

# Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses

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**Abstract:** Cognitive impairment is a core feature of schizophrenia (SZ) and bipolar disorder (BD). A neurocognitive profile characterized by widespread cognitive deficits across multiple domains in the context of substantial intellectual impairment, which appears to antedate illness onset, is a replicated finding in SZ. There is no specific neuropsychological signature that can facilitate the diagnostic differentiation of SZ and BD, notwithstanding, neuropsychological deficits appear more severe in SZ. The literature in this field has provided contradictory results due to methodological differences across studies. Meta-analytic techniques may offer an opportunity to synthesize findings and to control for potential sources of heterogeneity. Here, we performed a systematic review of meta-analyses of neuropsychological findings in SZ and BD. While there is no conclusive evidence for progressive cognitive deterioration in either SZ or BD, some findings point to more severe cognitive deficits in patients with early illness onset across both disorders. A compromised pattern of cognitive functioning in individuals at familiar and/or clinical risk to psychosis as well as in first-degree relatives of BD patients suggests that early neurodevelopmental factors may play a role in the emergence of cognitive deficits in both disorders. Premorbid intellectual impairment in SZ and at least in a subgroup of patients with BD may be related to a shared genetically determined influence on neurodevelopment.

**Keywords:** schizophrenia, bipolar disorder, psychosis, neuropsychological tests, cognition, meta-analysis, psychiatry

## Introduction

Cognitive impairment is a common feature in schizophrenia (SZ) and a determinant of poor functional outcome. A neurocognitive profile characterized by cognitive deficits across multiple domains in the context of a general intellectual impairment has been consistently reported in the SZ literature.<sup>1,2</sup> More recently, the evaluation of neuropsychological profile in young individuals at clinical high risk (CHR) for psychosis and in individuals with familiar high risk (FHR) has become a focus for research designed to explore putative neurocognitive predictors of transition to full-blown psychosis.<sup>3,4</sup> In youth, prodromic conditions associated with increased risk of psychosis are operationally defined by the presence of either an attenuated psychosis syndrome or brief limited intermittent psychotic symptoms or genetic/familial risk to psychosis associated with functional decline.<sup>5</sup> Evidence suggests that cognitive dysfunction occurs in individuals with FHR to psychosis and in young populations at ultra-high-risk (UHR) to psychosis.<sup>6</sup> In addition, reduced premorbid intelligence quotient ( $\sim 0.5$  standard deviations [SDs] below average)<sup>7</sup> during childhood has been associated with a higher risk to develop SZ.<sup>1,8</sup>

For bipolar disorder (BD), substantial albeit less severe cognitive dysfunction has been consistently shown across several domains in affected individuals even

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during the first episode as well as in unaffected relatives.<sup>9,10</sup> In contrast to SZ, there is little evidence of premorbid global intellectual impairment in BD.<sup>11</sup> In keeping with this, it has been posited that neurodevelopmental deficits may occur in SZ but not necessarily in BD. However, some experts have argued that neurodevelopmental factors may also contribute to cognitive deficits during the premorbid phase of at least a subgroup of individuals who would subsequently develop full-blown BD.<sup>12</sup> Similarly, prodromic features in BD have been consistently described in the literature, notwithstanding the specificity and predictive validity of a putative bipolar prodrome remain unclear.<sup>13–15</sup>

Some methodological discrepancies may limit the comparability of studies of cognitive dysfunction in BD and/or SZ, including differences in study design (eg, different neuropsychological tests across investigations and practice effects) and sample characteristics (eg, illness duration, age of illness onset, clinical state, treatment status, as well as the inclusion of appropriately age- and sex-matched healthy individuals as controls). Furthermore, a nonunivocal definition of neuropsychological domains based on the grouping of specific tasks is a further source of inconsistency across studies. Meta-analytic techniques allow the incorporation of data across different studies, and may aid in the identification of potential sources of heterogeneity across studies, albeit being influenced by inherent limitations of included studies.

Thus, we performed a systematic review of meta-analyses of neuropsychological studies performed in samples with established diagnoses of BD and/or SZ, as well as in young individuals with a first manic or psychotic episode, unaffected first-degree relatives (FDRs) of patients with BD/SZ, and in individuals at FHR and/or CHR for either BD or SZ.

## Methods

The PubMed database was searched from inception to August 10, 2015 with combinations of the following search terms: (“Cognitive deficits” OR “cognitive dysfunction” OR “Executive Function” OR “Attention” OR “Memory” OR “neuropsych\*” AND (“Schizophrenia” OR “Psychotic Disorder” OR “Bipolar Disorder” OR “familial-high risk” OR “clinical-high risk”) AND “Meta-Analysis”. Reference lists of included articles were hand searched to augment this search strategy.

Meta-analyses published in English were included if the primary focus was on neurocognitive performance in the following populations: i) participants with a diagnosis of either SZ or BD (established through a structured diagnostic interview according to either the *Diagnostic and*

*Statistical Manual of Mental Disorders* or the International Classification of Diseases criteria); ii) individuals on their first-episode manic or psychotic episode; iii) unaffected relatives; and iv) young individuals at-risk to develop BD or SZ. CHR herein refers to a prodromal state associated with a higher risk of developing psychosis within the first 3 years of presentation, while FHR is defined by the presence of a parent or sibling with SZ or at least two relatives with SZ.<sup>3,4</sup>

This search strategy provided 717 references that were screened for potential inclusion on the basis of the title and abstract. We decided to specifically focus on quantitative analyses of neurocognitive performance and/or global cognitive functioning, while meta-analyses on social cognition were not considered for this review. A total of 58 meta-analyses met the inclusion criteria: 14 on cognitive dysfunction in BD and in FDRs (Table 1 for single references), 24 on SZ (Table 2), seven meta-analyses of studies comparing cognitive performance between individuals with BD and SZ, and 13 meta-analyses of studies on individuals at CHR or FHR to psychosis. Figure 1 provides a description of the search terms and included studies.

We considered standardized effect sizes (ESs) <0.5 as small, ≥0.5 and <0.8 medium, and ≥0.8 large.<sup>16</sup>

## Cognitive dysfunction in BD Cognitive impairment in individuals with BD

Notwithstanding a certain degree of inconsistency in the results of separate meta-analysis, BD has been consistently associated with cognitive dysfunction across a broad range of cognitive domains (Table 1). Neurocognitive deficits persist in periods of euthymia and thus have been considered trait-related markers of the disorder. For example, medium-to-large ES differences in neurocognitive performance have been reported between euthymic patients and controls in the domains of attention, processing speed, episodic memory, and executive functions.<sup>17</sup> A separate meta-analysis indicated that individuals with BD during euthymia exhibit neuropsychological impairment of medium-to-large ES, notably in measures of verbal learning and memory.<sup>18</sup> During manic/mixed states, additional decrements on measures of verbal learning were also observed, while patients in a depressed state exhibited greater impairment in measures of phonemic fluency.<sup>18</sup> Subsequently, widespread medium-to-large ES cognitive impairment across several domains in BD compared to healthy controls was reported,<sup>19</sup> similar to the observed non-specific cognitive deficits in SZ but less pronounced.<sup>20</sup> More recently, an individual patient meta-analysis of 31 datasets

**Table I** Meta-analytic evidence of neurocognitive impairment in BD and in FDRs listed in chronological order of publication

References	Included studies and sample composition	Affected cognitive domains in BD patient groups (ES expressed by Cohen's <i>d</i> )
44	31 studies comparing cognitive performance between BD and SZ	Individuals with BD outperformed individuals with SZ in nine of eleven cognitive domains, with small-to-moderate ES for concept formation and shifting ( $d=0.34$ ), delayed verbal memory ( $d=0.34$ ) and moderate ES for verbal fluency ( $d=0.63$ ), verbal working memory ( $d=0.60$ ), mental speed ( $d=0.50$ ), executive control ( $d=0.55$ ), immediate verbal memory ( $d=0.43$ ), delayed visual memory ( $d=0.51$ ), and IQ ( $d=0.36$ )
17	Studies comparing cognitive performance between euthymic BD patients and HC	Medium-to-large ( $0.5 < d < 0.8$ ) ES differences in attention, processing speed, episodic memory, and executive functioning
36	Ten studies comparing cognitive performance between a pediatric BD population and HC	Moderate ES deficits in verbal memory ( $d=0.77$ ), attention ( $d=0.62$ ), executive functions ( $d=0.62$ ), visual memory ( $d=0.51$ ), visual perception skills ( $d=0.48$ ), and verbal fluency ( $d=0.45$ ). Small ES deficits in measures of reading ( $d=0.40$ ) and motor speed ( $d=0.33$ )
23	28 studies comparing cognitive performance between BD patients, FDRs of BD patients, and HC	Large ES ( $d > 0.8$ ) differences in BD patients vs controls in working memory, executive control and fluency, and verbal memory; medium ES for concept shifting, mental speed, visual memory, and sustained attention and small ES for visuo-perception FDR exhibited small ES differences vs controls in verbal memory and in executive functions
18	60 studies (1,197 euthymic BD patients, 314 BD patients in manic/mixed phase, 96 patients in a depressed state)	Large ES differences in verbal learning ( $d=0.81$ ) and delayed verbal and nonverbal memory ( $d=0.8-0.92$ ) and small-to-moderate ES differences in visuospatial abilities ( $d < 0.5$ ) in euthymia vs controls. Individuals in manic/mixed phases exhibited additional impairment in verbal learning, while individuals in a depressed stage showed greater decrements in phonemic fluency
22	45 studies (1,423 euthymic BD patients and 1,524 HC); 17 studies on FDRs ( $n=443$ )	Medium-to-large ES differences in response inhibition, set shifting, executive functions, verbal memory, and sustained attention in BD patients, while differences were of small-to-medium ES in FDRs. Significant impairment in processing speed, visual memory, and verbal fluency was evident only in BD patients
28	Eleven studies comparing cognitive performance between BD patients with history of psychosis ( $n=435$ ) and BD patients without history of psychosis ( $n=339$ )	Patients with history of psychosis exhibited worse performance as compared to BD patients without history of psychosis in global cognition ( $d=0.20$ ), processing speed ( $d=0.20$ ), verbal memory ( $d=0.39$ ), working memory ( $d=0.28$ ), planning/reasoning ( $d=0.31$ ) Significant between-group ES differences were observed for individual tests: TMT-B ( $d=0.30$ ), Stroop interference ( $d=0.32$ ) and Semantic Fluency ( $d=0.37$ ), Learning ( $d=0.45$ ) and Delayed Recall ( $d=0.34$ ), Digit Span backward ( $d=0.30$ ), WCST Perseveration scores ( $d=0.31$ )
30	Eleven studies comparing cognitive performance between BD I patients ( $n=444$ ) and BD II patients ( $n=285$ )	BD I patients exhibited medium ES deficits in verbal memory ( $d=0.52$ ) and small ES deficits in visual memory and semantic fluency ( $d=0.38$ )
29	27 studies on individuals with AP ( $n=550$ with BD and 213 with Major Depressive Disorder) and HC ( $n=1,823$ )	Individuals with AP showed large ES deficits ( $d < 0.8$ ) in 11 of 15 cognitive measures with largest ES for symbol coding, Stroop interference, verbal learning, and category fluency tasks
20	28 studies on euthymic BD patients ( $n=1,026$ ) and HC ( $n=1,384$ )	Medium-to-large ES differences ( $0.5 < d < 0.8$ ) between BD patients and controls in processing speed, episodic memory, executive functioning, working memory, fluency, perceptual/problem-solving No significant differences in intellectual/verbal abilities were observed
21	Individual patient meta-analysis of 31 datasets ( $n=2,876$ BD euthymic patients)	Moderate ES (ranging from 0.26 to 0.63) after controlling for age, sex, and IQ in eleven measures of four tests: California/Rey Verbal Learning Test, TMT, Digit Span, and WCST

(Continued)

**Table 1** (Continued)

References	Included studies and sample composition	Affected cognitive domains in BD patient groups (ES expressed by Cohen's <i>d</i> )
45	13 studies comparing semantic inhibition performance among BD (n=292) and SZ (176) and HC (on the Hayling Sentence Completion test)	Both BD and SZ groups exhibited medium-to-large ES deficits vs controls in task A (initiation; ES for BD=0.71 to 0.89; ES for SZ=0.75) and task B (inhibition); no significant differences between BD and SZ emerged
39	Eleven studies comparing cognitive performance between euthymic late-life BD patients (n=382 individuals, mean age 69.2 years) and HC (n=363)	Moderate to large ES differences ( $0.61 < d < 0.88$ ) between patients and controls in sustained attention, digit span, delayed recall, and serial learning, being largest for cognitive flexibility and phonemic fluency
38	12 longitudinal studies on BD patients (n=357) of cognitive performance with a follow-up of at least 1 year Six longitudinal studies comparing cognitive performance between BD patients (n=233) and HC (n=165)	No significant test-retest ES differences as well as patients vs controls differences were observed across 14 measures of neurocognitive performance
10	12 studies on FEBD patients (n=341, mean age 28.2 years) and controls (n=1,009) including HC, nonpsychotic controls (two studies) and first- or second-degree relatives (two studies)	Medium-to-large ES differences ( $d > 0.50$ ) between FEBD individuals and controls in attention, psychomotor speed, working memory and cognitive flexibility Small ES differences ( $0.2 < d < 0.49$ ) in verbal memory and learning, attentional switching and verbal fluency
11	28 studies on measures of premorbid and postonset intellectual functions in BD and in SZ	Moderate premorbid intellectual impairment in SZ ( $d = 0.597$ ), associated with large postonset impairment ( $d = 1.369$ ) Small premorbid intellectual impairment in BD were evident only when assessed retrospectively, but not prospectively
9	22 studies comparing cognitive performance among individuals with FEBD (n=605) or FES (n=822) and HC (n=1,417)	FEBD patients exhibited small-to-moderate ES deficits ( $0.26 < d < 0.80$ ) in processing speed, verbal memory, verbal fluency, and working memory, as well as in current and premorbid IQ FES patients underperformed FEBD patients with small-to-moderate ES ( $0.05 < d < 0.63$ ) in most cognitive domains and on individual tasks

**Abbreviations:** AP, affective psychosis; BD, bipolar disorder; ES, effect size; FDRs, first-degree relatives; FEBD, first-episode BD; FES, first-episode schizophrenia; HC, healthy controls; IQ, intelligence quotient; SZ, schizophrenia; TMT-B, trail making test B; WCST, Wisconsin Card Sorting Test.

assessing measures of four specific tests (Verbal learning tests, Trail Making Test, Digit Span, and Wisconsin Card Sorting Test) indicated deficits in euthymic individuals with BD of small-to-medium ES after controlling for age, intelligence quotient, sex, and residual mood symptoms.<sup>21</sup> Young adults after a first episode of BD exhibit a widespread cognitive impairment,<sup>10</sup> the level of which appears comparable to that reported for individuals with recurrent episodes.<sup>21</sup> In comparison to previous meta-analyses on euthymic BD patients with recurrent episodes reporting a large degree of impairment,<sup>17,18,20,22,23</sup> this meta-analysis on adults with a first episode of BD indicates a more modest level of mood-state-independent cognitive dysfunction<sup>21</sup> which is consistent with a staging model for the disease based on neuroprogression<sup>24</sup> characterized by progressive impairment over time in the majority of BD patients. In fact, greater neuropsychological dysfunction (notably deficits in verbal memory) has been associated with the number of previous manic episodes and hospitalizations as well as with illness duration.<sup>25–27</sup> In keeping with this view, another meta-analysis indicated

a negative correlation between illness duration and age with cognitive performance.<sup>20</sup> However, other quantitative studies failed to replicate this finding, possibly because of methodological factors including those related to sample selection and inherent limitations of meta-regression techniques.<sup>22</sup> Conversely, earlier age of onset has been associated with greater impairment in verbal memory and psychomotor speed,<sup>22</sup> although this result was not confirmed by other meta-analyses.<sup>10</sup>

Psychotic features in BD have been associated with worse cognitive performance as compared to nonpsychotic BD in tasks of verbal memory and executive function (planning/reasoning measures), working memory and processing speed.<sup>28</sup> Another meta-analysis of cognitive impairment in individuals with affective psychosis (AP) indicated that individuals with AP perform approximately 0.8 SD lower than HC<sup>19</sup> in 11 of 15 studied cognitive measures, with larger ES for measures of attention, working memory, and executive function.<sup>29</sup> The pattern of cognitive impairment in AP appears comparable to that reported for euthymic BD

**Table 2** Meta-analytic evidence of neurocognitive impairment in SZ listed in chronological order of publication

References	Included studies and sample composition	Affected cognitive domains in BD patient groups
46	204 studies comparing cognitive performance between SZ patients and community controls	Overall mean impairment of 0.92 standard deviation in SZ patients as compared to controls, associated with medium-to-large ES deficits ( $-0.63 < g < -1.11$ ) across cognitive domains
65	29 studies comparing WCST performance between SZ patients and HC	Large ES differences in category achieved ( $d=0.91$ ), moderate ES differences in perseveration ( $d=0.53$ ), and small ES differences in perseverative errors ( $d=0.18$ ). Large ES differences for the Wechsler Adult Intelligence Scale IQ ( $d=1.23$ )
49	71 studies comparing the performance on the WCST/HCT, verbal/design fluency, Trail Making B (TMB), and the Stroop Color-Word Test between SZ patients and HC	Large ES difference in both complex (ie, WCST/HCT) ( $\Delta=-1.42$ ) and less complex (ie, TMB/Stroop) ( $\Delta=-1.58$ ) measures of executive functions in SZ patients vs controls
55	13 studies comparing verbal fluency performance between SZ patients ( $n=526$ ) and HC ( $n=389$ )	Large ES differences in SZ patients vs controls, with greater deficits in semantic fluency ( $d=1.23$ ) in comparison to letter fluency ( $d=1.01$ )
50	84 studies comparing recognition memory performance between SZ patients and HC	Moderate ES difference ( $d=0.76$ ) in overall recognition memory performance in SZ patients vs controls
66	84 studies comparing verbal fluency performance between SZ patients and HC	Larger ES differences for semantic relative to phonemic fluency, reflecting a general intellectual impairment in SZ patients vs controls
47	37 studies comparing cognitive performance between SZ patients ( $n=1,961$ ) and community controls ( $n=1,444$ )	Overall mean impairment of 0.98 standard deviation in SZ patients as compared to controls, associated with large ES deficits in digit symbol coding ( $g=-1.57$ )
8	18 studies comparing IQ between individuals that later developed SZ and controls	Moderate premorbid intellectual impairment ( $d=0.540$ ) in future SZ cases vs controls
2	53 longitudinal studies evaluating cognitive performance in SZ patients ( $n=2,746$ ) and in HC ( $n=324$ ) with a median test-retest time of 4 months	SZ patients exhibited mild improvements in learning and delayed recall tests ( $d=0.4$ ), cognitive flexibility ( $d=0.38$ ), and attention ( $d=0.35$ )
70	88 studies evaluating the correlations between executive functions and positive, negative symptoms and disorganization	Small-to-moderate range correlations between both negative symptoms ( $r=-0.21$ ) and disorganization ( $r=-0.17$ ) with executive dysfunction, as well as with current IQ ( $r=-0.21$ ) but not with positive symptoms
77	47 studies comparing cognitive performance between FES patients ( $n=2,204$ , mean age 25.5) and age and sex-matched HC ( $n=2,775$ )	Medium-to-large impairment across 10 domains ( $0.64 < d < 1.2$ ), being largest in immediate verbal memory and processing speed
73	Studies comparing cognitive performance between HC and SZ patients with youth-onset (23 studies), SZ patients with adult-onset (78 studies) or late-onset (after 60 years old) (nine studies)	SZ patients with youth onset and adult-FES exhibited large ES deficits ( $d > 0.8$ ) in the majority of domains SZ patients with youth onset had larger deficits as compared to patients with FES in IQ, executive functions, psychomotor speed, arithmetic, and verbal memory. SZ patients with late-onset had minimal deficits in arithmetic and vocabulary, but larger deficits in attention, fluency, IQ, and visuospatial construction
85	31 studies comparing cognitive performance between SZ patients ( $n=1,972$ ) and individuals with affective psychosis or schizoaffective disorder ( $n=1,314$ )	SZ patients underperformed individuals with affective psychosis on measures of verbal memory, working memory, IQ, TMT-B, and WCST with small between-group ES differences ( $0.25 < d < 0.42$ )
52	Eleven studies comparing prospective memory between SZ patients ( $n=485$ ) and HC ( $n=409$ )	Large ES impairment in time ( $d=-1.33$ ), event ( $d=-0.83$ ), and activity-based ( $d=-0.73$ ) prospective memory in SZ patients vs controls
67	91 studies comparing performance in tests that measure semantic memory between SZ patients and HC	Large ES impairment in naming and category fluency, medium ES impairment for word-picture matching and association tests, and small ES impairment for categorization and priming tests
51	187 studies (441 separate results) comparing working memory performance between SZ patients and HC	Large ES differences across working memory domains in SZ patients vs controls
86	Studies comparing cognitive performance between patients with SZ and affective disorders	Impairments in intellectual ability and speed of information processing, in encoding and retrieval, rule discovery and in response generation and response inhibition both in patients with SZ and affective disorders. In most cognitive domains participants with SZ had higher (and large) ES estimates

(Continued)

**Table 2** (Continued)

References	Included studies and sample composition	Affected cognitive domains in BD patient groups
58	29 cross-sectional studies involving SZ patients aged >65 years and 14 longitudinal studies on cognitive performance (n=954 SZ patients followed up to 6 years)	Cross-sectional analysis revealed large ES differences in global cognition ( $d=-1.19$ ) and in measures of language ( $d=-1.30$ ), immediate memory ( $d=-1.25$ ) as well as executive functions ( $d=-1.14$ ). Longitudinal analysis revealed small ES differences for measures of global cognition ( $d=-0.097$ )
56	47 studies comparing the performance on measures of processing speed between SZ patients (n=4,135) and HC (n=2,292)	Largest ES differences in coding tasks ( $g=-1.50$ ) and category fluency ( $g=-1.31$ )
87	12 studies comparing cognitive performance between individuals with early onset SZ (n=296, mean age 15.7) and subject with BD (n=374, mean age 13.6) and HC	Individuals with early onset of SZ exhibited moderate to large ES differences as compared to HC in general cognitive abilities ( $g=-1.15$ ), processing speed ( $g=-1.27$ ) and motor skills ( $g=-0.58$ ), while BD patients exhibited milder deficits, ranging from $g=-0.42$ for general cognitive abilities to $g=-0.83$ for verbal learning and memory
63	12 longitudinal population-based studies (4,396 cases and over 745,000 controls) evaluating premorbid IQ among individuals that later developed SZ	Moderate decrements in premorbid IQ (ES=0.43) among future cases. Risk of SZ increased by 3.7% for every point decrease in IQ
68	36 studies comparing the performance on Stroop interference between SZ patients (n=1,081) and HC (n=1,026)	Increased Stroop interference effect in response time ( $g=0.43$ ) and accuracy ( $g=0.62$ ) in SZ patients vs controls
53	240 studies comparing cognitive performance between SZ patients (n=10,120) and HC (n=7,929)	Large ES differences in IQ ( $-0.96$ ), memory functioning ( $-1.22$ ), language ( $-0.99$ ), executive functions ( $-1.10$ ), and attention ( $-0.99$ )
64	23 prospective studies assessing cognitive and motor function in individuals aged <16 years who later developed SZ or a SZ spectrum disorder	Moderate intellectual impairment ( $d=0.51$ ) and deficits in motor function ( $d=0.56$ )
54	100 studies comparing cognitive performance between SZ patients (n=9,048) and HC (n=8,814)	Impairment in all cognitive domains (grand mean ES difference Hedges' $g=-1.03$ ), with largest impairment in processing speed ( $g=-1.25$ ) and episodic memory ( $g=-1.23$ )
1	14 studies comparing intellectual abilities between SZ patients (n=280) and HC (n=306)	IQ change per year was +0.33 for SZ patients vs 2.08 for controls, with medium-sized deficits for IQ change in patients vs controls
78	23 studies comparing cognitive performance between drug-naïve FES patients (n=1,106) and HC (n=1,885)	Large ES differences in verbal memory (SMD=-1.03), processing speed (SMD=-1.03), and working memory (SMD=-0.97); medium ES differences in attention (SMD=-0.8), visual memory (SMD=-0.78), and executive functions (SMD=-0.74)

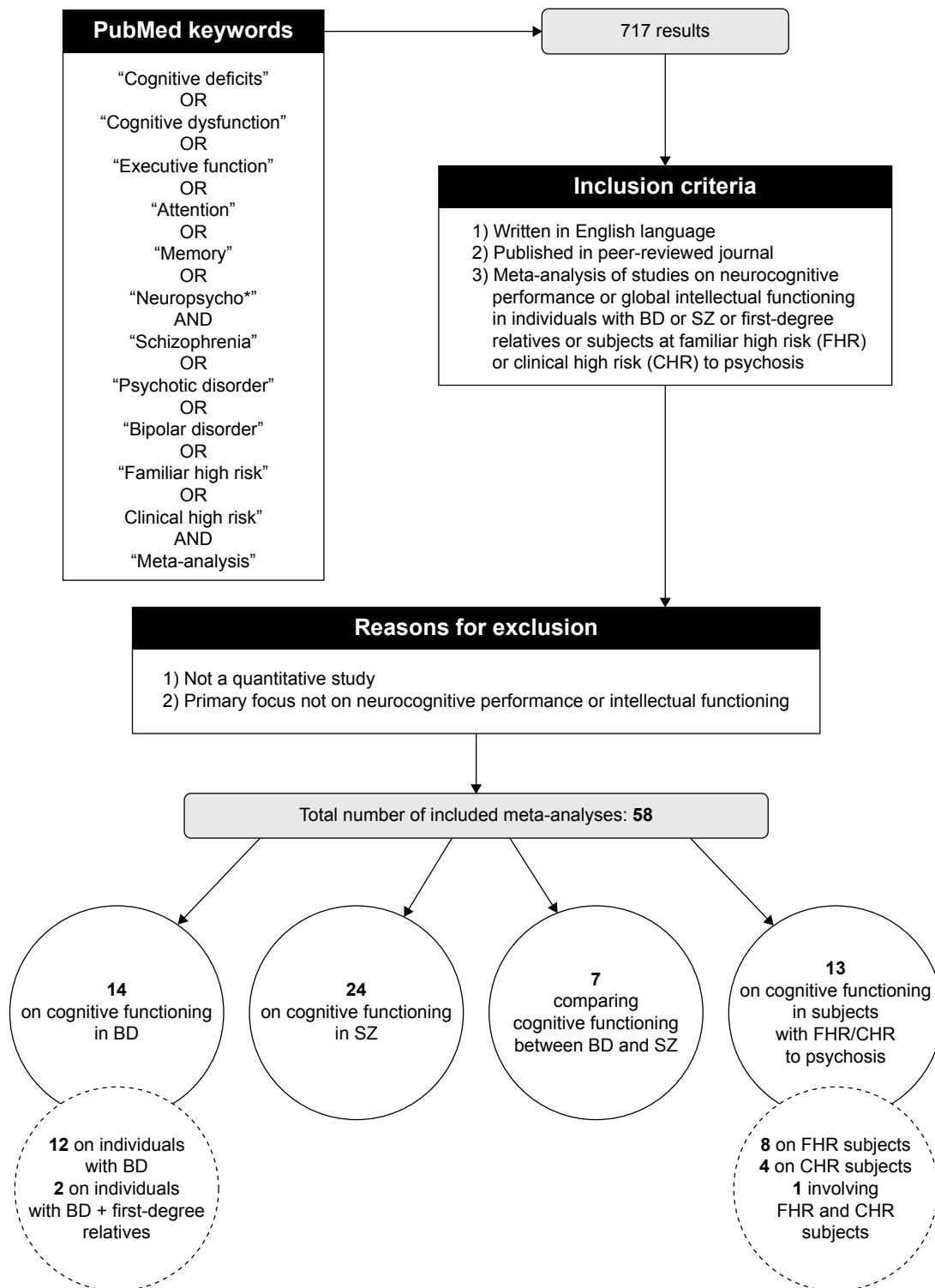
**Note:** See the text for meta-analyses of studies focusing on cognitive performance in individuals at FHR and CHR to psychosis.

**Abbreviations:** BD, bipolar disorder; CHR, clinical high risk; ES, effect size; FHR, familiar high risk; FES, first-episode schizophrenia; HC, healthy controls; HCT, Halstead Category Test; IQ, intelligence quotient; SMD, standardized mean difference; SZ, schizophrenia; TMT-B, trail making test B; WCST, Wisconsin Card Sorting Test.

patients, but more pronounced. However, as a result of the inclusion in this analysis of studies with heterogeneous patient population (ie, individuals with Major Depressive Disorder and with BD), these results must be interpreted with caution. Only one meta-analysis investigated the possible differences in neurocognitive performance between individuals with BD type I and BD type II. This study indicated a relatively specific greater impairment in verbal memory of medium ES (Cohen's  $d=0.52$ ) in BD I, while no differences between these BD subgroups were observed in global cognition, attention, working memory, and executive function.<sup>30</sup> Thus, the authors postulated that memory impairment, reflecting neuroanatomical medial temporal abnormalities, might be a specific endophenotype for type I BD, possibly resulting from neuroprogressive damages associated with manic episodes.<sup>30</sup>

Neurocognitive performance represents a moderate determinant of functional impairment and disability in BD as well

as a predictor of unfavorable employment outcomes.<sup>7,31,32</sup> This is particularly relevant considering that up to two-third of individuals with BD do not achieve functional recovery even when affective remission is evident. A meta-analysis documented a significant correlation between cognitive deficits and reduced functional abilities for all the considered cognitive domains, being largest ( $r=0.29$ ) for deficits in working memory ( $r=0.29$ ).<sup>33</sup> Notably, the contribution of cognitive impairment to disability appears to be independent of symptoms, as indicated by the absence of difference in ES between studies including only euthymic patients vs studies enrolling actively symptomatic BD participants. Further evidence of the relevance of cognitive performance on psychosocial functioning is the fact that certain interventions, mainly based on ecological cognitive training, proved effective in improving functional outcome in euthymic BD patients.<sup>34</sup>



**Figure 1** Flow-chart describing the search strategy for the inclusion of eligible meta-analyses.

**Abbreviations:** BD, bipolar disorder; SZ, schizophrenia.

Regarding the longitudinal course of cognitive deficits, available data are scarce and inconsistent. BD has been conceptualized as a neuroprogressive illness with a subtle neurodevelopmental component preceding illness onset, followed by neurodegeneration after the first episode and

progressive cognitive decline as a function of recurrences.<sup>35</sup> The presence of a neurodevelopmental component of cognitive dysfunction in BD is supported by quantitative analyses in pediatric BD populations, showing cognitive deficits of small-to-moderate ES across different cognitive

domains.<sup>36</sup> However, the hypothesis of the association between cognitive impairment and the cumulative number of episodes,<sup>25</sup> as a proxy of the neuroprogressive nature of BD,<sup>37</sup> is based on cross-sectional studies and the direction of causality remains unclear. A meta-analysis evaluating available data on the longitudinal course of neurocognitive performance in BD did not document test–retest differences in ES for any of the cognitive variables studied.<sup>38</sup> Additionally, no significant patient-control ES differences in neurocognitive performance were observed. These findings do not support the hypothesis of a progressive deterioration of cognitive abilities in BD. A previous quantitative analysis of cognitive dysfunction in euthymic late-life BD individuals further argues that deficits appear stable over time, showing similar ES differences to those reported for young adults with BD.<sup>39</sup> In particular, half of late-life BD patients exhibited cognitive dysfunction on average between 0.6 and 0.9 SD below that of healthy controls, with a medium ES for sustained attention and category fluency and large ES for cognitive flexibility and phonemic fluency (parts of executive function). An alternative explanation is that BD represents a heterogeneous phenotype, in which different illness trajectories could lead to distinct degrees of cognitive impairment as a function of recurring episodes.<sup>40</sup> Moreover, these findings could have been heavily influenced by the fact that longitudinal studies only assess the patients who stay on treatment and who are adherent to follow-up. Several studies indicate that the patients receiving lithium maintenance treatment do not progressively deteriorate in cognitive functioning.<sup>41,42</sup> Furthermore, some longitudinal studies assess baseline cognitive performance shortly after hospital discharge or after a recent episode, which leaves little room for the detection of changes over time because patients show an already well-established significant impairment. Other several limitations of the available evidence should be considered in future prospective studies in order to elucidate the nature of cognitive dysfunction in BD, including i) a short duration of follow-up periods; ii) small sample sizes (and high attrition rates in prospective studies resulting in an unintended selection of the less deteriorated patients over time); iii) the absence of a healthy control group; and iv) the lack of a proper control for affective symptomatology across different follow-up assessments.

## Cognitive impairment in first-degree relatives of BD patients

The presence of cognitive impairment not only in BD patients but also in FDRs led to the hypothesis that specific aspects

of cognitive dysfunction may be trait markers of the disorder and potential candidate endophenotypes. For instance, while large ES were observed for euthymic individuals with BD for deficits in verbal memory and in executive functions (eg, executive control, fluency), FDRs exhibited deficits of smaller magnitude but significantly different compared to healthy controls in verbal memory and executive functions.<sup>23</sup> A subsequent meta-analysis suggested that deficits in response inhibition could be a potential endophenotype for BD and a potential marker of ventral prefrontal dysfunction in BD.<sup>22</sup> In this quantitative study, deficits of small-to-medium ES were reported for set shifting and verbal memory as well, and have been postulated to represent potential generic markers of psychosis, being candidate endophenotypes for both BD and SZ. Moreover, separate components of sustained attention have been postulated to have a role as potential endophenotypes for BD and SZ (ie, target detection impairment [false negatives] vs false alarms [false positives]).<sup>43</sup>

## Cognitive dysfunction in schizophrenia Cognitive impairment in individuals with SZ

The first large-scale meta-analysis of cognitive impairment in SZ, including more than 200 studies performed between 1980 and 1997, documented an overall mean impairment of 0.9 SD relative to community control groups.<sup>46</sup> Subsequently, updated meta-analyses confirmed such nonspecific neurocognitive impairment encompassing across several domains in SZ, with largest ES in episodic memory and processing speed<sup>47,48</sup> (Table 2). Consistent with this, several meta-analyses documented deficits of large ES in different cognitive areas including intellectual function, learning and memory, attention, working memory, language and executive function, despite great clinical and methodological heterogeneity across included studies.<sup>49–53</sup> More recently, the robustness of these findings has been confirmed in a meta-analysis documenting significant nonspecific cognitive deficits (grand mean ES  $g=-1.03$ ), with most pronounced impairment in processing speed ( $g=-1.25$ ) and episodic memory ( $g=-1.23$ ).<sup>54</sup> Processing speed has been identified as a central feature of cognitive decline in SZ, with largest ES for coding tasks and category fluency.<sup>55,56</sup> With regard to deficits in episodic memory, a meta-analysis of functional neuroimaging studies documented a prominent prefrontal dysfunction in individuals with SZ during encoding and retrieval tasks compared to healthy volunteers, supporting the role of abnormal cognitive control processes in contributing to episodic memory deficits.<sup>57</sup>



When considering only elderly SZ patient populations (ie, aged >65 years), quantitative analysis of cross-sectional and longitudinal studies provided evidence of large ES deficits in a broad range of neuropsychological domains including processing speed, language, memory, and executive functions.<sup>58</sup> As cognitive impairment remained stable over a 6-year period in this study,<sup>58</sup> these results do not support a neurodegenerative or neuroprogressive nature of SZ.<sup>59</sup>

In keeping with this, meta-analyses of longitudinal studies on neurocognitive performance in SZ have provided no clear evidence for a progressive cognitive decline and indicated the possibility of small-to-moderate improvements in several domains after illness onset,<sup>60,61</sup> with largest ES estimates observed in tests of memory and attention as well as in tests of cognitive flexibility.<sup>2</sup> However, the lack of a control group in most studies that have investigated neurocognitive changes in SZ, as well as the short median follow-up period, does not allow us to differentiate whether cognitive changes in SZ represent true improvements or nonspecific effects of practice-related learning.<sup>62</sup> Furthermore, another meta-analysis of longitudinal population-based studies documented decrements of moderate ES ( $d=0.43$ ) in premorbid IQ among individuals who later converted to full-blown SZ, with a positive association between greater premorbid IQ decrements and earlier onset of illness.<sup>63</sup> Additional evidence indicates a decline in intellectual functions before or around illness onset, associated with a relative lack of gain in global cognitive abilities in longitudinal assessments after illness onset (defined by medium-sized deficits in IQ changes in patients with SZ),<sup>1</sup> in accordance with findings in a previous meta-analysis.<sup>8</sup> Moderately reduced IQ appears evident even in early to mid-adolescence and seem to precede the prodromal phase of illness.<sup>64</sup> Convergent evidence supports the hypothesis that generalized intellectual deficits contribute to executive dysfunction in SZ, despite the use of heterogeneous neuropsychological tools in the evaluation of this domain. For instance, large ES deficits in measures of cognitive flexibility<sup>65</sup> as well as of verbal fluency<sup>66,67</sup> have been posited to reflect a generalized intellectual impairment rather than specific difficulties in executive control processes. On the other hand, global executive functioning does not refer to a unitary cognitive dimension, but represents a set of basic low-level cognitive subcomponents (eg, shifting, updating, inhibition of dominant responses, and planning) and it has been more recently postulated that global executive dysfunction may at least in part be driven by specific deficits in cognitive inhibitory processes.<sup>68</sup> A meta-analysis of functional neuroimaging studies on individuals with SZ

during executive tasks (eg, delayed match to sample, N-back, and Stroop test) indicated that patients' executive deficits are accompanied by hypo-activity in the dorsolateral prefrontal cortex and rostral–dorsal cingulate cortex as well as compensatory hyper-activity of other prefrontal regions.<sup>69</sup>

Chronicity, severity of symptoms, comorbidity, as well as medication status and dosage act as possible moderators of cognitive performance in SZ populations. Negative symptoms and disorganization appear to be correlated with deficits in executive functions as well as with impaired intellectual functioning in SZ.<sup>70,71</sup> The presence of obsessive-compulsive symptoms and comorbid obsessive-compulsive disorder in the context of SZ may be associated with greater impairment in abstract thinking and in functional capacity.<sup>72</sup> With regard to the age of illness onset, there is some evidence that early onset is associated with greater severity of cognitive impairment as compared to individuals with an adult-onset of SZ, with larger deficits in IQ, executive functioning, psychomotor speed, and verbal memory.<sup>73</sup> However, these results should be interpreted with caution considering that the definition of early vs late age of onset is arbitrary and the inclusion of studies involving not only SZ patients but also individuals with schizoaffective disorder, schizophreniform, or delusional disorder.

With regard to the effect of medications, modest improvements in overall cognitive functions as well as specific improvements in learning and processing speed have been associated with the use of atypical as compared to typical antipsychotics,<sup>74,75</sup> while high dosage of antipsychotic medications emerged among the factors exerting a negative influence on processing speed.<sup>56</sup> Different antipsychotic drugs differ in long-term effects on overall cognition and on specific cognitive domains. Quetiapine and olanzapine may be associated with more positive effects in terms of neurocognition, followed in order by risperidone, ziprasidone, amisulpride, and haloperidol.<sup>76</sup>

Meta-analyses of studies specifically focusing on first-episode SZ patients documented widespread neurocognitive deficits as compared to healthy controls of medium-to-large ES.<sup>77</sup> The severity of deficits in this population approached that of adults with chronic illness, being greater in immediate verbal memory and processing speed. Individuals with first-episode SZ also exhibited a substantial intellectual impairment, the degree of which was comparable to that showed in more advanced phases of illness, which supports the notion that cognitive deficits in SZ are to a large extent neurodevelopmental. A subsequent meta-analysis of studies comparing the neurocognitive profile of drug-naïve

SZ patients at first episode with that of controls corroborate these results, demonstrating a similar ES impairment in verbal and visual memory, executive functions, and attention.<sup>78</sup> It is noteworthy that the ES were comparable in these two meta-analyses despite the use of disparate neuropsychological tools.<sup>77,78</sup> Importantly, the magnitude of these deficits is in accordance with the findings in meta-analyses of studies involving SZ patients receiving antipsychotic medications and with multiple illness episodes.<sup>32,54</sup> These data suggest that the degree of cognitive impairment is at least partially independent of medication status.

The inadequate effect of conventional antipsychotics on cognitive dysfunction has led to an active search for pro-cognitive treatments for SZ.<sup>79</sup> A meta-analysis of double-blind, placebo-controlled studies investigating the potential cognitive-enhancing properties of adjunctive medications targeted at cholinergic, glutamatergic, or serotonergic receptor classes, documented small improvements in verbal learning and memory ( $d=0.23$ ), while the cholinergic agonist donepezil exerted a moderate effect ( $d=0.58$ ) on spatial learning and memory.<sup>80</sup> These data are particularly relevant since neurocognitive functions are critical determinants of functional outcome in SZ.<sup>81</sup> Neurocognitive measures of crystallized verbal ability, working memory, processing speed, as well as executive function appear to be associated with objective measures of quality of life with small-to-moderate ES differences.<sup>82</sup> Furthermore, intellectual abilities along with preserved memory and executive functions are among the determinants of self-appraisal mechanisms required for developing clinical and cognitive insight in SZ.<sup>83,84</sup>

## Cognitive impairment in individuals with familiar risk and CHR to psychosis

The presence of substantial cognitive impairment also in FDRs of individuals with SZ has provided evidence supporting a role of certain cognitive deficits as candidate endophenotypes for SZ. Meta-analyses of studies on nonaffected adult relatives of SZ patients indicated the presence of medium ES differences as compared to controls in the domains of declarative and verbal memory and executive functions, while smaller ES differences were observed for attention.<sup>43,88–90</sup> Consistently, subsequent analyses of cognitive performance in adult relatives of SZ patients confirmed prior findings of moderate ES deficits in tasks of working memory, sustained attention, as well as set-shifting and response inhibition, supporting a model of neurocognitive impairment defined by a deficit in demanding executive control.<sup>91,92</sup> Recently, there has been growing emphasis on the

examination of cognitive performance in younger relatives and in individuals with familiar history of SZ (FHR) or at CHR to psychosis.<sup>93</sup> Individuals with familiar risk (FHR) of psychosis aged <30 years exhibit cognitive deficits with moderate ES differences as compared to controls, with largest ES on estimates of full-scale IQ ( $d=-0.77$ ), followed by vocabulary ( $d=-0.749$ ) and single word reading test ( $d=-0.698$ ), which are often used as IQ estimates.<sup>94</sup> In line with previous meta-analyses,<sup>91</sup> more modest ES differences were observed for measures of declarative memory, sustained attention, and working memory.<sup>94</sup> Data from a meta-analysis of studies comparing the cognitive performance of CHR individuals ( $n=1,188$ ) with that of HC ( $n=1,029$ ) indicated the presence in the CHR population of small-to-medium ES reduction in general intelligence as well as across several domains including verbal fluency, executive functions, verbal and visual memory, attention, and working memory.<sup>95</sup> In this study, more pronounced baseline deficits in general intelligence, verbal fluency, verbal and visual memory, as well as working memory predicted increased risk of transition to psychosis within 19 months from the first assessment. Consistently, another quantitative analysis that compared neurocognitive functioning among 583 CHR subjects between psychosis converters and nonconverters documented a worse cognitive profile in psychosis converters with small-to-medium ES differences in working memory ( $ES=-0.29$ ) and visual learning ( $ES=-0.40$ ).<sup>3</sup>

Small-to-medium ES ( $-0.26 < d < -0.67$ ) cognitive deficits in subjects at clinical risk to develop psychosis across various neurocognitive domains appear consistent findings across separate meta-analyses.<sup>96</sup> In a recent quantitative analysis individuals with clinical risk to develop psychosis exhibited deficits with an intermediate degree of severity between HC and SZ patients and comparable to the level of impairment in individuals with a “genetic” familiar risk.<sup>96</sup> Moreover, the degree of cognitive dysfunction was more pronounced among CHR who were also at familiar risk. Transition to psychosis was associated with additional cognitive impairment, characterized by deficits of medium/large ES ( $-0.35 < d < -0.84$ ) across several domains.<sup>96</sup>

Subsequently, a meta-analysis synthesized studies comparing the cognitive profile of FHR individuals (defined by the presence of a parent or sibling with SZ or at least two relatives) with that of UHR individuals and young healthy controls (aged <30 years).<sup>4</sup> The UHR paradigm represents a CHR model targeting the identification of psychotic features in the prodromal period and is defined by the presence of one or more of three psychosis risk syndromes, including i) recent

onset or worsening of attenuated positive symptoms (APS); ii) recent onset of significant psychotic features that do not fulfill the inclusion criteria for *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* psychotic disorder (brief limited intermittent psychotic syndrome); and iii) genetic/familial risk to psychosis associated with functional decline syndrome. Both risk paradigms were associated with widespread cognitive deficits of moderate ES across neurocognitive domains, with greater severity in the case of the occurrence of genetic risk and attenuated symptoms. Individuals with familiar genetic risk exhibited more pronounced decrements in premorbid general intelligence as compared to individuals with clinical risk to psychosis. Moreover, more severe baseline cognitive deficits predicted increased risk of transition to psychosis in the UHR paradigm.

Quantitative analysis of prospective studies evaluating the course of neurocognitive profile over a period of 5 years in individuals with first-episode psychosis (n=905) and in UHR individuals (n=560) as compared to healthy controls (n=405) did not provide evidence of a significant cognitive decline over time,<sup>6</sup> in accordance with previous meta-analyses.<sup>2,58</sup> These data provide support to a neurodevelopmental model characterized by the presence of substantial cognitive impairment preceding the prodromic phases of psychosis and not associated with a significant decline during longitudinal assessments. On the contrary, improvements of comparable magnitude in global cognition were observed in all three groups. Substantial small-to-moderate ES improvements were observed both in UHR individuals and in individuals with first episode of psychosis in verbal memory, processing speed, attention, executive functions, while large improvements in all cognitive domains were also observed in healthy controls. In individuals with first-episode psychosis, the degree of improvement in verbal memory and executive functions was significantly associated with reductions in negative symptoms. The pattern of cognitive improvement appears to reflect practice-related effects, characterized by an early improvement followed by a plateau, with most consistent improvements observed in tasks of memory and executive functions (which are more sensitive to practice effects) and more limited improvements in tasks poorly associated with learning effects (eg, verbal fluency).<sup>6</sup>

## Cognitive impairment in studies comparing the neurocognitive profile in BD and SZ

Few meta-analyses have compared the neurocognitive performance of BD individuals with that of individuals with SZ.

The first meta-analysis comparing these groups indicated that BD patients outperformed SZ patients in nine out of eleven cognitive measures, with largest differences in ES for verbal fluency and moderate ES also for verbal working memory, mental speed, executive control, and immediate verbal memory.<sup>44</sup> A subsequent meta-analysis comparing the neurocognitive performance of SZ patients and individuals with AP indicated worse performance in SZ patients in 6 out of 12 cognitive domains.<sup>85</sup> This meta-analysis therefore does not support the existence of a different neurocognitive profile for BD and SZ based on categorical distinction. Nevertheless, the differences were small and the distribution of ES showed substantial heterogeneity, driven by a higher percentage of male participants, more severe negative symptoms, and earlier illness onset in SZ samples.<sup>85</sup> Notwithstanding, these results corroborate with another meta-analysis that showed widespread cognitive impairment in both SZ and affective disorders, with quantitative rather than qualitative differences between diagnostic groups.<sup>86</sup> Further evidence that the nature of cognitive deficits does not distinguish BD and SZ per se is provided by a meta-analysis showing a similar degree of impairment in measures of executive dysfunction in both disorders.<sup>45</sup>

A recent meta-analysis of premorbid and postonset intellectual function in BD and SZ relative to controls indicated that SZ patients exhibit moderate premorbid reduction in intellectual function (standardized mean difference = -0.597), while there is no univocal evidence of reduced premorbid intellectual capacity in BD.<sup>11</sup> This is consistent with meta-analytical evidence for a premorbid IQ reduction of approximately 0.5 SD in young individuals that subsequently develop SZ.<sup>8</sup>

With regard to data on the early phases of BD and SZ, one meta-analysis specifically compared the neuropsychological performance of first-episode manic BD patients to first-episode SZ patients and healthy controls.<sup>9</sup> This confirmed the existence of widespread cognitive impairment also in first-episode mania, the severity of which was lower than in first-episode SZ individuals.<sup>9</sup> In particular, individuals with first-episode mania exhibited a level of impairment comparable to that observed in patients with greater chronicity.<sup>11,22</sup> These findings may be explained by indirect effects of cross-sectional illness severity. Additionally, another quantitative study comparing the neurocognitive profile of individuals with early onset SZ with that of individuals with pediatric BD confirmed the presence of deficits of mostly large ES in multiple domains in SZ and a similar profile of cognitive dysfunction in BD but characterized by lower severity, with deficits in the moderate-to-large ES range.<sup>87</sup>

Taken together, these data support the relevance of neurodevelopmental factors as possible contributory factors for neurocognitive impairment in SZ as well as at least in a subgroup of individuals with BD. Moreover, convergent evidence supports that cognitive impairment is relatively independent of chronicity and treatment exposure.

## Concluding remarks

Data from the available meta-analytic literature suggest a significant overlap of impairment between the neuropsychological profiles in established BD and SZ, with differences being more quantitative than qualitative. Cognitive deficits are recognizable early in the trajectory of both disorders and are evident in individuals at their first manic or psychotic episode. A significant impairment during childhood and in the early adolescence before the onset of psychosis supports the role of neurodevelopmental factors in SZ and for at least in a subgroup of individuals with BD.<sup>12</sup> Premorbid reduction in intellectual ability and developmental lags, consisting in a relative lack of gain in cognitive abilities before or around illness onset, has been consistently documented in SZ<sup>1,75</sup> and has been associated with common susceptibility genes.<sup>97</sup> On the contrary, data on premorbid intellectual functioning in BD provide equivocal results.<sup>11</sup> Longitudinal studies investigating the trajectory of premorbid cognitive deficits in BD are scarce compared to SZ, but a review of available literature to date suggest an inverted U-shaped relationship between premorbid cognitive functioning and risk to develop BD, with both poor and “brilliant” cognitive/scholar functioning associated with increased risk to develop BD in adulthood.<sup>12</sup> Thus, it is plausible that shared susceptibility genes in SZ and BD are associated with neurodevelopmental abnormalities, which may predict early cognitive dysfunction at least in subgroups of patients.<sup>98,99</sup> On the other side, another subgroup of BD patients may have excellent baseline cognitive skills, which might, or might not deteriorate over time depending on the course of illness, treatment adherence, and healthy habits.<sup>100</sup> Early deleterious effects of psychosocial stress and epigenetic modulation of genes related to increased oxidative stress and dysfunctional cellular energy metabolism play a role both in SZ and BD.<sup>101–103</sup> Thus, these shared pathophysiological pathways may contribute to similar early cognitive deficits in both illnesses.

A better understanding of the longitudinal trajectory of cognitive dysfunction as well as of predictors of transition to full-blown SZ and BD would advance our knowledge on potential early psychological and pharmacological interventions prevent cognitive deterioration and illness onset. Psychoeducation, cognitive behavioral therapy, functional

remediation in BD,<sup>104</sup> cognitive remediation in SZ,<sup>73</sup> as well as pharmacological interventions may reduce conversion rates, but their effect on functional outcome remains unclear.<sup>105</sup> More research into potential sources of heterogeneity is warranted to elucidate the timing and trajectory of cognitive dysfunction in BD and in SZ in order to provide more effective and individualized treatment interventions. Finally, it should be noted that both SZ and BD are heterogeneous phenotypes (ie, an established diagnosis of either SZ or BD may encompass distinct psychopathological entities with otherwise deceptively similar neurobiological underpinnings).

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