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**Current understandings of the trajectory and emerging correlates of cognitive impairment
in bipolar disorder: an overview of evidence**

Running title: *Trajectories and correlates of cognition in BD*

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Abstract

Objectives: Cognitive dysfunction affects a significant proportion of people with bipolar disorder (BD), but the cause, trajectory and correlates of such dysfunction is unclear. Increased understanding of these factors is required to progress treatment development for this symptom dimension.

Methods: This paper provides a critical overview of the literature concerning the trajectories and emerging correlates of cognitive functioning in BD. It is a *narrative* review in which we provide a qualitative synthesis of current evidence concerning clinical, molecular, neural, and lifestyle correlates of cognitive impairment in BD across the lifespan (in premorbid, prodromal, early onset, post-onset, elderly cohorts).

Results: There is emerging evidence of empirical links between cognitive impairment and an increased inflammatory state, brain structural abnormalities and reduced neuroprotection in BD.

However, evidence regarding the progressive nature of cognitive impairment is mixed, since consensus between different cross-sectional data is lacking and does not align to the outcomes of the limited longitudinal studies available. Increased recognition of cognitive heterogeneity in BD may help to explain some inconsistencies in the extant literature.

Conclusions: Large, longitudinally focussed studies of cognition and its covariation alongside biological and lifestyle factors are required to better define cognitive trajectories in BD, and eventually pave the way for the application of a precision medicine approach for individual patients in clinical practice.

1. Introduction

It is now widely recognized that a substantial proportion of individuals with bipolar disorder (BD) experience cognitive impairments that persist even beyond the resolution of mood symptoms (1, 2). While it is becoming increasingly clear that these impairments adversely impact psychosocial functioning, key questions remain regarding their cause, trajectory and correlates. A better understanding of the factors associated with impairments in cognition is critically needed to progress the development of intervention strategies directly targeted at remediating cognitive dysfunction and preventing subsequent cognitive decline in the illness. This will require the implementation of more refined experimental designs that build on understandings of the neurobiological correlates and lifestyle risk factors for cognitive functioning, integrated with current knowledge about the cognitive course of illness - including new work suggesting the presence of cognitive subgroups within BD that potentially map onto different cognitive pathways (3-5). To this end, we aim to provide a qualitative overview and update of current literature that speaks to potential trajectories and emerging correlates of cognitive functioning in BD. By providing a narrative synthesis of evidence concerning clinical, molecular, neural, and lifestyle correlates of (non-social) cognitive impairments in BD emerging from cross-sectional and longitudinal data in cohorts across the lifespan, this review has a view to informing future research from which the outcomes will enhance our capacity to develop effective, personalised interventions for this symptom dimension.

2. Trajectory of cognitive functioning in BD

2.1 Cognitive functioning pre-onset and in cohorts at familial risk for BD

Several large *cohort studies* have examined the relationship of premorbid cognition to psychiatric outcomes. Findings from these studies are mixed, but in general do not strongly support premorbid cognitive dysfunction in people who later develop BD, in contrast to similar studies of schizophrenia (SZ) – a genetically and phenotypically related illness. A large cohort study (baseline $n=1037$) from New Zealand found that language and cognitive impairments in very early childhood were associated with SZ-spectrum disorders but not mania (6), and that while low IQ was associated with risk for SZ, mania risk was actually associated with higher IQ premorbidly (7). This is consistent with a recent cohort study of $n=1881$ individuals from the UK, showing that higher childhood IQ, particularly verbal IQ, is predictive of subsequent mania symptoms (8). However, 68 subjects identified through Israeli National Registers later diagnosed with nonpsychotic BD did not differ from matched control subjects on premorbid intellectual abilities, in contrast with 536 individuals later diagnosed with SZ (9). Data from a Swedish conscripts study, including 362 patients who developed SZ and 108 patients who developed BD, also found no association between IQ and risk for BD, but a linear relationship between IQ and risk of SZ (10). Yet a more recent study of $n=213,693$ Swedish conscripts found that lower risk for BD ($n=1495$) was associated with higher cognitive functioning, as defined by spatial recognition, general knowledge and linguistic understanding, in late adolescence (11). In contrast, a large study of 195,191 Finnish conscripts found that both high arithmetic reasoning *and* low visuospatial reasoning increased the risk of developing BD ($n=100$) in the same cohort of patients (12).

Other evidence suggests that early developmental and school delays may be associated with later development of BD, especially a more severe illness phenotype (psychosis, early onset), though these delays may not be due to cognitive deficits per se. One study showed that school difficulties were associated with a moderately increased risk for hospital admissions for 193 patients with a non-schizophrenia psychosis (including BD) (13); however, to a lesser extent than in 195 patients with SZ. Additionally, an Australian cohort analysis of $n=1934$ participants found that developmental delays predicted early-onset mania symptoms (14), findings consistent with those from another study of 1613 adults, which found that school problems, but not lower

IQ during childhood, was associated with development of affective psychosis in 51 individuals later on (15).

Retrospective studies of BD patients generally find little evidence of pronounced premorbid cognitive impairment at the group level. Indeed, a recent review found that premorbid cognitive deficits were significantly more pronounced in patients with SZ than in patients with BD (16). Here, converging evidence indicated a linear risk trend in SZ, but a trend for an association between both high *and* low premorbid academic performance and an increased risk of BD. Thus, while some evidence suggests that people who later develop BD may experience some early developmental and academic difficulties, the majority of cohort and retrospective studies did not find strong evidence of premorbid cognitive dysfunction.

Findings in *high risk cohorts* comprising biological relatives of patients with BD show fairly consistent deficits in several select domains including verbal learning and memory, processing speed, and executive functioning compared to healthy controls (17-19). Cognitive deficits may be evident in both unaffected *adult* siblings/offspring of BD probands who are approaching or past the modal age of BD onset, as well as in *youth* still at risk of developing BD (20, 21). Meta-analytic investigations indicate that the effect size of deficits in both younger and older BD relatives are at least small to medium in size (17, 22). Thus, current evidence in familial high-risk cohorts demonstrates the presence of cognitive deficits irrespective of clinical disease expression (19). This suggests that cognition in BD is at least partially influenced by heritable factors and that neurodevelopmental abnormalities play a role, assuming that at least some familial high-risk youth go on to develop the illness. Notably, clear inferences to this end are hampered by the extremely limited prospective data in youth at high risk for BD and unaffected relatives to date. However, there is some evidence to indicate that subtle deficits in selective cognitive domains may be present prior to onset of BD in at least some individuals. Indeed, one study found that 9 familial high-risk youth who converted to BD in early adulthood had an increased history of early attentional problems as well as reduced premorbid performance IQ and executive function compared to 86 non-converting subjects (23). A further study showed poorer premorbid academic achievement and cognitive performance at age seven, in 99 patients later developing a psychotic disorder including BD. Subsequent stratification showed that premorbid cognition in the 35 BD patients was intermediate to the 101 controls and 45 SZ patients, but did not differ significantly from either (24).

In putatively *prodromal individuals*, one study examining individuals at clinical high risk for SZ found that a small number of subjects (n=8) who converted to BD had qualitatively lower, but non-significant pre-diagnosis baseline differences in global cognition compared to 115 individuals in a non-converting control subjects (25). In an exploratory prospective study on the prodrome of mania, the 16 youths who later developed BD had a similar cognitive functioning to 46 subjects at ultra-high risk for psychotic disorders who did not transition to BD or psychotic disorder (26). However, they underperformed 66 healthy controls on measures of global intelligence, abstract visual reasoning, and attention/processing speed. In contrast, a recent study showed that 10 prodromal individuals at clinical high risk for BD had non-significantly better baseline performance compared to both the 60 clinical high-risk SZ individuals and the 12 individuals converting to SZ during the 1 year follow up (27). However, as the group of 4 individuals who converted to BD were not included in the analysis, it is unknown whether cognitive performance in these individuals was impaired before or after the transition.

2.2 Post-onset cognitive functioning in paediatric, first episode, established BD and elderly cohorts

Studies of cognition in *paediatric BD* (PDB) – typically defined by an onset prior to 18 years of age – are limited. An initial meta-analysis of 12 studies of BD youth across several mood states showed widespread, medium effect size deficits in cognition generally, and in most individual domains (28). In contrast, a subsequent meta-analysis focussing on studies of euthymic BD youth exclusively, found impairments only in the domains of verbal and visual memory/learning as well as working memory compared to healthy controls (29). While memory deficits are consistent with that of euthymic adult BD samples, the absence of processing speed, reasoning and problem-solving, and attention/vigilance deficits that are commonly seen in euthymic BD adults suggests a less pervasive trait-like dysfunction in younger onset patients. Interestingly, the one study of longitudinal cognitive changes in PDB (30) found impairments in most cognitive domains in predominantly euthymic patients ranging in age between 9 to 14 years. The impairments were evident both at baseline and at 3-year follow up, indicating an inability of those with PDB to cognitively catch-up to their healthy peers over time. A slower rate of improvement in executive functions and verbal memory in the PDB group also provided evidence of a cognitive delay.

In mixed age adult samples, evidence is varied with regards to whether an *early-onset* of BD is associated with more severe cognitive deficits. One study explicitly comparing cognition in patients with early, mid, or late onset ages found no between-group differences, although premorbid functioning in terms of academic and social achievement was worse in those whose illness began earlier (31). A meta-analysis of cognitive impairment in *first episode* BD employing onset age as a continuous variable in a meta-regression, also found no significant age effects on global cognition in adult patients (32). However, when cognitive performance was explicitly compared between first-episode patients with either a paediatric or an adult onset in this meta-analysis, large differences were evident favouring better performance in the latter. This is consistent with findings from a prior meta-analysis of established illness in euthymic adults indicating that an earlier manifestation of BD predicts worse verbal learning and processing speed (17).

It is becoming increasingly recognized that cognitive impairment in BD is present from as early as the first episode, with small-large deficits in all cognitive domains found in euthymic adult BD patients following a first episode in a recent meta-analysis (32). Although cognitive performance in these patients was better than that of first episode SZ, differences were modest and consistent with comparisons of BD and SZ in more chronic samples. Relevantly, the size of effects in first episode BD compared to controls were qualitatively similar to that seen in a prior meta-analysis (17) of chronic BD for most domains. However, effects for executive measures in first episode BD patients were smaller, providing some evidence that deficits in this domain could follow a progressive course.

In *cross-sectional* studies explicitly comparing patients with a single mood episode to those with multiple episodes, larger cognitive impairments have generally been found in the latter irrespective of mood state (33, 34). In the context of an absence of age differences between single and multi-episode groups, this has been taken by some to indicate progressive cognitive dysfunction that may directly owe to the cumulative biological toxicity associated with repeated mood episodes – a key notion of the clinical staging framework (35, 36). However, given evidence of cognitive dysfunction in adult first degree relatives of BD that frames cognitive impairment as the outcome of genetic liability, it is also plausible that more severe cognitive impairment in those with repeated episodes represents a marker of a more severe illness phenotype rather than a function of illness progression (37). Indeed, available evidence shows

that multi-manic episode patients with worse cognitive functioning manifested the illness between 2 to 5 years earlier than single episode patients (33, 34). This is consistent with some, but not all findings showing more pronounced cognitive impairments in BD patients manifesting other indicators of a more severe phenotype, such as a history of recurrent and/or more severe (including psychotic) mood episodes, longer illness durations (greater chronicity) and/or more hospitalisations (38-40, see 41 for an exception). Relevantly, in one study where euthymic patients with either a single and multi-episode (both mania and depression) history had an equivalent onset age, widespread cognitive worsening in patients with more than one episode was *not* evident (42). Relatedly, another study comparing young and old BD patients showed equivalent cognitive performance despite substantial differences in illness duration (43). While differences in mood episode history between the BD groups was not explicitly analysed, the study was based on the assumption that the number of mood episodes experienced was likely to be increased in the older BD group. In a separate cognitive follow-up study, these same authors (44) reported a relationship between cognitive performance at the end of the study and the number of episodes and time spent ill during the study. However, these clinical variables did not correlate with *cognitive change* across the 73-month study time-frame. This further suggests that previously observed associations between episode number and cognitive impairment in BD in other studies are indicative of a more severe subtype rather than cognitive decline on account of clinical course.

Importantly, a recent meta-analysis of the few published *longitudinal* studies of BD samples found no good evidence of decline in cognition over short (~1.5years) or longer-term (~5.5 years) periods (37). There was also no evidence for an effect of age, gender, education or changes in mood symptoms on cognitive change (37). Cognitive changes in BD patients also did not differ from healthy controls or SZ patients, and were largely consistent with an earlier meta-analysis on the topic (45). Longitudinal data are arguably more useful for informing us about the drivers of cognitive impairment in BD than cross-sectional studies. Thus, the disparity between evidence of stability in cognition from these studies versus (some) cross-sectional evidence of worse cognition alongside a more aggressive and/or chronic clinical course, further supports arguments that the findings of the latter reflect the outcome of a more severe form of illness in the more impaired patients.

Nonetheless, it should be noted that relatively limited follow-up times of ≤ 5 years in most studies may not be sufficient to demonstrate cognitive deterioration. Indeed, the study with the longest follow-up time of ~ 9 years (46) revealed progressive deficits in executive function (but not other domains), which is consistent with findings indicating progressive decline in this domain by proxy of smaller executive deficits in first-episode vs chronic BD samples (47). Executive deficits in the ~ 9 year follow up study correlated with a longer duration of illness; and there was a significant baseline to follow-up increase in the number of both depressive and manic mood episodes occurring alongside increasing chronicity (46). This supports theories that episode recurrence *may* play a role in this decline, although only in the context of executive function.

In *elderly* cohorts of BD patients with a long illness history, illness duration does not appear to impact cognition (41, 48). Indeed, findings from a meta-analysis showed that the effect sizes of deficits in euthymic elderly BD (excluding those with a late-onset) are of medium size and are comparable to that of younger BD patients (49). This is consistent with longitudinal evidence of stable cognitive impairment in the illness. Patients with a late onset of illness after age 40 however, appear to represent a unique subgroup with more severe and widespread cognitive deficits than that of patients whose illness begins prior to this age (50). Although not always consistent (51), evidence tends to indicate that older onset patients have a greater incidence of neurological comorbidities (50) and are less likely to have a family history of psychiatric illness (52), suggesting that different etiological factors may be involved. Relevantly, there are case reports suggesting that early stage neurodegenerative disease can mimic psychosis and BD, such that a late manifestation of BD and associated cognitive impairment may represent a putative prodrome marker from which dementia or Alzheimer's Disease may emerge (53-55). Nonetheless, BD patients appear to be at an increased risk of developing pre-senile and senile dementia compared to those with other psychiatric or medical conditions as well as the general population, irrespective of onset age (56-60). A register-based study of $>4,200$ patients with BD revealed that the long-term risk of dementia increases with the number of manic and depressive mood episodes, with a 6% increased risk for every new episode (61). Thus, it remains unclear whether those that go on to develop dementia are showing progressive impairment as a result of mood episodes or are simply manifesting a more severe BD phenotype associated with a higher risk for dementia.

2.3 Summary and insights into cognitive trajectories from new methods of assessing cognition in BD

Post-onset studies indicate clear evidence of cognitive impairments in first episode, established and late-life BD cohorts. In contrast, the findings from prospective, retrospective and high-risk studies collectively indicate no strong evidence for premorbid cognitive and academic difficulties in patients who later develop BD. However, this inference is tempered as *some* studies have shown subtle deficits in attention and executive functions that are present prior to illness onset; and indicated that poor premorbid academic achievement may be associated with worse post-onset cognition in the illness (62). In combination with findings of cognitive impairment in samples of youth at

familial risk for BD who may still go on to develop the illness, it thus remains possible that there is at least a subset of patients in whom subtle cognitive impairments manifest in the premorbid developmental course.

Importantly, there may be substantial heterogeneity of premorbid intellectual functioning in BD(63), as has been demonstrated in post-onset patients where some score lower on proxy measures of premorbid cognitive dysfunction and others do not (5, 64, 65). A recent cross-diagnostic clustering study also indicated the presence of at least one subgroup comprising ~53% patients with BD and ~47% with SZ that demonstrated poor premorbid *academic* adjustment relative to controls (66). Heterogeneity in premorbid factors may have complex implications for BD risk. For example, Parellada and colleagues (16) concluded in their review, that while premorbid cognition and risk for SZ appear to have a linear relationship, this association is better characterized by a U-shaped curve in BD, with both above average and below average IQ associated with greater illness risk.

There is clear evidence of cognitive impairment at first episode in BD, but worse impairments in paediatric vs adult onset first episode BD patients suggest that clinical manifestation of the illness at a younger age is more cognitively detrimental. While the effect sizes of impairments in most cognitive domains in adult first episode samples can be considered similar in magnitude to those seen in patients with more established illness, cross-sectional evidence directly comparing multi-episode and first episode patients indicate that the former are more cognitively impaired than the latter. While this *may* be indicative of a progressive worsening of cognitive functioning with relapse, worse cognitive functioning in multi-episode patients could also represent one manifestation of a more severe clinical phenotype that is prone to increased episode recurrence and an earlier onset age. This hypothesis is arguably more plausible in light of evidence from longitudinal studies showing that the magnitude of cognitive impairment generally remains stable over time, with the exception of executive function which may decline (46). Of course, it is possible that existing longitudinal studies are not adequately capturing cognitive deterioration that occurs at a much greater time lag than evident in the typical 5-10 year follow up period. However, other cross-sectional evidence showing comparably sized deficits in both elderly BD cohorts with long histories of illness and younger BD patients, support arguments for cognitive stability. Yet evidence that the risk of dementia increases with repeated mood episodes further muddies the waters as it is unclear whether cognitive degeneration occurs directly as a result of the cumulative toxicity associated with each

episode, or whether those with an increased risk of dementia also simply have a greater tendency toward relapse.

In so much as the evidence for cognitive impairment as progressive or stable is mixed, it is strikingly clear that much of the findings that speak to the evolution of cognitive impairment in BD is derived from cross-sectional studies that to date, have only considered BD as a single entity and have thus analysed cognitive performance at the group level. In most papers focused on cognitive trajectory in BD, an important caveat is noted but not discussed in any detail – that is the clear and pronounced heterogeneity that is seen in patients with BD. The importance of heterogeneity cannot be overemphasized as we begin to test models of change over time in the illness. Substantial clinical heterogeneity has been well described and the mere presence of multiple BD diagnostic subtypes (BD I vs BD II; psychotic vs non-psychotic subtypes; rapid-cycling) highlights this point. Beyond the diagnostic and clinical heterogeneity, there is now compelling evidence from many independent groups that strongly supports the presence of cognitive heterogeneity in BD (3-5, 65).

Early studies on cognitive heterogeneity in BD used cut-off scores to identify which patients were impaired and which were considered neuropsychologically-normal (e.g. defining the presence of cognitive impairment based on a threshold) (67). This approach emphasized that there may be “cognitive subgroups” that exist within BD, paving the way for a multitude of additional work that has focused on this insight. In an effort to parse the cognitive heterogeneity in BD, Burdick et al. (5) used an empirical statistical approach to identify and define more homogeneous subgroups using individual cognitive profiles as classifying variables. Discrete subgroups were described in this work – anchored by one ‘intact’ and one globally impaired subgroup respectively, with a selectively impaired group intermediate. Similar findings are evident in several independent studies using the same or very similar approaches (e.g. 3, 68, 69). Nearly all of the studies that have identified and characterized cognitive subgroups in BD have converged to suggest that there may be important differences between cognitive subgroups with regard to premorbid functioning, clinical course, and cognitive change over time (4, 5, 64, 65, 70). Indeed, impaired subgroups have been shown to have reduced premorbid IQ relative to controls, and a greater discrepancy between their premorbid IQ and current cognitive performance than patients with normal cognitive performance (64).

Relevantly, Burdick et al.'s study showed that patients with a selectively impaired profile and a milder level of impairment had a history of more depressive mood episodes compared to an intact subgroup (5). While not significantly different to intact patients, the number of past episodes (both manic and depressed) was also qualitatively increased in the globally and more severely impaired subgroup, although not to the same extent as the selectively impaired subgroup. In this context, the absence of significant age differences between subgroups indicates a possible link between cognitive impairment and a more aggressive, but not necessarily more chronic, clinical course in at least some patients – which may represent a mechanism of cognitive decline. However, at least two studies with larger samples did not find any subgroup differences in the number of past mood episodes (68, 69), making it unclear whether this is truly important factors for distinguishing levels of cognitive functioning in BD.

Nonetheless, the results of cognitive subgrouping studies indicate that one size does not fit all when making assumptions about the cause of cognitive impairment nor the trajectory of cognitive change in an individual with BD. As can be inferred from cross-sectional subgroup studies, it is likely that some but not all BD patients have an abnormal neurodevelopmental component to illness and/or will demonstrate significant cognitive decline over its course. There are only a few longitudinal studies that have been conducted to better track cognitive change with time in BD and the results are inconsistent with some cross-sectional work. These inconsistencies are likely due to small samples, short and inconsistent follow-up lengths, and perhaps most importantly a lack of accounting for heterogeneity within the illness. Additional longitudinal studies are needed to evaluate cognitive change over time within the now relatively well-defined cognitive subgroups. Novel approaches that use trajectory-based data to classify differential trajectories will be important as we try to understand how cognition changes over time in BD at a subgroup level.

3. Emerging correlates of cognitive impairment in BD

3.1. Molecular changes

The neurobiological correlates of cognitive dysfunction in BD are not yet fully understood, but increasing evidence suggests that cognition may be impacted by molecular changes associated with inflammation and oxidative stress (71). According to several meta-analyses, BD patients show elevated peripheral levels of C-reactive protein (CRP) and cytokines,

such as interleukin-6 (IL-6) and Tumor Necrosis Factor alpha (TNF- α), compared to healthy controls (72, 73). This suggests that BD is associated with a low-grade, systemic pro-inflammatory state. In most studies of patients with BD, serum levels of TNF- α and its receptors, IL-1 and IL-6 have been associated with worse performance on executive and visuospatial cognition, memory and attention, even during remission (74). While the majority of research has been conducted with chronic patients, a recent study also found that TNF α levels were associated with poorer cognition during earlier stages of BD I (75).

Cognitive dysfunction has also been associated with decreased levels of neurotrophins, such as Brain-Derived Neurotrophic Factor (BDNF) (76). BDNF is a neuroprotective protein that promotes the survival of neurons and plays a role in the growth, maturation (differentiation), and maintenance of these cells. To date, most studies have focused on a specific BDNF gene variation in which the valine (Val) allele is replaced by the methionine (Met) allele at codon 66. A recent review of nine genetic studies found that the BDNF Val66Met polymorphism may modulate several cognitive functions in adults with BD (77). Specifically, Met allele carriers were found to have worse executive and verbal learning/memory functioning, whereas the reverse was found for Val homozygotes.

Regarding the peripheral expression of BDNF, two studies found no correlation with cognitive performance (78, 79), whereas serum BDNF levels correlated with better verbal fluency (80) and executive performance (81) in two others. In patients with an excellent response to lithium, plasma BDNF levels and cognitive performance were different compared to non-responders but similar to those of healthy controls (82). However, the association between BDNF and cognition was not explicitly examined. Moreover, in a 12-week treatment study, changes in plasma BDNF levels correlated with improved executive cognition (83). After stratification of BD patients by diagnostic subtype and Val66Met polymorphism, this association was found only in BD I Met carriers. This suggests a likely interaction between BDNF polymorphisms, peripheral BDNF levels and cognitive performance in BD. Hence, growing evidence supports the notion that abnormalities in BDNF genotype/expression may be involved in cognitive dysfunction in BD.

Although the direction of influence remains unclear, it is possible that immune/inflammatory dysfunction catalyses cognitive dysfunction by impairing neuroplasticity / neurogenesis, altering levels of monoamines, over-activating microglia and dysregulating the

HPA axis (74, 84). Cellular dysregulation resulting in chronic low-grade inflammation, increased oxidative stress and decreased neuroplasticity may thus synergistically disrupt the structure and function of key brain regions subserving cognition (85, 86). Moreover, metabolic dysfunction, which is frequently comorbid with BD (87), may further compound chronic inflammation and contribute to cognitive impairment. Indeed, insulin resistance associated with inflammation has been linked with cognitive impairment in diabetes (84; see section 3.3 for further detail).

A recent study showed that in female BD patients, increased CRP was associated with more past manic and depressive episodes (88). BDNF and cytokine levels have been shown to change from the early to the late stages of BD and may thus represent molecular markers of illness progression (89). Growing evidence of their association with cognitive impairments in BD has thus been taken as support for the notion that cognitive impairments represent the outcome of a neuroprogressive process (76, 90). However, longitudinal studies examining whether these biological factors track with cognition over time in BD are required to explicitly test this. As it stands, there is limited longitudinal data on BDNF changes in the same patients, and high variability regarding the neuropsychological tests and the biological samples (serum, plasma, whole blood cells, and mRNA levels) used to assess cognitive performance and biomarkers respectively. Thus, caution should be taken in interpreting pertinent findings.

Studies are also often limited by small sample sizes and lack control of potential confounders, such as smoking, medications and body mass index (74). Moreover, BD patients are often recruited in different clinical states and it is known that cognition and particularly inflammatory and neurotrophic factor levels change accordingly. Indeed, BDNF seems to return to normal levels during clinical remission (91), which may reduce the likelihood of finding correlations with cognitive impairment in euthymic patients. Despite these limitations, growing evidence supports the notion that within BD, impaired cognition is associated with increased inflammation and decreased neuroprotection. Thus, therapeutic strategies aimed at these molecular targets have the potential to improve cognitive dysfunction and possibly counteract illness associated cognitive impairments.

3.2. Brain structure and neuroplasticity

The literature explicitly examining relationships between cognition and brain structure in BD is sparse, although preliminary studies show *some* positive, albeit non-regionally consistent correlations between memory/executive functions and volume or thickness of fronto-temporal structures (92-94). Brain structural abnormalities are now widely recognized as characteristic of established BD, with several meta-analytic studies providing convincing evidence for ventricular enlargement, increased white matter hyperintensities, and reduced whole brain, prefrontal, anterior cingulate and insula volumes in patients with the illness (95-98). However, it is unclear whether these brain changes are progressive given the relatively limited imaging studies examining patients early in the illness course. One meta-analysis of four cross-sectional studies of first episode patients and 17 of established BD found less widespread brain volume reductions in the former than the latter (95). This same meta-analysis found an effect of illness duration on volume in a large cluster comprising the basal ganglia, subgenual anterior cingulate and amygdala in the *chronic* patients, which is consistent with the findings of a separate meta regression of cross-sectional data that indicated an effect of illness duration on grey matter volume (97). However, another meta-regression of cross-sectional data showed no evidence of a relationship between brain structural abnormalities and illness duration or age (98), while a recent review of the *longitudinal* literature indicated stable whole brain grey matter volume but progressive frontal and cingulate grey matter volume loss over periods ranging from 1 – 48 months (96).

At the single study level, reduced amygdala and insula volumes have been repeatedly found in high risk cohorts and those with PBD (99, 100). In contrast, only prefrontal but not subcortical volumetric abnormalities have been found in first episode adult BD cohorts (101, 102), though not consistently (103). In established BD, several imaging studies indicate prefrontal *and* hippocampal complex volume reductions, with a recent large-scale study from the BD working group of the ENIGMA consortium showing more pronounced hippocampal volume reductions in older versus younger BD patients (104). This is consistent with other cross-sectional work showing hippocampal volumes reductions in only late-stage BD (105) and ventricular alterations in multi-episode but not first episode BD patients (106, 107); as well as longitudinal work showing prefrontal volume reductions in patients who experienced at least one manic episode over a six-year follow-up versus those that experienced none (108).

Brain volume reductions, particularly in the hippocampus, may be caused by stress induced glucocorticoid overexposure and suppression of neuroplasticity processes (such as neurogenesis and long-term potentiation) by inflammation or altered BDNF expression (109-112). Relevantly, restoration of neuroplasticity is a putative mechanism of long-term mood stabilizing drug treatment (113). Specifically, long-term lithium treatment increases hippocampal volume (114) and white matter integrity (115). These treatment-associated structural changes are likely to result from increase in neurotrophic factors including BDNF in the hippocampus, dendritic branching and other plasticity mechanisms (113). Consistent with such upregulation of neuroplasticity, continued lithium treatment of BD patients may reduce the risk of dementia (116) while exposure to lithium in the drinking water has been associated with lower incidence of dementia in the general population (117). Taken together, the putative role of neuroplasticity in cognitive impairments and long-term treatment of BD calls for interventions with direct and enduring effects on neuroplasticity to improve cognition in BD.

Recently, two interventions targeted at neuroplastic brain change have emerged as promising candidate cognition treatments, including the multifunctional growth factor erythropoietin (EPO) and neuroplasticity-informed cognitive remediation (118, 119). In particular, a randomized controlled trial (RCT) showed that eight weekly infusions of high-dose EPO (40,000 IU) improved a global measure of sustained attention, verbal memory and executive functions in remitted BD patients (120) which was accompanied by structural hippocampal volume increase (118). However, as there was only a trend toward EPO-associated improvement of the primary outcome, verbal memory, the findings must be considered preliminary (120). Further, a recent RCT of intensive internet-based cognitive remediation revealed robust cognitive benefits in remitted BD patients on global cognition (119).

While the results of both trials require replication, their observed benefits across several cognitive domains are encouraging, particularly given that both are based in on the premise of modulating brain plasticity to enable observable cognitive change. Erythropoietin is produced in the brain and plays a key role in neuroprotection and neuroplasticity (for review see 121). Systemically administered EPO also crosses the blood brain barrier and has neuroprotective and neurotrophic effects in animal models of acute brain injury, neurodegenerative and neuropsychiatric conditions (for reviews see 121, 122). Similarly, the cognitive remediation treatment conducted by Lewandowski and colleagues (119) involved intensive neuroplasticity-informed training. Specifically, the repetitive ‘drill and practice’ approach was a key element, involving thrice-weekly training to a total of 70 hours, to affect cognitive change by inducing experience-dependent potentiation (learning) (123). Taken together, the emerging findings from these cognition trials support the notion that novel treatments that directly target neuroplasticity represent a key strategy for improving cognition in BD.

3.3 Lifestyle factors

Unhealthy lifestyle habits, such as impaired sleep, poor diet, sedentary behaviour, smoking, and substance/alcohol misuse are associated with increased inflammation and impaired neuroplasticity; and are known to increase mood symptoms and cardio-metabolic burden in mood disorders (124). All of these behaviours are modifiable, with growing evidence indicating that multimodal lifestyle interventions targeting exercise, nutrition and wellness are feasible and effective in improving physical and emotional health in BD (125). Surprisingly, the relationship between lifestyle factors and cognition has not received much research attention.

Aerobic physical activity/exercise has been shown to improve cognition, especially executive functioning, in healthy adults and in patients with other psychiatric conditions (126, 127). Since exercise exerts effects on inflammation, insulin sensitivity, neurogenesis and neurotransmitter systems, similar cognitive benefits would be expected also in BD (128). In a small, non-randomized study, overweight outpatients with BD and SZ improved their performance on working memory and processing speed tasks after an 8-week resistance training intervention (129). Moreover, in the first large study to analyse the association between cognition and level of physical activity in BD during euthymia, female participants in a vigorous physical activity group showed significantly better performances in most cognitive domains compared to females with moderate or low physical activity (130). Thus, preliminary evidence suggests that physical activity/aerobic exercise confers benefits beyond an impact on physical health, including the potential to ameliorate cognitive impairments in BD.

Besides sedentary behaviour and physical inactivity, abnormal sleep is usually associated with BD (131, 132). In healthy individuals and those with insomnia, sleep disturbances have been associated with several cognitive deficits, including in attention, memory, and executive functioning domains. A seminal review proposed that sleep disruption may impact or worsen neurocognitive dysfunction in BD (133). However, only a few studies have examined this hypothesis empirically (134-137). In one study, fully remitted BD outpatients with more severe cognitive dysfunction reported higher rates of persistent sleep problems compared to those with intact cognitive performance (134). Specifically, these patients had worse psychomotor speed, divided attention, verbal memory and working memory performance. However, sleep disruptions were self-reported and measured with a depression scale, which is a non-sleep specific instrument. In a separate study, a post-hoc analysis found no significant relationships between cognitive function and sleep parameters, with the exception of a negative correlation between

working memory performance and daytime dysfunction occurring as a consequence of poor sleep (135).

Another study found that both perceived reductions in sleep efficiency and executive deficits were associated with impaired work performance in euthymic BD subjects. Moreover, higher levels of self-reported sleep disruptions contributed to deficits in the social cognition and working memory domains (136). In a fourth study, regardless of comorbid insomnia diagnosis, greater inconsistent total sleep time across the week predicted poorer working memory and verbal learning performance during the euthymic phase of BD (137). In sum, chronic disruptions in sleep and other circadian rhythms may contribute to the persistence of neurocognitive impairment, particularly working memory, during euthymia, and both may interact to worsen the social and occupational disability seen in BD.

In addition to impaired sleep and physical inactivity, the diet quality of patients with BD has been reported to be poor (138). Except for the dementias, the emerging field of nutritional psychiatry has paid less attention to the potential cognitive-enhancing effects of diet/nutrition (139). However, diet and nutrients may influence several biological pathways that are dysregulated in BD but relevant to cognition, such as monoaminergic activity, inflammation, oxidative stress, neuroplasticity, and the gut microbiome (140). Growing preclinical and clinical evidence has shown that diet and physical activity are key to maintaining brain health and cognitive function, especially during aging (141). Nutritional factors in particular, may stimulate adult neurogenesis and help to protect cognitive function in the elderly, as well as those with brain disorders (142). However, the evidence for the link between cognition and diet/nutrition in BD is scarce, although findings from a recent 6-week randomized trial did indicate that an adjunctive nutraceutical, creatine monohydrate, was associated with improved verbal fluency in depressed BD patients (143).

Finally, BD is associated with substantial rates of alcohol/substance misuse, which in turn may further worsen patients' cognitive function, especially in the executive and verbal memory domains (144). This, as well as other unhealthy lifestyle factors may contribute to obesity and metabolic syndrome, which are prevalent comorbidities of BD as well as risk factors for cognitive decline. Hence obesity may also mediate or moderate cognitive function in BD. Both cross-sectional and longitudinal evidence indicates an association between elevated BMI and cognitive performance (145, 146). In one study of 18-35-year-old BD patients, worse baseline

performance on attention, verbal memory and working memory tests predicted BMI increase over a one-year follow up. However, the rate of increase in the latter six months was lesser for those showing higher working memory scores following the first six months (147).

5. Discussion

The aim of this review was to provide an update and overview of the current literature concerning the course and emerging correlates of cognitive impairment in BD. In general, evidence regarding the progressive nature of cognitive impairment is mixed (Table 1). Longitudinal studies suggest stable cognitive functioning in BD irrespective of mood changes, at least over 5-10 years. Cross-sectional studies on the other hand, indicate worse cognitive impairment in multi versus single episode patients, with meta-regression analyses showing that a longer duration of illness predicts worse cognition. In the context of cross-sectional data indicating changes in brain structure, BDNF and cytokine expression from early to chronic stages of illness – levels of which correlate with cognition, this data provides some indirect evidence for progression of cognitive impairment in the illness.

However, this inference is tempered by other cross-sectional studies of elderly BD patients that show effect size deficits comparable to younger samples with BD, and no statistical effect of illness duration on cognitive function. Further, in single versus multi-episode studies, BD patients with more episodes tend to have had an earlier onset age despite being of an equivalent chronological age at the time of testing. This is important in the context of evidence showing that those with an earlier onset age represent a more severe phenotype of illness (148) characterised by more severe cognitive deficits (47). Thus, it is unclear whether illness duration and episode history influence cognitive decline per se, or whether all of these variables are simply indicators of a more severe subtype of illness. Further, given insufficient data, the influence of the specific type of mood episode (if any) is not clear.

Together, the lack of consensus between different cross-sectional data and its poor alignment to the outcomes of the limited longitudinal studies available does not make for a compelling argument for cognitive progression or cognitive stability in BD either way. However, emerging evidence suggesting that there are subgroups of BD patients that differ in their cognitive profile and severity of impairment may help to explain some of the inconsistencies in the data to date. In particular, decrements on proxies of premorbid IQ in subgroups of patients with cognitive

impairment versus those without, suggests that cognitive impairment may manifest premorbidly in a subgroup of patients. This is contrary to evidence generally indicating an absence of obvious premorbid deficits at the whole group level but may explain the findings of some studies indicating subtle premorbid deficits in specific domains. Further, putative ‘decline’ in cognition from premorbid cognitive function is noted in subgroups of patients with cognitive impairment, particularly those with more severe and global deficits. Thus, the concept of neuroprogression may only apply in some cases, as different patients may follow different trajectories of cognitive functioning that potentially map onto different causal mechanisms.

In keeping with this hypothesis, a recent study demonstrated heterogeneity of cognitive performance within both BD patients themselves as well as their unaffected siblings. Here, siblings of only those patients with severe and global cognitive deficits exhibited impaired cognition, particularly in the verbal memory domain (4), while siblings of patients with selective cognitive impairments showed a qualitatively discordant pattern of performance from their affected sibling that did not differ significantly from controls at all. These data indicate that cognitive impairment may represent a susceptibility factor for some individuals with BD, while for others it could be a characteristic that is secondary to the manifest illness course and/or associated factors such as comorbidities and medications.

6. Future perspectives

Future studies following cognitive subgroups of BD longitudinally, and identifying consistency in subgroup assignment based on longitudinal cognitive changes are required, with specific focus on disentangling the impact of clinical variables. This is critical for identifying whether some patients decline while others remain cognitively stable, and whether specific clinical factors are associated with different cognitive pathways. Prospective follow-up of high risk individuals or those following a first-episode would be ideal in this context, to address questions concerning the timepoint(s) at which cognitive deterioration may occur. In SZ, it has been argued that there is a critical period characterised by aggressive psychopathological deterioration that occurs early in the illness course and then later plateaus (149). In BD the limited studies that have examined cognition in first-episode cohorts longitudinally over 1-2 years show no decline and even some improvement over time. However, it remains possible that

these studies, by nature of analyzing data at the group level, were unable to capture deterioration in a subset of patients.

Given emerging evidence of the link between cognitive impairment and an increased inflammatory state, brain structural abnormalities and reduced neuroprotection in BD, differences on these variables across cognitive subgroups of BD patients is to be expected. However, this has not yet been clearly addressed empirically. Further studies are required to identify whether individual differences in these variables map onto different cognitive profiles, and research should be focussed longitudinally to determine how cognitive functioning and abnormalities in inflammatory and neuroprotective biomarkers, and brain structure covary over time.

The clear link between cognitive performance and these factors in other populations including healthy individuals and those with neurodegenerative disorders and SZ, highlight the potential for direct intervention targeting them in BD to go some way toward ameliorating cognitive deficits, and potentially halting subsequent cognitive decline in the illness (if it occurs). Indeed, pharmacological agents with anti-inflammatory properties as well as neuroplasticity informed interventions show early promise in BD cohorts, but the research is still in its infancy and needs further attention.

Likewise, studies targeting nutritional health and exercise in BD are severely lacking but are critically needed to better understand lifestyle predictors of cognitive impairment and their associated biological pathways. Recent work in SZ patients showed that supported physical exercise training resulted in moderate improvements in several domains of cognition across a 12 week period (150). Converging evidence suggests that physical activity can enhance neuroplasticity by regulating growth factors such as BDNF, which may augment treatments directly training cognition (151). Thus, it is possible that the pro-cognitive effects of exercise therapy can extend to BD, and we anticipate that multimodal interventions targeting modifiable lifestyle risk factors such as exercise, sleep and diet alongside cognitive training, might be one of the most powerful means by which to enhance cognitive functioning in the illness. Further, treatment studies using neuroplasticity-based cognitive training interventions will be important in furthering our understanding of the role that abnormalities in neuroplasticity play in the illness.

In sum, we suggest that future studies in this area ideally aim to better define cognitive trajectories and their biological and/or environmental correlates in BD, which will in turn inform

treatment strategies to enhance cognitive and functional outcomes in the illness. As per Table 2, we recommend that future studies recruit patients at or soon after their first episode of mania (or preferably during the pre-onset period), and/or follow patients over extended periods (e.g. 5-10 years) to maximize the opportunity to identify decline. The assessment of cognition alongside several other measures (clinical, imaging, biomarker and lifestyle factors) in such studies will be important, as will the combined use of machine learning and cluster analytic approaches to analyse the data. This may result in improved knowledge of the heterogeneity of cognitive functioning in BD, and identification of signatures of cognitive dysfunction that could eventually pave the way for the application of a precision medicine approach for individual patients in clinical practice (152).

Likewise, the field will benefit from increased attention on those patients that do not demonstrate obvious cognitive deficits, to identify protective factors. In this context, assessment of unaffected biological siblings of such patients (preferably in a discordant twin-pair design) could help us to ascertain whether their cognition is truly ‘intact’, based on whether their performance deviates at all from their ‘genetic cognitive destiny’(see 153 for a discussion of this notion in relation to SZ). A continued focus on testing and refining cognition - enhancing interventions will be important so long as they continue to be informed by growing knowledge of the biological and environmental correlates of cognitive functioning and their covariation over time and illness phases; it is likely that multi-modal interventions will be among the most efficacious means by which to improve cognitive dysfunction in the illness. In light of the above, it is clear that the way ahead for research and clinical practice is promising, yet complex. Undoubtedly, collaborative effort within the field will be required to meet the challenge.

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Conflicts of interest

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Table 1. Summary of studies relating to the cognitive course of BD

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Approach	Type of study	Notes	
High risk	Prospective / retrospective / high risk	Cohort and retrospective studies	Favours progression from illness onset. No strong evidence for premorbid impairment, although some studies show academic/school delays in a subset of patients.
		At risk individuals (relatives)	Favours genetic/neurodevelopmental origins of cognitive impairment.
Whole-group studies	Post-onset	Cross-sectional comparisons of 1 st and multi-episode BD (adults)	Favours progression.
		Cross-sectional studies of elderly cohorts (inc correlations with age/illness duration and comparisons to younger samples)	Mixed evidence. Comparisons of deficits in elderly (excluding late-onset) vs younger cohorts favours stability. However, BD patients are at increased risk of developing dementia, particularly those who have had more episodes. Unclear if this reflects progression, or a more severe subtype.
		Paediatric BD	Some preliminary data favouring progression but minimal longitudinal evidence available. Worse cognition in those with earlier onset age may indicate a more severe phenotype, as cognitive deficits appear to be worse in first episode PBD vs first episode adult BD, but similar between first episode adult BD vs chronic BD.
		Longitudinal (mostly adults)	Favours stability.
	Correlates	Imaging: cross-sectional	Favours progression although findings are mixed.
		Imaging: longitudinal	Favours progression although may be regionally specific.
		Biomarkers: cross-sectional	Favours progression.
	Biomarkers: longitudinal	Minimal evidence available.	
	Patients with BD	Larger scores on proxies of 'decline' indicate potential progression with illness in subgroups with cognitive impairment.	

Cluster analytic studies		Lower scores on estimated premorbid IQ measures indicate potential neurodevelopmental origins in those with the most severe cognitive impairment.
	Unaffected relatives (siblings)	Cognitive deficits in the most severely impaired subgroup may be more strongly genetically (thus, neurodevelopmentally) influenced. Deficits may be secondary to manifest illness in other patients.

Table 2. Recommendations for moving targets in cognition research in BD

Type	Target
Study design	from cross-sectional to follow-up
Age groups	from mostly 30-40-year-old adult samples to the entire lifespan (especially pediatric and first episode)
Population	from a focus on patients (clinical phenotype) to including at-risk subjects (family studies; endophenotypes)
Statistics	from the group level (homogeneity) to subgroups (heterogeneity)
Aims	from understanding how the past explains the present to predicting future trajectories
Variables of interest	from clinical and demographics to emerging correlates (molecular, imaging, genetic, lifestyle...).
Medications	from concern about cognitive side-effects to searching for cognitive enhancers
Treatment	from focus on available psychopharmacological agents to multimodal interventions