

COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER

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Aim. Provide an overview of how bipolar disorder affects cognitive function in patients.

Methods. MEDLINE and PsycInfo data bases were searched for articles indexed by the combinations of MESH term or key word “bipolar disorder” with the following terms: “cognition”, “memory”, “neuropsychology”, “neuropsychological tests”, “lithium”, “anticonvulsants”, “antipsychotics”, and “schizophrenia”.

Constraints limiting time period of publications or their language were not applied. Reference lists of publications identified by these procedures were hand-searched for additional relevant citations.

Results. There is evidence of stable and lasting cognitive impairment in all phases of bipolar disorder, including the remission phase, particularly in the following domains: sustained attention, memory and executive functions. But research on the cognitive functions has yielded inconsistent results over recent years. There is a growing need for clarification regarding the magnitude, clinical relevance and confounding variables of cognitive impairment in bipolar patients. The impact of bipolar illness on cognition can be influenced by age of onset, pharmacological treatments, individual response, familial risk factors, and clinical features. In addition to the mood state, cognitive performance in bipolar patients is influenced by seasonality.

Conclusion. Previous optimistic assumptions about the prognosis of bipolar disorder were based on the success of the control of mood symptoms by pharmacotherapy. However, it is now clear that the “remitted” euthymic bipolar patients have distinct impairments of executive function, verbal memory, psychomotor speed, and sustained attention. Mood stabilizers and atypical antipsychotics may reduce cognitive deficits in certain domains and may have a positive effect on quality of life and social functioning.

INTRODUCTION

Cognitive impairment in bipolar disorder has been the focus of intensive investigation during the past decade, following an earlier wave of similar studies in schizophrenia. This delay was perhaps due to the fact that the impairment in euthymic bipolar disorder patients is generally less severe (and thus less obvious) than in schizophrenia¹.

Several motivations for the recent interest in this topic can be discerned. Psychiatric genetics has been searching for endophenotypes for various disorders^{2,3}, and cognitive impairment is seen as a candidate for that role⁴. Furthermore, there has been a controversy whether bipolar disorder and schizophrenia are best characterized as separate disorders or along a continuum⁵. Differences and similarities in cognitive impairments attending these disorders have the potential to contribute to the resolution of this controversy. Finally, it has been increasingly realized that the impairments are clinically important since they influence functional outcomes in bipolar patients.

The aim of the current review is to examine the published evidence on cognitive impairment in bipolar disorder in terms of its description, assessment, effects of the phase of illness, effects of medication, and impact on

functional outcomes. Finally, cognitive endophenotypes in bipolar disorder will be discussed.

Cognitive domains studied in bipolar patients

Cognitive domains examined in bipolar patients include executive function, memory, attention, psychomotor speed, and, more recently, social cognition. Executive function includes the ability to move freely from one situation to another and to think flexibly in order to respond appropriately (set shifting), response inhibition, concept formation, working memory, emotional control, and other aspects of mental control and self-regulation.

Short-term or immediate memory involves what one can repeat immediately after perceiving it. Working memory is the executive and attentional aspect of short-term memory involved in the interim integration, processing, disposal, and retrieval of information.

Theory of mind (ToM) is a component of social cognition. It refers to the ability to represent one's own or other's mental states.

Cognitive assessment in bipolar patients

Executive function is assessed using Part B of the Trail Making Test⁶ that focuses on set shifting, and the Stroop

test⁷ that can be seen as a test of response inhibition. Wisconsin Card Sorting Test assesses the capacity for set shifting and concept formation⁸. Verbal fluency is tested by asking the subjects to name, as fast as they can, either words from a certain category (e.g. animals), or words beginning with certain letters⁹. Verbal fluency tests assess capacity for organized thinking and memory.

Immediate verbal memory and learning are assessed using word list learning (California Verbal Learning Test (CVLT)¹⁰ or Auditory Verbal Learning Test (AVLT)¹¹ or Rey Auditory Learning Test (RAVLT) . Delayed recall version of these tests is used to assess delayed memory. Working memory is tested using the Digit Span¹². Continuous Performance Test (CPT) assesses sustained attention¹³. Trail Making Test part A (ref.⁶) and Digit Symbol Substitution Test¹² are used to measure psychomotor speed. Several tests of premorbid intelligence have been employed^{14,15}.

ToM testing uses stories or movies that are read or shown to the subjects. The subjects are then asked about the thoughts, emotions, and intentions of the characters in the story or a movie.

Features of cognitive impairment in euthymic (remitted) bipolar patients

The most recent meta-analysis available used 45 studies comparing 1423 euthymic bipolar patients with 1524 healthy controls⁴. The results showed group differences with medium to large effect sizes for measures of executive function, verbal memory, psychomotor speed, and sustained attention.

Meta-regression analyses were used to study the effects of demographic variables, medication (percentage of patients using antipsychotics, antidepressants, and lithium), and other variables. Medication effects will be discussed later.

Several ToM studies indicated impaired social cognition in bipolar disorder. One of the studies recorded the fMRI response to ToM and control visual stimuli and subsequent (off-line) subjects' verbal rating of the same stimuli¹⁶. The subjects were 20 euthymic bipolar patients and 20 healthy controls. The results of verbal ratings indicated that the patients were less able to assess intention than the controls when viewing ToM stimuli. The fMRI showed less activation in the patients than in controls in a large number of anatomical areas.

Since it had been hypothesized that ToM deficits increase vulnerability to psychosis, a study compared ToM deficits in bipolar patients with and without a history of psychosis¹⁷. The results were negative, thus ToM deficits do not appear to be a trait marker for psychosis. A detailed study of several ToM subtypes in bipolar disorder has been published recently¹⁸. Impairments of social cognition, including ToM, have a potential impact on functional outcomes; more studies of ToM relating the results to clinical variables are needed.

History of psychosis affects cognitive impairment in bipolar patients

Lifetime prevalence of hallucinations and delusions in Bipolar Disorder I is perhaps 50% or more¹⁹, and psychosis (and perhaps its treatment) may have enduring adverse effects on cognition. Accordingly, research studies have addressed this possibility in bipolar disorder.

Bipolar patients with a history of psychosis showed greater impairments of executive functioning and working memory (including spatial memory) than those without such history²⁰. In a large neuropsychological test battery, the number of categories (i.e., the number of runs of 10 correct responses) on WCST was the only variable that discriminated between euthymic bipolar patients with (N=45) and without (N=20) a history of psychosis²¹.

However, these authors²¹ noted that there were other clinical variables besides history of psychosis that affected cognitive performance. Most patients (N=63) were treated with lithium at the time of the neuropsychological assessments, and plasma levels were determined. Higher lithium levels, lower age of onset and lower level of education were correlated with impairment of memory performance. In a multiple regression analysis, this effect of lithium was statistically independent of the severity of current depressive symptoms.

Verbal memory was more impaired in bipolar patients with a history of psychosis than in those without it²². Another study aimed to determine whether the presence of psychosis during inpatient hospitalization was associated with greater cognitive impairment at the time of hospital discharge²³. Bipolar patients admitted with or without psychosis completed a neuropsychological test battery before discharge from the hospital. Patients admitted with psychosis had significantly poorer performance on the CVLT, logical memory subtest from Wechsler Memory Scale-Revised, Stroop test, and the WCST than those without psychosis. However, history of psychosis had no effect on performance on a ToM test in bipolar patients¹⁷.

Thus, in summary, it appears that history of psychosis affects executive functioning and various memory functions in bipolar patients. Other clinical factors that may interact with the history of psychosis influence cognitive functioning. These factors include current lithium treatment, history of early onset of bipolar disorder, and lower level of education.

Cognitive dysfunction in bipolar disorder in manic, depressed and euthymic states: state versus trait

A cross-sectional study compared 4 groups: manic or hypomanic bipolar patients, depressed bipolar patients, euthymic bipolar patients, and healthy controls using a neuropsychological test battery²⁴. Each of the three bipolar groups showed significant impairments in verbal memory and executive functions in comparison with controls. However, there were no substantial differences among the bipolar groups. Similar studies of this type were summarized in a review²⁵. The principal conclusion of these studies comparing various disease states within bipolar disorder is that the cognitive impairment in eu-

thymia is not substantially different from that in manic or depressive state. In view of the persistence of cognitive impairment, euthymia cannot be seen as a clinical recovery.

In a mixture of cross-sectional and longitudinal prospective design, 25 patients with bipolar I disorder underwent neuropsychological testing over a period of 30 months while hypomanic, depressed, or euthymic²⁶. Of the 25 patients, 13 were assessed in one phase only, and 12 in two or three phases (hypomanic, depressed, and euthymic). The results from these assessments were compared with tests in 25 healthy controls. In this comparison, depressed patients showed impairments across all cognitive domains tested (executive, memory, attention, and motor). Euthymic patients demonstrated only impaired recall, and hypomanic patients had executive, memory, and attention impairments. In comparisons within the bipolar group, depressed patients had more memory and motor impairment than euthymic patients, and hypomanic patients had more motor impairments than euthymic ones. Impairment on Global Assessment of Functioning (GAF)²⁷ was correlated with impaired performance on WCST in the set of bipolar patients.

In addition to the mood state, cognitive performance in bipolar patients is influenced by seasonality. Seasonal variation of mood and behavior was assessed in a group of bipolar patients, and a subgroup perceiving seasonal fluctuations as a problem was identified²⁸. These patients showed impaired cognitive performance in a number of domains in comparison with a subgroup without seasonal variation. Furthermore, cognitive performance was influenced by the season when the testing occurred: the results obtained in the winter were inferior to those obtained during other seasons. The patients' mood state at the time of testing was not determined, so we do not know whether this variable interacts with seasonal effects. Interestingly, no effects of seasonality were detected in a group of healthy controls²⁸. These data were obtained in Finland; it is not clear how they would generalize to patients living at lower latitudes.

Thus, in summary, each of the disease mood states or phases (mania, hypomania, depression, and euthymia) is associated with cognitive impairments, particularly in the domains of memory and executive function. It appears that the euthymic state is associated with less impairment than the other states; nevertheless, euthymic bipolar patients are still cognitively impaired in comparison with healthy controls. Seasonality influences the results of cognitive testing, and this effect should be accounted for in future research.

Potential deleterious effects of medication on cognition in bipolar disorder

For clinical and ethical reasons, it is difficult to obtain a sample of unmedicated bipolar patients. This complicates the efforts at assessment of medication effects on cognitive performance. One of the rare studies of unmedicated patients compared 17 bipolar II currently depressed unmedicated patients with healthy controls; a neuropsychological test battery showed no significant differences²⁹. A somewhat similar study used 49 unmedicated bipolar

(11 bipolar I and 38 bipolar II) patients in depressed phase and compared them with healthy controls³⁰. The patients performed worse on spatial working memory and several other tests. In another study using similar subjects, medicated (N=33) and unmedicated (N=32) bipolar disorder patients, all in depressed phase, were compared on a neuropsychological test battery with each other and with healthy controls³¹. The medication consisted of lithium or valproate monotherapy. The medicated patients had a significantly higher level of depressive symptoms than the unmedicated ones.

As mentioned above, higher lithium plasma levels were associated with impairment of memory performance in bipolar patients²¹. On the other hand, bipolar patients medicated with lithium (N=20) did not differ from those who were unmedicated (N=20) in terms of their cognitive performance³². This was an uncontrolled, open study; it is unclear how the patients were assigned to their treatment groups. Another small uncontrolled study suggested that the cognitive impairment in lithium-treated bipolar patients may depend on clinical response: the impairment was greater in lithium non-responders³³.

A meta-analysis of lithium effect on cognition summarized 12 studies involving 276 lithium-treated and 263 similar or the same subjects who were lithium-free³⁴. The subjects included patients with bipolar disorder (who comprised 44.2% of the entire sample), major depressive disorder, schizoaffective disorder, other disorders, and persons without mental illness. The results indicated small but statistically significant deleterious effects on immediate verbal learning and memory (ES = 0.24; 95% CI, 0.05–0.43) and creativity (ES = 0.33; 95% CI, 0.02–0.64). In patients with affective disorders, there was additionally a larger effect impairing psychomotor performance (ES = 0.62; 95% CI, 0.27–0.97). It is not clear to what extent these results apply specifically to lithium effects in bipolar disorder.

Meta-regressions of medication effects on cognitive performance in bipolar patients were a part of a meta-analysis discussed in a previous section⁴. Those meta-regressions indicated that medication was associated with impaired psychomotor speed and sustained attention: Studies that reported higher proportion of patients on antipsychotics reported lower psychomotor speed and more omission errors, antidepressants were associated with lower psychomotor speed and more impaired performance on Trail Making Test A. These associations between medication and test performance of course do not necessarily imply that medication had any direct causative effect on the performance. It is possible, for example, that the association was mediated by a third variable, such as depression, that could cause psychomotor slowing as well as trigger the prescription of an antidepressant.

In summary, lithium treatment was reported to be associated with impairments in learning, memory, and psychomotor performance. However, recent evidence suggests that this effect may be limited to certain subgroups of bipolar patients (e.g, lithium non-responders). Antipsychotic and antidepressant treatments were associated with impaired psychomotor performance and

various other impairments in bipolar patients. However, these associations were observed in uncontrolled trials (and their meta-analyses). Unmedicated patients that are used as controls in some studies are typically bipolar II patients in depressed phase. For clinical and ethical reasons, such subjects are probably easier to recruit and study than other unmedicated bipolar patients. However, the results of studies focusing on such patients are difficult to generalize.

Potencial options of treatment/remediation of cognitive impairment in bipolar disorder

Pharmacological approaches

Emerging evidence suggests that galantamine, a cognitive-enhancing agent approved for the treatment of Alzheimer disease, may alleviate some aspects of cognitive impairment in bipolar disorder. A double-blind, placebo-controlled study of this agent was conducted in euthymic patients with bipolar disorder³⁵. A total of 16 patients completed a neuropsychological test battery before and after treatment in this 3-months study. Galantamine treatment (but not placebo) was associated with a statistically significant improvement on CVLT (reflecting improvement of memory and learning), but there were significant improvements on several other tests that were limited to the placebo group. Between-group statistical tests showed no significant differences.

In another study, galantamine was administered for 4 months to 19 patients with bipolar disorder in remission, who reported subjective cognitive deficits³⁶. Mood and subjective cognitive questionnaires were administered monthly in this open trial. At the beginning and the end of the trial all subjects were administered neuropsychological tests, including tests of attention (CPT) and memory and learning (CVLT). The patients underwent proton magnetic resonance spectroscopy (1H-MRS) before and after treatment.

After treatment, the patients experienced significant improvement of subjective cognitive scores and on CPT as well as on CVLT. Spectroscopy demonstrated that in the left hippocampus, N-acetyl aspartate increased and choline-containing compounds decreased during treatment. These changes suggested increases in neuronal viability and normalization of lipid membrane metabolism in the left hippocampus³⁶.

Taken together, these two small studies suggest that galantamine merits further investigation as a potential treatment of cognitive impairment in bipolar disorder. We have not been able to locate any controlled randomized double-blind trials of antipsychotics or mood stabilizers for this indication.

Psychosocial approaches

An intensive psychosocial remediation program was administered to bipolar depressed patients in a randomized controlled trial³⁷. The remediation enhanced relationship functioning and life satisfaction. The authors concluded that "Alternate interventions focused on the

specific cognitive deficits of individuals with bipolar disorder may be necessary to enhance vocational functioning after a depressive episode"³⁷.

This suggestion was followed by a recent study that tried a new cognitive remediation (CR) treatment to improve psychosocial and neuropsychological functioning in patients with bipolar disorder³⁸. The neuropsychological test battery included the Frontal Systems Behavior Rating Scale (FrSBe). The FrSBe is a 46-item behavior rating scale that assesses behavioral changes commonly associated with frontal lobe pathology. It includes three subscales: Apathy, Disinhibition, and Executive Dysfunction. After a baseline neuropsychological and clinical assessment, 18 bipolar patients received 14 CR sessions. At the end of treatment, as well as at the 3-months follow-up, patients showed a statistically significant improvement of Executive Dysfunction, lower depressive symptoms, and improved occupational, as well as overall psychosocial functioning. Improvements in executive functioning were associated with improvements in occupational functioning. These results are encouraging, but the study was small, open, and uncontrolled³⁸. Replication is required.

In general, research into treatment of cognitive impairment in bipolar disorder is lagging behind the similar effort in schizophrenia. Much more work needs to be done in this area.

Cognitive impairment and functional outcomes

Functional disability in bipolar patients discharged from the hospital is a serious problem. After a 30-year follow-up, 33% of bipolar patients showed poor performance at work, and additional 24% were occupationally incapacitated due to mental illness³⁹. A 5-year follow-up study of 148 bipolar patients detected a decline in job status and income as well as deterioration in most areas of psychosocial functioning in comparison with healthy controls⁴⁰. In a study of 3681 patients with acute mania, there were only 11% of patients who showed no work impairment in the previous year⁴¹. A review of 13 studies involving a total of 813 bipolar patients found an unemployment rate of 55% (ref.⁴²).

Functional outcomes in bipolar disorder are affected by various factors such as neuroticism and current level of depressive symptoms⁴³ as well as age, course of disorder (single episode, multiple episodes, chronic deteriorating course) insight into positive symptoms, family history of schizophrenia, and lifetime substance use disorders⁴⁴; other clinical and demographic factors have been described⁴¹. However, there is increasing evidence indicating that cognitive impairment contributes substantially to functional outcomes.

Such contribution was demonstrated in a study testing cognitive performance in 77 euthymic bipolar patients with varying degrees of occupational functioning⁴⁵. The patients were divided into high-functioning and low-functioning groups. Tests of verbal recall and executive function showed more impairment in the low-functioning group. In another study using 25 bipolar patients in various mood states, scores on Global Assessment of Functioning²⁷ were

correlated with performance on WCST²⁶. Performance on tests of attention and ideational fluency was reported to predict functional outcome at a 12-month follow-up in 78 bipolar patients⁴⁶.

In a study comprising 73 bipolar disorder patients, verbal memory scores correlated with the GAF and with a quality of life scale⁴⁷.

A recent review identified 13 studies addressing relationship between cognitive impairments and functional outcomes in euthymic (8 studies involving 316 patients and 147 healthy controls) and non-euthymic (5 studies involving 497 patients and 55 controls) bipolar patients in comparison with healthy controls⁴². Significant relationships between cognitive impairments and functional outcomes were reported in 12 of the 13 studies reviewed.

Thus, social and vocational outcomes in bipolar disorder are generally poor, and cognitive impairments play an important role in this. The impairments and the poor outcomes are enduring, being less dependent on current mood states than was originally thought: even euthymic patients show neurocognitive impairments and are likely to be unemployed or show poor work performance as well as inadequate social engagement.

Nevertheless, current therapeutic efforts in bipolar disorder are still focused on reduction of mood symptoms and rely largely on pharmacotherapy. Cognitive behavioral therapy, psychoeducation, and other psychosocial approaches have been tried with some success in improving functional outcomes⁴⁸, but this has attracted much less interest than pharmacotherapy. This is an area that should receive more attention in the future.

Bipolar disorder and schizophrenia

The Kraepelinian classification of “manic-depressive insanity” and “dementia praecox” (schizophrenia) as two separate categories has survived 150 years. However, recent genetic, neurobiological, and clinical evidence showing similarities between schizophrenia and bipolar disorder⁵ has inspired a controversial view that these disorders can be better conceptualized on a continuum than as separate entities.

This controversy has inspired comparative investigations of cognitive impairments. A neuropsychological test battery was administered to 30 patients with schizophrenia and 22 psychotic bipolar patients⁴⁹. All patients were experiencing the first episode of their illness. Schizophrenia patients showed impairments over all domains tested. Bipolar patients had a similar test profile, but the impairments were less severe. Bipolar patients performed significantly better than schizophrenia patients on verbal memory, reasoning and flexibility.

The underlying structures of neuropsychological functioning in two sets of patients were determined using factor analysis⁵⁰. The first set (N=250) was comprised of schizophrenic and schizoaffective patients, the second set (N=155) contained bipolar patients. The two sets had a similar factor structure, but the bipolar patients performed better on tests of attention and non-verbal functioning.

Another study compared 73 euthymic bipolar patients, 89 stabilized patients with schizophrenia and 67 normal controls⁴⁷. The battery tested executive functioning, sustained attention, and verbal and visual memory. Patients in both patient groups demonstrated impairments in all domains in comparison with normal controls. Patients with bipolar disorder performed significantly better than patients with schizophrenia on executive functioning (Trail Making Test (TMT) part B), sustained attention (backward digit span), and verbal memory (CVLT). As mentioned in a preceding section, verbal memory impairment correlated with assessments of psychosocial function, thus confirming the clinical relevance of neuropsychological findings⁴⁷.

In summary, both bipolar disorder and schizophrenia patients are cognitively impaired in comparison with healthy controls. The two patient groups have a similar profile of neuropsychological dysfunction, but the impairments are more severe in schizophrenia. Thus, the differences between the impairments in these disorders are quantitative rather than qualitative.

Searching for cognitive endophenotypes: family studies of bipolar disorder

Endophenotypes are subclinical quantitative traits that are assumed to be located along the pathway between the genotype and the phenotypic disease (in this case, bipolar disorder or schizophrenia diagnosed by clinical criteria). Endophenotypes are conceived as subcomponents of the illness, providing an opportunity for a less complex genetic analysis than the diagnostic phenotype. Neurophysiological, anatomical, and neurocognitive measures are among the candidate endophenotypes for bipolar disorder and schizophrenia.

Endophenotypes should meet certain criteria: they should be associated with illness, they should be heritable, and co-segregate within families with illness³. Furthermore, they should be state-independent traits present in illness as well as in remission, and they should be more frequent in unaffected relatives of patients than in general population⁴. The endophenotype criterion of heritability has been met for certain neurocognitive functions in a study of a population-based Finnish sample of 110 individuals from 52 families with bipolar disorder who were administered a comprehensive test battery⁵¹. The results indicated high heritability of executive functions and psychomotor processing speed, but not of verbal learning.

Searching for neurocognitive endophenotypes in bipolar disorder, Finnish investigators administered a test battery to 32 familial bipolar I disorder patients, 40 of their unaffected first-degree relatives and 55 controls⁵². The relatives showed impairments in psychomotor performance speed and in executive function. Bipolar patients were impaired in verbal learning and memory compared with unaffected relatives and controls. They also differed from controls in tasks of executive functions. The authors suggest that impaired psychomotor performance speed and executive function may represent endophenotypes of bipolar disorder.

Another study by the same Finnish group⁵³ examined cognitive performance in two groups of bipolar patients: those who came from families containing affected relatives with bipolar disorder only (“bipolar families”), and those coming from families with both bipolar I disorder and schizophrenia or schizoaffective disorder (“mixed families”). A neuropsychological test battery was administered to 20 bipolar patients and 36 unaffected relatives from bipolar families, 19 bipolar patients and 28 relatives from mixed families and 55 healthy controls. Irrespective of the family group, patients and relatives were impaired in psychomotor processing speed in comparison with controls. Both patient groups were impaired in executive functioning, but the deficit was more severe in patients from mixed families. Patients from bipolar families scored lower than controls on tests of verbal memory. All relatives were slightly impaired in executive functioning. Psychopathology in the family had no major effects on the heritability of cognitive function. The authors concluded that impaired psychomotor processing speed and executive functions may represent markers of susceptibility to bipolar I disorder irrespective of psychopathology within the family.

Another, somewhat similar study of bipolar patients and their relatives showed deficits in verbal working memory and executive function in the relatives⁵⁴. These deficits were therefore proposed as candidates for neurocognitive endophenotypes in bipolar disorder.

Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives were implemented⁵⁵. Meta-analysis of bipolar patients and first-degree relatives comprised, respectively, 28 and 14 studies. In bipolar patients, comparisons with healthy controls yielded large effect sizes ($d > 0.8$) for executive functions (working memory, executive control, fluency) and verbal memory. Medium effect sizes ($0.5 < d < 0.8$) were reported for other tests of executive function (concept shifting, executive control), mental speed, visual memory, and sustained attention. In first-degree relatives, size effects were small ($d < 0.5$), but significantly different from healthy controls for executive function and verbal memory in particular. The authors concluded that executive function and verbal memory are candidate bipolar endophenotypes given large deficits in these domains in bipolar patients and smaller impairments in first-degree relatives.

Thus, in summary, family studies of bipolar disorder suggest the existence of cognitive endophenotypes for this disorder. Strong evidence supports executive function and processing speed as endophenotypes marking the vulnerability to bipolar disorder. Some studies also provide support for verbal memory in that role.

Searching for cognitive endophenotypes: family studies of bipolar disorder and schizophrenia

Genetic contribution to the risk of bipolar disorder and schizophrenia has been generally accepted, and a recent meta-analysis provided evidence for familial co-aggregation of the two disorders⁵⁶. Nevertheless, the genes that underlie the predisposition to both disorders seem

difficult to find. It is possible that the somewhat arbitrary categorical classification of these complex disorders developed by Kraepelin may not be the optimal way to define the heritable phenotype. Endophenotypes may be more useful for this purpose.

This line of reasoning led to a number of family studies of bipolar disorder and schizophrenia. A neuropsychological test battery comprising tests of executive function (Verbal Fluency Test, the Stroop Word Color Test, the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT)) was administered to 37 bipolar disorder probands, 33 of their unaffected first degree relatives, 25 schizophrenia probands, and 22 of their unaffected first degree relatives were compared with 20 normal controls⁵⁷. The unaffected relative groups did not differ from the proband groups, implying familial resemblance. Bipolar and schizophrenic probands as well as unaffected relatives showed impairment on the Stroop test in comparison with the controls. The other tests did not show this effect. The impairment on Stroop, implying enhanced susceptibility to interference and reduced inhibition, could thus be a shared endophenotype that marks a familial vulnerability common to bipolar disorder and schizophrenia⁵⁷.

The same French group of investigators who produced the publication reviewed above⁵⁷ used a similar design to study 95 bipolar probands, 63 of their unaffected relatives, 73 schizophrenia probands, 67 of their unaffected relatives, and 48 normal controls⁵⁸. The cognitive battery included only 2 tests: WCST and TMT. In comparison with the control group, both tests showed the greatest impairment in schizophrenic probands, followed by bipolar patients and then the two groups of relatives. Bipolar probands did not differ from their relatives on the WCST and part A and part B of the TMT, implying familial resemblance for the cognitive functions assessed by these tests. However, familial resemblance was not observed in schizophrenic probands and their relatives. The authors conclude that “executive measures, as assessed by the WCST or the TMT, should not be used as endophenotypes in genetic studies of schizophrenia unless confounders are identified and their effects eliminated” (p.131). It is not clear why these authors did not use the Stroop test to replicate the positive findings from their previous study⁵⁷.

Unaffected relatives of bipolar patients were compared with unaffected relatives of schizophrenic patients and normal controls on several versions of the Stroop test⁵⁹. An emotional bias towards mood-related information was detected in relatives of bipolar patients, and, in turn, impairment in cognitive inhibition was found in the relatives of schizophrenic patients. The findings suggest the existence of different endophenotypes marking the vulnerability to bipolar disorder and schizophrenia.

Thus, in summary, there is some evidence for enhanced susceptibility to interference and reduced inhibition (assessed by the Stroop test) as a candidate cognitive endophenotype shared by bipolar disorder and schizophrenia. However, more research is needed in this area.

CONCLUSION

Research into cognitive impairments in bipolar disorder has yielded results that lead to revisions of the clinical approach to the illness. Previous optimistic assumptions about the prognosis of bipolar disorder were based on the success of the control of mood symptoms by pharmacotherapy. However, it is now clear that the “remitted” euthymic bipolar patients have distinct impairments of executive function, verbal memory, psychomotor speed, and sustained attention. Social cognition is also affected.

The severity of impairment is increased by history of psychosis, history of early onset of bipolar disorder, and lower level of education. Other factors such as current pharmacological treatments are apparently involved, but more research is needed in this area. Patients who are currently manic or depressed are even more impaired than those who are euthymic.

Cognitive impairments play a role in the generally poor social and vocational outcomes in bipolar disorder. Nevertheless, current therapeutic efforts in bipolar disorder are still focused on reduction of mood symptoms and relies largely on pharmacotherapy. Cognitive behavioral therapy, psychoeducation, and other psychosocial approaches have been tried with some success in improving functional outcomes, but their study has attracted much less interest than pharmacotherapy. This is an area that should receive more attention in the future.

There is a controversy whether bipolar disorder and schizophrenia are distinct categories separated from each other, or whether they are better conceptualized on a continuum without categorical separation of the two entities. Cognitive research has therefore aimed at comparisons between these disorders. It has been established that both bipolar disorder and schizophrenia patients are cognitively impaired in comparison with healthy controls. The two patient groups have a similar profile of neuropsychological dysfunction, but the impairments are more severe in schizophrenia. Thus, the differences between the impairments in these disorders are quantitative rather than qualitative.

There are strong genetic influences on the risk for bipolar disorder and schizophrenia, and cognitive impairments have been proposed as potential endophenotypes for these disorders. Family studies of bipolar disorder suggest the executive function and processing speed as endophenotypes marking the vulnerability to bipolar disorder. Some studies also provide support for verbal memory in that role. There may be a common cognitive endophenotype shared by bipolar disorder and schizophrenia, but more data are needed in this area.

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