points to hot cognition abnormalities representing promising putative endophenotypes. Rather, extant findings within four of the five Robin and Guze criteria generally support the dimensional hypothesis that a shared neurobiological mechanism underlies cognitive impairment across bipolar disorder, unipolar disorder and schizophrenia: (1) there may not be a specific neuropsychological signature that differentiate cognitive deviances in bipolar disorder from those in schizophrenia and unipolar disorder (only potentially within hot cognition); (2) brain imaging or blood-based data does not at the current state of knowledge differentiate between cognitive dysfunction in bipolar disorder, schizophrenia or unipolar disorder; (3) probands to patients with bipolar disorder, schizophrenia, and unipolar disorder show similar cognitive deficits although with varying severity, except for within hot cognition. Investigations of genetic associations to cognitive deviances are in its early stages, only (4) treatment effects of pharmacological or psychological interventions on cognition do not seem to differ within bipolar disorder, schizophrenia and unipolar disorder. The fourth Robin and Guze criterion seems fulfilled as cognitive deficits in bipolar disorder seem either stable over time or progress during long-term supporting cognitive deficits as an intermediary phenotype.

It is further evident from the present summary of studies on cognition in bipolar disorder that a number of research initiatives are needed within all five of the Robin and Guze criteria.

1. Research is needed integrating "hot" and "cold" cognition in bipolar disorder. Few if any studies have investigated how emotion dysregulation (i.e., hot cognition) interact with cold cognition. As recently emphasized, cognitive biases, reward processing and motivation, rumination, and mood stability may play significant roles in the manner in which attention, appraisal, and response processes are deployed in mood disorders (71).

2. Emotion dysregulation (hot cognition) should be investigated across mood disorders and schizophrenia. Emotion dysregulation has emerged as a new research area that may characterize mood disorders, and potentially specifically bipolar disorder, rather than schizophrenia. Although these speculations are clinically plausible, emotion dysregulation has not been systematically investigated across mood disorders and schizophrenia.

3. Structural and functional neuroimaging data on cognitive features ("cold" and "hot") should be integrated across mood disorders. Such multimodal neuroimaging studies aiming to identify structure-function relationships in neural circuitry have previously been suggested in relation to bipolar disorder in general (24). As highlighted, a very small number of studies examined structure-function relationships in prefrontal cortical-amygdala circuitry in adults with bipolar disorder type I and bipolar disorder type II (24). We suggest integrating investigations of "cold" and "hot" cognitive features into the loop and across mood disorders.

4. Neurogenetics should be integrated into research in cognitive disturbances in patients with mood disorders and schizophrenia and in their first degree relatives.

5. Research in cognitive enhancement treatments. We have previously suggested implementation of a 'neurocircuitry-based' biomarker model to evaluate neural target engagement in cognitive enhancement (62). We suggest that a valid biomarker model for cognitive improvement must fulfill five key validity criteria: it must (i) be sensitive to a treatment with pro-cognitive effects, (ii) produce similar effects in patients with cognitive dysfunction and healthy participants, (iii) be sensitive to effective treatments with different neurochemical mechanisms, (iv) be unresponsive to ineffective treatments, and (v) be sensitive to both cognitive improvement and—decline. A potential solution to the problem is a step-wise approach with which we: (i) identify the most reliable functional neuronal correlates of cognitive deficits in neuropsychiatric disorders, (ii) select one of the most promising candidate treatments and test its ability to modulate the activity in these dysfunctional neural circuitries in a short-term proof-of-concept fMRI study, and (iii) if target engagement is shown in (ii), then test the effects of this candidate treatment in a longer-term clinical phase 2 trial in patients using fMRI to elucidate the neuronal changes underlying potential pro-cognitive effects.

More evidence is needed confirming whether cognitive deficits comprise a diagnostic intermediate phenotype in bipolar disorder. The long-term perspective is that cognitive deficits may aid diagnostic accuracy and represent a key treatment target in bipolar disorder.

AUTHOR CONTRIBUTIONS

LK developed the idea and drafted the first version of the paper. KM revised the paper and both authors accepted the final version of the paper.

REFERENCES

1. Tse S, Chan S, Ng KL, Yatham LN. Meta-analysis of predictors of favorable employment outcomes among individuals with bipolar disorder. *Bipolar Disord.* (2014) 16:217–29. doi: 10.1111/bdi.12148
2. Jensen JH, Knorr U, Vinberg M, Kessing LV, Miskowiak KW. Discrete neurocognitive subgroups in fully or partially remitted bipolar disorder: Associations with functional abilities. *J Affect Disord.* (2016) 205:378–86. doi: 10.1016/j.jad.2016.08.018
3. Jaeger J, Berns S, Loftus S, Gonzalez C, Czobor P. Neurocognitive test performance predicts functional recovery from acute exacerbation leading to hospitalization in bipolar disorder. *Bipolar Disord.* (2007) 9:93–102. doi: 10.1111/j.1399-5618.2007.00427.x
4. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry* (1970) 126:983–87.
5. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* (2003) 160:636–45. doi: 10.1176/appi.ajp.160.4.636
6. Kendler KS, Neale MC. Endophenotype: a conceptual analysis. *Mol Psychiatry* (2010) 15:789–97. doi: 10.1038/mp.2010.8
7. Bourne C, Aydemir O, Balanza-Martinez V, Bora E, Brissos S, Cavanagh JT, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr Scand.* (2013) 128(3):149-162. doi: 10.1111/acps.12133
8. Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatr Scand Suppl.* (2007) 434:17–26. doi: 10.1111/j.1600-0447.2007.01055.x
9. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord.* (2009) 113:1–20. doi: 10.1016/j.jad.2008.06.009
10. Mann-Wrobel MC, Carreno JT, Dickinson D. Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. *Bipolar Disord.* (2011) 13:334–42. doi: 10.1111/j.1399-5618.2011.00935.x
11. Miskowiak KW, Burdick KE, Martinez-Aran A, Bonnin CM, Bowie CR, Carvalho AF, et al. Assessing and addressing cognitive impairment in bipolar disorder: the International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians. *Bipolar Disord.* (2018) 20:184–94. doi: 10.1111/bdi.12595
12. Sole B, Jimenez E, Torrent C, Del Mar Bonnin C, Torres I, Reinares M, et al. Cognitive variability in bipolar II disorder: who is cognitively impaired and who is preserved. *Bipolar Disord.* (2016) 18:288–99. doi: 10.1111/bdi.12385
13. Bora E. Neurocognitive features in clinical subgroups of bipolar disorder: a meta-analysis. *J Affect Disord.* (2018) 229:125–34. doi: 10.1016/j.jad.2017.12.057
14. Bortolato B, Miskowiak KW, Kohler CA, Vieta E, Carvalho AF. Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatr Dis Treat.* (2015) 11:3111–25. doi: 10.2147/NDT.S76700
15. Porter RJ, Robinson LJ, Malhi GS, Gallagher P. The neurocognitive profile of mood disorders - a review of the evidence and methodological issues. *Bipolar Disord.* (2015) 17 (Suppl 2):21–40. doi: 10.1111/bdi.12342
16. Szmulewicz AG, Valerio MP, Smith JM, Samame C, Martino DJ, Strejilevich SA. Neuropsychological profiles of major depressive disorder and bipolar disorder during euthymia. a systematic literature review of comparative studies. *Psychiatry Res.* (2017) 248:127–33. doi: 10.1016/j.psychres.2016.12.031
17. Van Rheenen TE, Lewandowski KE, Tan EJ, Ospina LH, Ongur D, Neill E, et al. Characterizing cognitive heterogeneity on the schizophrenia-bipolar disorder spectrum. *Psychol Med.* (2017) 47:1848–64. doi: 10.1017/S0033291717000307
18. Kuswanto C, Chin R, Sum MY, Sengupta S, Fagiolini A, McIntyre RS, et al. Shared and divergent neurocognitive impairments in adult patients with schizophrenia and bipolar disorder: whither the evidence? *Neurosci Biobehav Rev.* (2016) 61:66–89. doi: 10.1016/j.neubiorev.2015.12.002
19. Hasselbalch BJ, Knorr U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect. Disord.* (2011) 134:20–31. doi: 10.1016/j.jad.2010.11.011

20. Jaeger J, Berns S, Uzelac S, Davis-Conway S. Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Res.* (2006) 145:39–48. doi: 10.1016/j.psychres.2005.11.011
21. Strakowski SM, Adler CM, Holland SK, Mills N, DelBello MP. A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharmacology* (2004) 29:1734–40. doi: 10.1038/sj.npp.1300492
22. Kerr N, Dunbar RI, Bentall RP. Theory of mind deficits in bipolar affective disorder. *J Affect. Disord.* (2003) 73:253–9. doi: 10.1016/S0165-0327(02)00008-3
23. Wessa M, Linke J. Emotional processing in bipolar disorder: behavioural and neuroimaging findings. *Int. Rev Psychiatry* (2009) 21:357–67. doi: 10.1080/09540260902962156
24. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *Am J Psychiatry* (2014) 171:829–43. doi: 10.1176/appi.ajp.2014
25. Miskowiak KW, Carvalho AF. 'Hot' cognition in major depressive disorder: a systematic review. *CNS Neurol Disord Drug Targets* (2014) 13:1787–803.
26. Miskowiak K, Glerup L, Vestbo C, Harmer CJ, Reinecke A, Macoveanu J, et al. Different neural and cognitive response to emotional faces in healthy monozygotic twins at risk of depression. *Psychol Med.* (2015) 45:1447–58. doi: 10.1017/S0033291714002542
27. Anticevic A, Schleifer C, Youngsun TC. Emotional and cognitive dysregulation in schizophrenia and depression: understanding common and distinct behavioral and neural mechanisms. *Dialogues Clin Neurosci.* (2015) 17:421–34.
28. de Brito Ferreira Fernandes F, Gigante AD, Berutti M, Amaral JA, de Almeida KM, de Almeida Rocca CC, et al. Facial emotion recognition in euthymic patients with bipolar disorder and their unaffected first-degree relatives. *Compr Psychiatry* (2016) 68:18–23. doi: 10.1016/j.comppsych.2016.03.001
29. Sheffield JM, Kandala S, Tamminga CA, Pearlson GD, Keshavan MS, Sweeney JA, et al. Transdiagnostic associations between functional brain network integrity and cognition. *JAMA Psychiatry* (2017) 74:605–13. doi: 10.1001/jamapsychiatry.2017.0669
30. Miskowiak KW, Carvalho AF. 'Hot' cognition in major depressive disorder: a systematic review. *CNS Neurol Disord Drug Targets* (2014) 13:1787–803.
31. Townsend JD, Torrisi SJ, Lieberman MD, Sugar CA, Bookheimer SY, Altshuler LL. Frontal-amygdala connectivity alterations during emotion downregulation in bipolar I disorder. *Biol Psychiatry* (2013) 73:127–35. doi: 10.1016/j.biopsych.2012.06.030
32. Cusi AM, Nazarov A, Holshausen K, Macqueen GM, McKinnon MC. Systematic review of the neural basis of social cognition in patients with mood disorders. *J Psychiatry Neurosci.* (2012) 37:154–69. doi: 10.1503/jpn.100179
33. Misiak B, Stanczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: a systematic review. *Schizophr Res.* (2018) 192:16–29. doi: 10.1016/j.schres.2017.04.015
34. Rosenblat JD, Brietzke E, Mansur RB, Maruschak NA, Lee Y, McIntyre RS. Inflammation as a neurobiological substrate of cognitive impairment in bipolar disorder: evidence, pathophysiology and treatment implications. *J Affect Disord.* (2015) 188:149–59. doi: 10.1016/j.jad.2015.08.058
35. Hope S, Hoseth E, Dieset I, Morch RH, Aas M, Aukrust P, et al. Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. *Schizophr Res.* (2015) 165:188–94. doi: 10.1016/j.schres.2015.04.004
36. Bora E. A comparative meta-analysis of neurocognition in first-degree relatives of patients with schizophrenia and bipolar disorder. *Eur Psychiatry* (2017) 45:121–8. doi: 10.1016/j.eurpsy.2017.06.003
37. Miskowiak KW, Kjaerstad HL, Meluken I, Petersen JZ, Maciel BR, Kohler CA, et al. The search for neuroimaging and cognitive endophenotypes: a critical systematic review of studies involving unaffected first-degree relatives of individuals with bipolar disorder. *Neurosci Biobehav Rev.* (2017) 73:1–22. doi: 10.1016/j.neubiorev.2016.12.011
38. Kaersgaard S, Meluken I, Kessing LV, Vinberg M, Miskowiak KW. Increased sensitivity to positive social stimuli in monozygotic twins at risk of bipolar vs. unipolar disorder. *J Affect Disord.* (2018) 232:212–18. doi: 10.1016/j.jad.2018.02.055
39. Kurnianingsih YA, Kuswanto CN, McIntyre RS, Qiu A, Ho BC, Sim K. Neurocognitive-genetic and neuroimaging-genetic research paradigms in schizophrenia and bipolar disorder. *J Neural Transm.* (2011) 118:1621–39. doi: 10.1007/s00702-011-0672-z
40. Burdick KE, Funke B, Goldberg JF, Bates JA, Jaeger J, Kucherlapati R, et al. COMT genotype increases risk for bipolar I disorder and influences neurocognitive performance. *Bipolar Disord.* (2007) 9:370–6. doi: 10.1111/j.1399-5618.2007.00384.x
41. Tramontina JF, Yates D, Magalhaes PV, Trentini C, Sant'anna MK, Fries GR, et al. Brain-derived neurotrophic factor gene val66met polymorphism and executive functioning in patients with bipolar disorder. *Rev Bras Psiquiatr.* (2009) 31:136–40. doi: 10.1590/S1516-44462009000200010
42. Miskowiak KW, Kjaerstad HL, Stottrup MM, Svendsen AM, Demant KM, Hoeffding LK, et al. The catechol-O-methyltransferase (COMT) Val158Met genotype modulates working memory-related dorsolateral prefrontal response and performance in bipolar disorder. *Bipolar Disord.* (2017) 19:214–24. doi: 10.1111/bdi.12497
43. Ryan KA, Assari S, Pester BD, Hinrichs K, Angers K, Baker A, et al. Similar trajectory of executive functioning performance over 5 years among individuals with bipolar disorder and unaffected controls using latent growth modeling. *J Affect Disord.* (2016) 199:87–94. doi: 10.1016/j.jad.2016.04.016
44. Rosa AR, Magalhaes PV, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, et al. Clinical staging in bipolar disorder: focus on cognition and functioning. *J Clin Psychiatry* (2014) 75:e450–6. doi: 10.4088/JCP.13m08625
45. Mora E, Portella MJ, Forcada I, Vieta E, Mur M. Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. *Psychol Med.* (2013) 43:1187–96. doi: 10.1017/S0033291712001948
46. Bora E, Ozerdem A. Meta-analysis of longitudinal studies of cognition in bipolar disorder: comparison with healthy controls and schizophrenia. *Psychol Med.* (2017) 47:2753–66. doi: 10.1017/S0033291717001490
47. Ryan KA, Assari S, Angers K, Marshall DF, Hinrichs K, Easter R, et al. Equivalent linear change in cognition between individuals with bipolar disorder and healthy controls over 5 years. *Bipolar Disord.* (2017) 19:689–97. doi: 10.1111/bdi.12532
48. Samame C, Martino DJ, Strejilevich SA. Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. *J Affect Disord.* (2014) 164:130–8. doi: 10.1016/j.jad.2014.04.028
49. Kessing LV, Dam H, Joergensen OS, Bolwig TG. Cognitive impairment in affective disorders. Relation to illness characteristics. *Nord J Psychiatry* (1996) 50:305–16.
50. Kessing LV. Cognitive impairment in the euthymic phase of affective disorder. *Psychol. Med.* (1998) 28:1027–38.
51. Hasselbalch BJ, Knorr U, Hasselbalch SG, Gade A, Kessing LV. The cumulative load of depressive illness is associated with cognitive function in the remitted state of unipolar depressive disorder. *Eur Psychiatry* (2013) 28:349–55. doi: 10.1016/j.eurpsy.2012.03.004
52. Beats BC, Sahakian BJ, Levy R. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol Med.* (1996) 26:591–603. doi: 10.1017/S0033291700035662
53. Paelecke-Habermann Y, Pohl J, Leplow B. Attention and executive functions in remitted major depression patients. *J Affect Disord.* (2005) 89:125–35. doi: 10.1016/j.jad.2005.09.006
54. Bhardwaj A, Wilkinson P, Srivastava C, Sharma M. Cognitive deficits in euthymic patients with recurrent depression. *J Nerv Ment Dis.* (2010) 198:513–5. doi: 10.1097/NMD.0b013e3181e4c5ba
55. Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. *Acta Psychiatr Scand.* (2017) 135:51–64. doi: 10.1111/acps.12667
56. da SJ, Goncalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: systematic review. *Br J Psychiatry* (2013) 202:177–86. doi: 10.1192/bjp.bp.111.101931
57. Kessing LV, Olsen EW, Mortensen PB, Andersen PK. Dementia in affective disorder: a case-register study. *Acta Psychiatr Scand.* (1999) 100:176–85.
58. Kessing LV, Nilsson FM. Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. *J Affect Disord.* (2003) 73:261–9. doi: 10.1016/S0165-0327(02)00004-6

59. Kessing LV. Depression and the risk for dementia. *Curr Opin Psychiatry* (2012) 25:457–61. doi: 10.1097/YCO.0b013e328356c368
60. Chen MH, Li CT, Tsai CF, Lin WC, Chang WH, Chen TJ, et al. Risk of subsequent dementia among patients with bipolar disorder or major depression: a nationwide longitudinal study in Taiwan. *J Am Med Dir Assoc.* (2015) 16:504–8. doi: 10.1016/j.jamda.2015.01.084
61. Wu KY, Chang CM, Liang HY, Wu CS, Chia-Hsuan WE, Chen CH, et al. Increased risk of developing dementia in patients with bipolar disorder: a nested matched case-control study. *Bipolar Disord.* (2013) 15:787–94. doi: 10.1111/bdi.12116
62. Miskowiak KW, Carvalho AF, Vieta E, Kessing LV. Cognitive enhancement treatments for bipolar disorder: a systematic review and methodological recommendations. *Eur Neuropsychopharmacol.* (2016) 26:1541–61. doi: 10.1016/j.euroneuro.2016.08.011
63. Alda M, McKinnon M, Blagdon R, Garnham J, MacLellan S, O'Donovan C, et al. Methylene blue treatment for residual symptoms of bipolar disorder: randomised crossover study. *Br J Psychiatry* (2017) 210:54–60. doi: 10.1192/bjp.bp.115.173930
64. Miskowiak KW, Ott CV, Petersen JZ, Kessing LV. Systematic review of randomized controlled trials of candidate treatments for cognitive impairment in depression and methodological challenges in the field. *Eur Neuropsychopharmacol.* (2016) 26:1845–67. doi: 10.1016/j.euroneuro.2016.09.641
65. Harvey PD, Bowie CR. Cognitive enhancement in schizophrenia: pharmacological and cognitive remediation approaches. *Psychiatr Clin North Am.* (2012) 35:683–98. doi: 10.1016/j.psc.2012.06.008
66. Harvey PD, Sand M. Pharmacological augmentation of psychosocial and remediation training efforts in schizophrenia. *Front Psychiatry* (2017) 8:177. doi: 10.3389/fpsyt.2017.00177
67. Keefe RS, Davis VG, Spagnola NB, Hilt D, Dgetluck N, Ruse S, et al. Reliability, validity and treatment sensitivity of the Schizophrenia Cognition Rating Scale. *Eur Neuropsychopharmacol.* (2015) 25:176–84. doi: 10.1016/j.euroneuro.2014.06.009
68. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry* (2011) 168:472–85. doi: 10.1176/appi.ajp.2010.10060855
69. Revell ER, Neill JC, Harte M, Khan Z, Drake RJ. A systematic review and meta-analysis of cognitive remediation in early schizophrenia. *Schizophr Res.* (2015) 168:213–22. doi: 10.1016/j.schres.2015.08.017
70. Lewandowski KE, Sperry SH, Cohen BM, Norris LA, Fitzmaurice GM, Ongur D, et al. Treatment to Enhance Cognition in Bipolar Disorder (TREC-BD): efficacy of a randomized controlled trial of cognitive remediation versus active control. *J Clin Psychiatry* (2017) 78:e1242–9. doi: 10.4088/JCP.17m11476
71. Malhi GS, Byrow Y, Fritz K, Das P, Baune BT, Porter RJ, et al. Mood disorders: neurocognitive models. *Bipolar Disord.* (2015) 17 (Suppl. 2):3–20. doi: 10.1111/bdi.12353

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