REVIEW

Neurocognitive Correlates of the Course of Bipolar Disorder

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Abstract: Significant cognitive dysfunction has been recognized as an important state and trait feature of bipolar disorder. In this article, longitudinal studies comparing cognitive performance in bipolar disorder patients and healthy controls are reviewed. In contrast to cross-sectional reports, current longitudinal research findings do not support a progressive cognitive decline over time. However, a higher within-person instability in cognitive performance was found relative to controls. The need for larger samples remains, as well as for longer and more frequent observations.

Keywords: attention, bipolar disorder, cognition, executive function, longitudinal, memory, processing speed

INTRODUCTION

During the last decades, research on various cognitive deficits in bipolar disorder (BD) has yielded some important results. Various clinical factors—such as the number of manic episodes and hospitalizations, the length of illness, and poorer psychosocial adjustment in the long term—have been found to be associated with cognitive impairments.[1–3] In addition, the cognitive deficits observed in unaffected first-degree relatives of BD patients seem to suggest that specific cognitive impairments may be good candidate endophenotypes for BD (see recent meta-analyses).[4,5] Since the beginning of the twenty-first century, the traditional view that cognitive impairment in BD is transient and limited to affective episodes has been challenged by evidence of impairment during euthymic states.[4,5] These findings suggest a need for studies that run continuously during the course of BD. Only longitudinal studies will be able to elucidate the impact of affective symptoms on cognitive functioning, whether cognitive impairments are progressive or not, and whether BD patients and healthy controls differ in the intra-individual variability of cognitive functioning. In 1988, Engelsmann and colleagues[6] published the first long-term follow-up study on lithium and memory in BD patients. More than 20 years later, longitudinal studies with adult patients are still rare. This review aims to integrate findings from the existing literature and discusses challenges for the future.

METHODS

Articles published through January 2013 were identified via a literature search in PubMed and PsycINFO using the keywords "bipolar disorder" or "manic depress*" and "longitudinal" or "follow up" or "course" with "cognit*" or "neuropsych*." The following criteria were used for inclusion: (1) the study measured cognitive performance using standardized and reliable neuropsychological testing procedures; (2) the study compared adult BD patients who were diagnosed using a recognized criterion-based diagnostic system against healthy controls; (3) neuropsychological testing was performed when patients were either remitted or symptomatic but clinically stable; (4) cognitive performance was assessed at a minimum of two time points in patients and controls. The references of the selected articles were hand searched for further relevant articles. We did not include studies comparing cognitive performance in BD to that in other patient groups, such as those with schizophrenia or unipolar depression. Nor did we include studies comparing cognitive performance in acute versus remitted BD patients since a thorough review of these aspects would be beyond the scope of this article.

RESULTS

Based on the criteria described above, a total of eight longitudinal studies was selected comparing healthy controls to BD patients in euthymic or subacute states with a follow-up interval of three months to four years. Information about sample characteristics and follow-up assessments are listed chronologically in Table 1. Further details on the instruments used for measuring cognitive function and on the main results of the studies can be found in Supplemental Table 1, (http://links.lww.com/HRP/A7).

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Table 1
Characteristics of the Eight Studies Reviewed

Study	Sample size (n)	Gender distribution (% female)	Mean age (approximate)	Symptomatic level	Follow-up assessments
Moorhead et al. (2007)[7]	20 BD I 21 HC	BD: 50% HC: 50%	40 years	Euthymic	2 assessments: baseline & follow-up after 4 years
Depp et al. (2008)[8]	35 BD (34 BD I, 1 BD II) 35 HC	BD: 28.6% HC: 58.8%	60 years	Mild level of affective symptoms	2 assessments: baseline & follow-up at 1–3 years
Mur et al. (2008)[9]	33 BD (24 BD I, 9 BD II) 33 HC	BD: 48% HC: 48%	41 years	Euthymic	2 assessments: baseline & follow-up after 2 years
Gildengers et al. (2009)[10]	33 BD (28 BD I, 5 BD II) 36 HC	BD: 72.7% HC: 55.6%	70 years Adults > 50 years	Euthymic	2–4 assessments: baseline & follow-up at 1, 2 & 3 years
Arts et al. (2011)[11]	76 BD (57 BD I, 17 BD II, 2 schizoaffective bipolar type) at baseline; 39 patients remaining at final interview 61 HC	BD: 54% HC: 62%	45 years	Mild level of affective symptoms	Patients: assessment every 2 months for 2 years (i.e., maximum of 12 assessments) HC: twice at 2-month intervals
Chaves et al. (2011)[12]	29 BD (22 BD I, 7 BD II) 30 HC	BD: 50% HC: 50%	BD: 40 years HC: 32 years	Clinically stable with mild to moderate affective symptoms	2 assessments: baseline & follow-up after 3 months
Delaloye et al. (2011)[13]	15 BD (BD I & BD II) 15 HC		68 years	Euthymic	2 assessments: baseline & after 2 years
Depp et al. (2012)[14]	42 BD (36BD I, 6 BD II) 49 HC	BD: 40.5% HC: 57.1%	42 years	Clinically stable with mild depressive or manic symptoms	2–4 assessments: baseline & follow-up after 6, 12 & 26 weeks

BD, bipolar disorder; HC, healthy controls.

Table 2 aggregates results from seven studies on the question whether BD patients show a greater decline in cognitive performance over time than healthy controls. As can be seen from Table 2, most of the studies find that cognitive deficits in different domains in BD patients are quite stable over time and follow a similar trajectory of change as in healthy controls. Only Gildingers and colleagues[10] observed a greater deterioration in the General Dementia Rating Scale score in BD patients compared to healthy controls in a sample of older adults. This finding is contrary to two other publications with samples of older adults, both reporting a lack of significant differences between groups in the trajectory over time.[8,13] In one other study, BD patients showed no deterioration but less improvement in verbal memory measures over time than healthy controls.[9] Table 2 also shows that in many domains, group effects (BD patients vs. healthy controls) are not found consistently in all studies.

In addition to comparing the means of groups (BD patients vs. healthy controls) over time, three studies[8,10,14] focused on the variability or stability of cognitive performance within persons over time. All three studies report a higher within-person instability in cognitive performance over time in BD patients compared to healthy controls.

In four of the eight reviewed studies, patients were not fully euthymic but suffered from subsyndromal affective symptoms.[8,11,12,14] Looking at the impact of these symptoms on cognitive performance, no significant,[8,14] or only small[12] to modest,[11] effects were reported.

DISCUSSION

Focusing on mean differences between BD patients and healthy controls over time, the longitudinal studies reviewed here suggest that cognitive function in BD remains stable over time and follows a similar trajectory of change as in healthy controls (due to practice effects or the effects of aging). It is noteworthy that for many cognitive domains, differences in cognitive performance could not be consistently found in all studies (see Table 2). However, given the strong evidence for

Table 2

Trajectory of Change in Bipolar Disorder Patients Versus Healthy Controls in Single Cognitive Domains and for General Cognitive Scores

Cognitive domain[a]		
	Greater deterioration, or less practice effects, in BD than in HC	Similar trajectory in BD and HC[b]
Executive functioning	0	Mur et al. (2008)[9] Gildengers et al. (2009)[10,c] Chaves et al. (2011)[12,c] Delaloye et al. (2011)[13,c]
Inhibition	0	Mur et al. (2008)[9]
Working memory	0	Delaloye et al. (2011)[13,c]
Memory	0	Moorhead et al. (2007)[7,c,d]
Abstraction	0	Gildengers et al. (2009)[10,c]
Verbal memory	Mur et al. (2008)[9,c]	Gildengers et al. (2009)[10] Chaves et al. (2011)[12,c] Delaloye et al. (2011)[13]
Visual memory	0	Mur et al. (2008)[9,c]
Attentional span	0	Mur et al. (2008)[9,c] Gildengers et al. (2009)[10] Chaves et al. (2011)[12]
Processing speed	0	Mur et al. (2008)[9] Chaves et al. (2011)[12] Delaloye et al. (2011)[13]
Visuospatial ability	0	Gildengers et al. (2009)[10,c]
Verbal IQ	0	Moorhead et al. (2007)[7,c]
Performance IQ	0	Moorhead et al. (2007)[7,c]
General cognitive scores		
	Greater deterioration, or less practice effects, in BD than in HC	Similar trajectory in BD and HC[b]
Global composite neurocognitive score	0	Depp et al. (2008)[8] Depp et al. (2012)[14]
General Dementia Rating Scale score	Gildengers et al. (2009)[10]	0

BD, bipolar disorder; HC, healthy controls.

[a] The listed cognitive domains are not necessarily disjunctive (e.g., working memory is part of the executive functions).

[b] No significant group (BD vs. HC) x time (T1 vs. T2) interaction was found; that is, no changes were found, or changes observed in BD patients were comparable to those in HC in matters of direction and degree of change.

[c] No group effect was found (BD vs. HC).

[d] Memory was assessed by the Extended Rivermead Behavioural Memory Test,[15] which predicts everyday memory problems and combines different subscales.

cognitive impairment in BD from cross-sectional studies, the question arises as to why this discrepancy emerges. One explanation might be found in methodological issues—for example, sample sizes, sample characteristics, or the instruments used. But these aspects also vary considerably in cross-sectional studies. Another explanation might be a bias toward patients with better overall function in longitudinal compared to cross-sectional studies. Participating in and completing a study with repeated assessment sessions may be too demanding for patients with a more severe form of BD.

Most of the studies listed included two consecutive neuropsychological assessments per person. Only three recent studies applied more observation points.[10,11,14] The findings by Gildingers and colleagues[10] are described above. Performing neuropsychological tests in patients every two months over two years, Arts and colleagues[11] observed that cognitive function varied in most domains. Variation included relatively

high rates for improvement and deterioration, with a net improvement over time, except for sustained attention and motor speed. A limitation of this study is that healthy controls were assessed only twice and not every two months over two years, as were the patients—which makes it hard to control for practice effects or variability of cognitive performance in healthy controls. Interestingly, the cognitive function in BD patients appeared to covary with subjective cognitive complaints. In the most recent publication by Depp and colleagues,[14] four assessments (follow-ups after 6, 12, and 26 weeks) were conducted. An improvement in cognitive performance over time in patients was found, but only to a similar degree as in healthy controls, meaning that these results can be interpreted as practice effects. In summary, although the current state of the literature does not support a progressive cognitive impairment in BD patients, a well-replicated finding from cross-sectional studies is that the severity of cognitive deficits is directly associated with the number of past mood episodes,[3] indicating a cognitive deterioration. The disparity could arise from this review's limited longitudinal evidence, which is confined to less than a handful of studies covering a relatively short time period (up to four years). The time period may be insufficient to detect progressive impairment developing over decades and multiple mood episodes. Thus, at this time, the longitudinal findings on cognitive stability have to be interpreted with caution. Systematic research with more frequent follow-up and longer follow-up intervals is needed.

Intra-individual Variability in Cognitive Performance

Another question that has been addressed in the literature is whether the intra-individual variability in cognitive performance between time points in BD patients is greater relative to healthy controls. As expected, such a difference was found regarding within-person variability.[8,10,14] Moreover, research on intra-individual variability in cognitive performance has revealed some interesting findings, with possible implications for BD patients. First, intra-individual variability increases in later adulthood and seems to be connected to age-related cognitive decline.[16] Second, associations have been found between higher intra-individual variability and neurodegenerative and other brain-related disorders such as dementia, traumatic brain injury, and attention-deficit/hyperactivity disorder.[16] The neurobiological basis of this variability needs to be further explored, but abnormalities in the frontal lobes, in particular—such as reduced gray matter density and white matter abnormalities—seem to play an important role.[16] Thus, greater intra-individual variability in cognitive performance in BD patients could hint at underlying neurodegenerative processes. The greater within-person variability compared to healthy controls also poses a methodological challenge. Particularly in cross-sectional studies, one cannot control for this effect, so the high variability could lead to a flawed estimation of mean differences between groups. Intra-individual variability in cognitive performance seems to represent a promising field for future research concerning the static or progressive nature of cognitive deficits in BD.

Impact of Current and Lifetime Psychopathology on Cognitive Performance

In four of the selected eight studies, BD patients were assessed when they did not fully meet criteria for euthymia but suffered from subsyndromal affective symptoms.[8,11,12,14] This sample characteristic enables researchers to evaluate the impact of these symptoms on changes in cognitive performance. In summary, no significant,[8,14] or only small[12] to modest,[11] effects of psychopathological symptoms on cognitive functioning were found. Of course, these findings are limited to the impact of relatively mild symptoms and cannot simply be assumed to apply to more severely ill patients. Interestingly, one study found that the subjective mood of the patients rather than clinician-rated psychiatric symptoms had a relatively large effect on motor speed and selective attention.[11]

One of the clinical factors that could potentially be associated with cognitive performance in BD is a history of psychotic symptoms. Two of the cited studies evaluated the role of this possible predictor and found no significant effect.[9,11]

The Relationship Between Cognitive Impairment and Psychosocial Functioning, and Implications for Therapeutic Intervention

Both cross-sectional and longitudinal studies support a non-negligible relationship between cognitive impairment and psychosocial functioning in BD patients. Deficits in processing speed have been found to be associated with worse work adaptation.[9] Changes in cognitive functioning—together with symptom severity and premorbid adjustment at baseline—have been suggested as good predictors of changes in functioning over the follow-up period.[17] Further, global functioning scales show a relation between global cognitive functioning and cognitive complaints.[11] These findings about the actual impact of cognition on overall functioning highlight the clinical importance of research on cognitive impairment in BD. Of primary importance, the cognitive impairment itself—particularly in the domains of memory and concentration—can be a limiting factor in patients' functionality. Patients' subjective experience of being cognitively restricted[11] could also lead to frustration and an additional loss of assertiveness and confidence in their capacity to work or to organize their everyday lives. Therefore, in addition to efforts to reduce affective symptoms and relapses, cognitive impairment should be kept in mind as an important therapeutic target. Whereas cognitive training has come to be common in the treatment of schizophrenia, in BD this approach is still in its infancy.[18]

Challenges and Future Demands

Longitudinal research on cognitive deficits in BD faces several challenges (Text Box 1). First, apart from the well-known organizational and methodological challenges of longitudinal studies (attrition, complex statistical approaches), longitudinal designs increase the need for appropriate sample

Text Box 1
Challenges in Longitudinal Research on Cognitive Deficits in Bipolar Disorder

- Using appropriate sample sizes
- Comparing bipolar patients to healthy controls at all time points
- Assessing subjects at appropriate intervals over an extended period while controlling for practice effects
- Attaining a consensus on the optimal outcome measures for cognitive functioning (see Burdick et al. [2011])[19]
- Controlling for possibly influencing variables such as medications, comorbidities, and subsyndromal affective symptoms
- Differentiating between bipolar disorder I and II

sizes. Chronologically ordered studies (see Supplemental Table 1, http://links.lww.com/HRP/A7) display a trend toward larger and more homogeneous samples with healthy controls matched for age, sex, and education. Much remains to be achieved, however, since such studies are still rare and not yet comparable in power and robustness to most cross-sectional designs. Second, comparisons with matched healthy controls at all assessments are needed in order to evaluate whether the observed trajectory of cognitive changes over time is specific to BD patients or due to practice effects or normal decline in aging. Third, most of the reviewed studies cover a time period of up to three years, and with a baseline and one follow-up assessment. More frequent assessments over a sufficiently large time span would provide important information on the course of cognitive performance in BD.[11,14] Finally, a great variety of instruments for measuring cognitive functioning have been used (Supplemental Table 1, http://links.lww.com/HRP/A7), rendering comparisons difficult. In this regard, the use of a consensus battery as suggested by Burdick and colleagues[19] would be a step in the right direction.

Cross-sectional research suggests that certain clinical factors (e.g., age at onset, number of mood episodes, history of psychotic symptoms, or history of substance abuse) may predict cognitive performance in BD. Most of the longitudinal studies cited above do not analyze the possible effects of these variables; future research is required to supply important answers.

The impact of medication is another fundamental issue related to research on cognitive deficits in BD (or any other mental illness). Discussing this topic in detail is beyond the scope of this review. Although medication effects are surely not the sole explanation for cognitive deficits in BD,[20] their influence—especially in the context of polypharmacy—should not be neglected. Both positive and negative effects of lithium have been reported during the discussion on its neuroprotective or neurotoxic effects.[21]

Last but not least, most samples of the reviewed studies included BD I and BD II patients. At present, no consensus has been reached about potential differences between BD I and BD II in terms of severity or pattern of cognitive impairment.[22] It would therefore be desirable to differentiate between these two patient groups or at least to consider the type of disorder as a covariate.

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