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A Meta-analytic Investigation of Neurocognitive Deficits in Bipolar Illness: Profile and Effects of Clinical State

Matthew M. Kurtz and **Raphael T. Gerraty**
Department of Psychology and Program in Neuroscience and Behavior, Wesleyan University

Abstract

A meta-analysis of neuropsychological studies of patients with bipolar disorder in euthymic, manic/mixed or depressed phases of illness was conducted. Measures of attention, working memory, verbal and non-verbal memory, visuospatial function, psychomotor speed, language, and executive-function were evaluated in 42 studies of 1197 patients in euthymia, 13 studies consisting of 314 patients in a manic/mixed phase of illness, and 5 studies of 96 patients in a depressed state. Cohen d-values were calculated for each study as the mean difference between patient and control group score on each neuropsychological measure, expressed in pooled standard deviation units. Results for patients in euthymic, depressed and manic/mixed phases were evaluated separately and then a subset of measures on which patients in all three phases were tested were compared. For euthymia, results revealed impairment across all neuropsychological domains, with d-values in the moderate-large range (d=.5–.8) for the vast majority of measures. There was evidence of large effect-size impairment on measures of verbal learning (d=.81), and delayed verbal and non-verbal memory (d=.80-.92), while effect-size impairment on measures of visuospatial function was small-to-moderate (d≤.55). Patients tested during a manic/mixed or depressed phase of illness showed exaggerated impairment on measures of verbal learning, while patients tested during a depressed phase showed greater decrement on measures of phonemic fluency. Consistent with previous meta-analyses (Arts et al, 2007; Bora et al., 2009; Robinson et al., 2007), these results suggest that bipolar illness during euthymia is characterized by generalized moderate level impairment across an array of neurocognitive domains, with particular marked impairment in verbal learning and memory. These results also show that a subset of these deficits moderately worsen during acute disease states.

Keywords

bipolar illness; neurocognition; mania; depression; euthymia

Over the past 10–15 years a growing number of studies have revealed that individuals with bipolar illness show deficits on standardized neuropsychological measures with particularly marked deficits in executive-function and verbal learning (see Arts et al, 2007; Bora et al., 2009; Robinson et al., 2006). Particular significance has been attached to these deficits as they have been linked to the intensity of the disease process (e.g., Denicoff et al., 1999; Ferrier et al., 1999), are persistent despite psychiatric symptom reduction (e.g., Joffe et al. 1998) and

Correspondence regarding this article should be addressed to: Matthew M. Kurtz, Ph.D., Department of Psychology, Judd Hall, Wesleyan University, Middletown, CT. 06459; mkurtz@wesleyan.edu.

have been linked to psychosocial and competitive employment status (e.g., Altshuler et al., 2008; Martinez-Aran et al., 2004).

Three recent meta-analytic investigations of neurocognitive deficits in bipolar illness have revealed largely consistent findings across a variety of neurocognitive measures in patients assessed during euthymia. Robinson et al. (2006), in a survey of 26 studies, showed large effect size impairment (d=.90–1.09) for two aspects of executive-function: category fluency and working memory (digits backward), as well as verbal learning. Moderate-to-large size effects (d=.47-.78) were evident for aspects of immediate and delayed verbal memory, concept shifting and perseverations, speeded set-shifting, sustained visual and auditory attention, response inhibition and psychomotor speed. Small effect-size impairment (d=.34) was evident for letter fluency. Arts et al. (2007), in a survey of 29 studies investigating cognitive functioning in euthymic patients, reported similar findings, with large effect-size impairment (d=.82–1.02) for executive functions (working memory, perseverations, category fluency) and verbal memory, and moderate-to-large effect-size impairment (d=.52-.73) in concept shifting and response inhibition, mental speed, visual memory, and sustained visual attention. Small effect-size (d=.22-.37) impairment was evident in visuoperceptual function and sustained auditory attention. Lastly, Bora et al. (2009), in an analysis of 45 studies of patients in a euthymic state, found large effect-size impairments (d=.83.-86) in speeded set shifting, verbal learning and sustained visual attention, moderate-to-large size effects (d=.59-.77) in processing speed, working memory (digits backward), conceptual flexibility and perseverations, visual memory and verbal fluency, with processing speed deficits linked to medication effects. Small effects were evident in visual copy and auditory attention (digit span; d=.23-.37).

The consistency in meta-analytic studies of the extant literature has lent support to contention that neurocognitive deficits in bipolar illness are a putative endophenotype of the disorder, representing a more direct biological consequence of genes and a feature of the illness underlying clinical traits of the phenotype (e.g., Hasler et al., 2006). To be considered an endophenotype, however, several criteria for neurocognitive deficits must be met including, (a) heritability, (b) that they are evident in unaffected relatives of people with the illness at a higher rate than the general population, (c) they are evident in patients with the disorder during remission, and (d) that these impairments are not state specific (Gottesman & Gould, 2003; Hasler et al., 2006). There is growing support for criteria (b) and (c; see Arts et al., 2007). The degree to which neurocognitive deficits in bipolar illness are state-specific (criteria d), however, is still largely unknown.

Thus, while the meta-analytic literature on neuropsychological deficits in bipolar illness has revealed important insights regarding the pattern and magnitude of deficit in people with the illness, no meta-analytic investigation of the literature has evaluated whether neurocognitive deficits are state-independent or phase-linked. This meta-analysis will contribute to distinguishing which measures of neurocognitive dysfunction might best serve as putative endophenotypes versus illness markers.

A small but growing number of primary research studies have investigated the effects of mood state on neuropsychological deficits in patients with bipolar illness. For example, Martinez-Aran et al. (2004), in a study of 30 depressed, 34 manic or hypomanic patients, and 44 euthymic patients, found deficits in verbal memory and executive functions in all three groups relative to healthy controls with more pronounced deficits in verbal recognition memory, verbal immediate and delayed recall, and visual delayed recall in acute disease states. Depressed patients were more impaired in visual immediate recall and phonemic fluency. Fleck et al. (2003), in a study of verbal memory in 14 euthymic and 14 manic bipolar I patients, showed impairments in verbal recognition memory during mania that were not evident during euthymia. Verbal recall deficits were similar in euthymic and manic patients. In the only

longitudinal study, to our knowledge, of performance on a neuropsychological test battery across illness phases in bipolar I disorder, Mahli et al. (2007), found that deficits in verbal memory became more pronounced during episodes of hypomania and depression. State specific impairment was noted for motor speed during depressed phase of illness and reaction time during hypomania. Taken together, these results suggest that acute disease states are associated with more profound deficits in verbal and visual memory, with evidence of decreased phonemic fluency and motor slowing during the depressed phase specifically.

The goal of the current meta-analytic investigation then was two-fold. First, we attempted to replicate previous meta-analyses of neurocognitive deficits of patients in euthymia. Second, no meta-analysis, to our knowledge, has studied the pattern and magnitude of neurocognitive impairment in patients with bipolar illness in manic/mixed and/or depressed states as compared to euthymia. Thus, a second goal of the current paper was to compare the magnitude and pattern of neurocognitive deficits during acute illness states to determine whether state and trait effects are specific or whether they overlap.

We also evaluated whether sample demographic and clinical characteristics of age, education, and duration of illness would impact observed findings. For patients in a euthymic state we predicted moderate, widespread deficits across a broad range of neurocognitive domains, with more marked impairment in executive-function and verbal memory. We hypothesized that acute mood states would be linked with larger effect-size impairment in verbal memory and that the depressed phase would be linked to greater deficits in phonemic fluency.

Methods

Search Strategy

Articles included in the meta-analysis were identified through a computer-based PsychInfo (American Psychological Association, 2000) search conducted from 1980 to 2008. The search was conducted using the following key words: bipolar, bipolar illness, manic-depressive illness, neurocognition, neuropsychology, cognition. A parallel search using the same key terms was completed with the MEDLINE (National Library of Medicine, 1994) database from 1980 to 2008. Nineteen-eighty was selected as a cut-off in light of the introduction of the DSM-III for more reliable diagnostic criteria for bipolar illness (APA, 1987). The reference sections of articles located from both searches were studied for relevant citations.

Inclusion Criteria

Articles were included if they met the following criteria: (a) research design included a control group comprising healthy volunteers, (b) there was characterization of clinical state and data from patients in different clinical states were not grouped together, (c) study statistics were convertible to effect size *d* (e.g., means and standard deviation, F, t-values or exact *p*-value), (d) publication between 1980–2008, and (e) a peer-reviewed English language journal.

Measures studied in the meta-analysis are presented in Table 1. These measures were selected based on use in at least three different studies to ensure stability of findings. Effect-sizes were calculated and aggregated from individual cognitive tests with consistent outcome measures to minimize the combination of effect-sizes from different tests, and different outcome measures from the same test, that could be tapping different neurocognitive constructs. For example, categories achieved and perseverative errors from the Wisconsin Card Sorting Test (WCST), while clearly related, measure different presumed underlying constructs; concept formation and flexibility on the one hand, and set-shifting on the other. These outcome measures were consistent with those selected in previous meta-analyses (Arts et al., 2007; Bora et al., 2009; Robinson et al., 2006). For the purposes of the meta-analysis, results from a variety

of different modifications of the visual Continuous Performance Test (CPT) were included together given that in all versions demands were placed on sustained visual vigilance. Some studies reported CPT sensitivity measures that rely on signal detection theory and account for both true and false positive responses, while other studies reported true positive or omissions only. A comparison of these outcome variables across studies produced similar mean effect-sizes (sensitivity, d=.60, CI: .36/.84 vs. hits, d=.75; CI: .56/.94; $Q_B[1]$=.86; p=.35) . Thus, effect-size measures from these two outcomes were combined across studies for analysis with sensitivity measures selected first when both measures were reported in the same sample. In light of the high degree of test similarity, outcome measures of total words recalled and delayed free recall scores were each combined for two verbal list learning measures, the Rey Auditory Verbal Learning Test (RVLT) and the California Verbal Learning Test (CVLT). Results from the CVLT and CVLT-II were combined. Results from Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale (WMS) and Wechsler Memory Scale-Revised (WMS-R) were also combined, as were results from the paper-and-pencil and computerized versions of the WCST. Lastly, studies reported a variety of outcome measures for the interference condition of the Stroop Color Word Test (SCWT). Comparisons of mean effect-sizes from studies using a total or an interference score from the SCWT were not significantly different (total score: d=.79; CI: .63/.96, vs. interference score: d= .76, CI: . 42/1.09; $Q_B[1]$=.04; p=.85) and thus were combined. Measures of executive-function as measured by the Hayling's Sentence Completion Test, Intradimensional/Extradimensional (ID/ED) Shift Test, Stockings of Cambridge Test, and Tower of London, while appearing in 3 or more studies, were not included in the analysis secondary to reporting of highly discrepant measures of task performance across studies.

Five studies reported two groups of bipolar patients stratified by a third variable, such as first versus multi-episode patients, or patients with and without co-morbid alcoholism. In these studies effect-sizes were combined across samples to provide a larger overall sample and to make samples more comparable to samples used in the meta-analysis as a whole (Bora et al., 2007; Ferrier et al. 1999, Nehra et al. 2006; Torrent et al. 2006 Van Gorp; 1998). Effect-sizes were computed for each subsample and then combined, weighted by sample-size. One study meeting entry criteria (Thompson et al., 2007), reported means and SDs for several neuropsychological measures that were identical to a study already included in the meta-analysis (Thompson et al., 2005), and thus was excluded. A summary of the percentage of studies selected for the current meta-analysis using the most commonly reported inclusion criteria for studies of bipolar illness during euthymia, mania/mixed states and depression is presented in Table 3.

Statistical Analysis

Analyses were conducted according to procedures suggested by Rosenthal (1986) and Hedges and Olkin (1985). *DSTAT v. 1.11* (Johnson, 1993) was used to calculate effect sizes and to carry out subsequent homogeneity and moderator variable analyses. The unit of analysis in a meta-analysis is the effect size (*d*). For purposes of the present study, the *d* score was always defined as the difference between patients diagnosed with bipolar illness and healthy controls on each neurocognitive measure expressed in standard deviation units. Study statistics were converted to *d* using formulas provided by Glass (1977). We used the pooled standard deviation using the formula of Rosenthal (1994). Nonsignificant results lacking supporting statistical information were coded as an effect size of zero (Lipsey & Wilson, 2001). By expressing effect size in standard deviation units, we were able to make a direct comparison of outcomes across studies. Effects were categorized as small (d<.5), medium-large (d=.5-.8) or large (d>.8; Cohen, 1977). Effect sizes were expressed in a way such that positive values always indicated poorer performance in patients with bipolar illness relative to healthy controls.

Each analysis was conducted in several steps. First, Hedges *g* was derived for each study using raw means and standard deviations, *t, F*, or exact *p* statistics reported in the individual study (Hedges & Olkin, 1985; Rosenthal, 1994). Although Hedges *g* is an estimate of effect size, the *g*-statistic is known to overestimate the population effect size when sample sizes are small (Rosenthal, 1994). In order to correct for this bias, Hedges *g* was subsequently transformed into an unbiased measure of effect size, Cohen's *d* (Hedges, 1981; Hedges & Olkin, 1985). Individual values of *d* were thereafter combined across studies and weighted according to their variance using a fixed-effects model. Potential differences in effect size between studies were analyzed using the method of Hedges and Olkin (1985). This procedure computes mean weighted effect sizes and 95% confidence intervals (CI) for each variable subset and allows for the testing of the influence of each individual factor on the overall results using the Q statistic. To assess stability of underlying effects we used a test for heterogeneity Q_T which is based on the sum of squares of the individual effect sizes around the mean when each square is weighted by the inverse of the estimated variance of the effect size. Q has an asymptotic χ^2 distribution and is analogous to the analysis of variance. Studies were evaluated for within-group differences (Q_W) and between-group differences (Q_B) following the same model.

To partially address the "file-drawer" or publication bias problem in meta-analytic investigations, in which null results in a research area are collected but not reported in the literature, we calculated a fail-safe N for each class of outcome variable by the method of Orwin (1983). This measure provides an estimate of the number of studies with null results that would be needed to reduce the obtained mean effect-size to a non-significant level. In the absence of a universally accepted significance level for effect sizes, an effect-size of .20 was considered nonsignificant (Orwin, 1983).

Moderator Variable Analyses—Moderator analyses were conducted when the test for heterogeneity (Q_T) for a specific neuropsychological measure was significant. Sample characteristics of mean age, percentage male, mean years of education, and mean duration of illness were selected as moderator variables. Each moderator variable was analyzed with a continuous model (Rosenthal, 1986) with a z-test for significance of model fit. Results are not reported for non-significant moderator analyses.

Comparisons of Clinical State

Mean-weighted effect-sizes were directly compared between patients with bipolar illness in a manic/mixed state vs. a stable euthymic phase of illness, and patients in a depressed state vs. euthymia for neurocognitive measures that were: (1) represented among those selected for analysis among patients with euthymia, and (2) that were administered across at least 3 studies of patients in an acute mood state. This resulted in a smaller number of neurocognitive measures for comparison across state (attention, verbal learning and memory, language and executive-function). Direct comparisons in effect-sizes were only made between studies including independent samples of patients and healthy controls. Significance tests for all analyses were two-tailed and p was set at .05.

Results

Study Characteristics

A summary of sample characteristics of the 42 studies of euthymia, 13 studies of mania and 5 studies of depression that met inclusion criteria for the meta-analysis are presented in Table 3.

Neurocognitive Deficits in Euthymia

Attention—As can be seen in Table 4, during euthymia effect-sizes were in the small range for auditory attention (Digits Forward, d=.41, CI: .24/.57), and in the moderate-large range for

sustained visual vigilance and speeded visual scanning (CPT, *d=.69, CI: .54/.83* and Trails A, *d=.65, CI: .58/.77*). Findings from the CPT were significantly heterogeneous, suggesting that the weighted mean effect-size did not reflect a stable underlying effect. Moderator analyses revealed that more years of sample education was linked to larger effect-size impairment (*Z=6.99, p<.001*).

Working Memory—Patients in a euthymic state showed moderate-large effect-size impairment (*d=.65, CI: .50/.81*) on a measure of working memory (Digits Backward). Heterogeneity measures suggested this overall weighted mean effect was not stable. Moderator analyses revealed that more years of sample mean education (*Z=−2.00, p<.05*) was linked to less working memory impairment.

Verbal Memory—Patients in a euthymic state showed large effect-size impairment on measures of verbal learning (R/CVLT Total, *d=.81, CI; .69/.93*) and moderate-large effect-size impairment for long-delay, verbal free recall (R/CVLT LDFR, *d=.78, CI: .61/.95*). Significant heterogeneity in effect-sizes was evident for verbal learning on the R/CVLT. Moderator analyses revealed that more sample mean years of education was associated with greater effect-size impairment (*Z=2.50, p<.05*) for total scores,. Moderate-large effect-size impairment was evident for immediate (WMS-LMI, *d=.74, CI: .44/1.03*) and delayed (WMS-LM II, *d=.83, CI: .53/1.13*) prose recall for patients in a euthymic state.

Executive Function—Patients tested during euthymia showed moderate-large effect-size impairment on measures of executive function that were similar for problem-solving tasks (WCST CAT, *d=.54, CI: .41/.66*, WCST PE, *d=.61, CI; .48/.74*), verbal interference (SCWT, d=*.75, CI: .60/.89*) and set-switching tasks (Trails B, *d=.73, CI: .61/.85*). Significant heterogeneity was evident on all three measures of executive-functioning for patients in euthymia. For the WCST, moderator analyses revealed that older sample age (z=−4.21, p<. 001), and more years of education (*Z=−2.59, p<.05*), were linked to smaller effect-size impairment. For the SCWT, moderator analyses revealed that older sample age (*Z=−3.27, p<. 005*) was associated with poorer mean test performance. For Trails B, moderator analyses revealed larger percent male samples (*Z=−2.18, p<.05*), older mean age (*Z=−3.37, p<.005*), and greater mean years of education (*Z=−23.29, p<.005*) were associated with smaller effect-size impairment.

Other Neurocognitive Domains—Patients in a euthymic state showed moderate-large effect-size impairment on two non-verbal memory tasks (RCFT-Imm, *d=.73, CI: .43/1.03* and WMS-VRI, *d=.63, CI: .33/.92*) at an immediate test. Slightly more pronounced findings were evident at delayed recall (RCFT-Del, *d=.80, CI: .51/1.10*, WMS-VRII, *d=.92, CI:.62/1.22*). Patients in a euthymic state also showed small-to-moderate effect-size impairments on measures of visuospatial function (Block Design, *d=.55, CI: .31/.79*, RCFT copy, *d=.26: CI: -.02/.56*). Moderate-large effect-size impairment on measures of phonemic (*d=.51, CI: . 38/.64*) and semantic (*d=.75, CI:.56/.94*) fluency were also evident during euthymia. Patients in a euthymic state showed moderate-large effect-size impairment on measures of psychomotor speed relative to healthy controls (*d=.66, CI: .50/.83*). Measures of non-verbal memory, visuospatial function, language and psychomotor speed were not heterogeneous and thus, moderator analyses were not conducted for these measures.

Neurocognitive Deficits in Manic/Mixed States

As can be seen in Table 5, in a manic/mixed state, moderate-to-large effect-size impairments were evident in attention (visual sustained vigilance, *d=.79; CI: .50/1.06*; and speeded visual scanning, *d=.90; CI: .62/1.18*). Patients in a manic state showed large effect-size impairments on measures of verbal learning and memory (verbal learning, *d=1.43; CI: 1.17/1.68*; and

delayed free recall, *d=1.05; CI: .76/1.35*). Patients in a manic state showed moderate-large effect-size deficits in language (letter fluency, *d=.51; CI: .24/.77*; and semantic fluency, *d=.59; CI: .31/.87*). Patients in a manic state showed moderate-large effect-size impairment on measures of executive function (perseveration, *d=.72; CI: .45/1.00*; and speeded set-shifting, *d=.64; CI: .37/.91*).

Neurocognitive Deficits in Depression

Attention—As can be seen in Table 6, patients in a depressed phase of illness showed moderate-large effect-size impairment in speeded visual sequencing (*d=.70; CI: .46/1.13*).

Verbal Memory—Patients in a depressed phase of illness showed large effect-size impairment in verbal learning (*d=1.31; CI; .88/1.53*).

Language—Patients in a depressed phase of illness demonstrated large effect-size impairment in phonemic fluency (*d=.93; CI; .65/1.22*)

Executive-Function—Patients in a depressed phase of illness showed moderate effect-size impairment in speeded set-shifting (*d=.55, CI: .30/.97*)

Comparison of Neurocognitive Deficits between Manic and Euthymic States

As can be seen in Figure 1, comparison of R/CVLT performance between patients in a manic and euthymic state revealed differences, with greater mean effect-sizes evident in the manic phase of illness for verbal learning ($Q_B[1]=20.19$, $p<.001$). Similar mean effect-size impairment was evident in attention (sustained visual vigilance and speeded visual sequencing), verbal long-delay free recall, phonemic and semantic fluency, problem-solving (WCST) and speeded set-shifting in patients during mania as compared to patients in a euthymic state.

Comparison of Neurocognitive Deficits between Depressed and Euthymic States

As can be seen in Figure 2, depressed phase patients had greater mean effect-size impairment on total scores from R/CVLT ($Q_B[1]=4.93$, $p<.05$) and phonemic fluency ($Q_B[1]=6.94$, $P<.01$) Impairment on measures of speeded visual scanning and speeded set-shifting was similar in depressed and euthymic phases of illness.

Discussion

The results of this meta-analysis yielded three important findings. With respect to our first goal, our findings largely replicated those of previous meta-analyses for bipolar patients in a euthymic state (Arts et al., 2007; Bora et al., 2009; Robinson et al., 2006). Moderate impairments were evident across a variety of neurocognitive measures including attention, working memory, language, psychomotor speed, and executive-function relative to healthy control performance. Impairment on measures of verbal learning was in the large effect-size range (d=.82), as was impairment on delayed verbal and visual memory measures (d=.80-.92). An area of more modest impairment was in visuospatial function in the moderate-small (d≤.55) effect-size impairment range. We did not replicate large effect-size impairment on measures of executive-function or control evident in previous meta-analyses. Second, and also consistent with hypotheses, patients in a manic or depressed state had significantly greater effect-size impairment in verbal learning than patients in a euthymic state, and that patients in a manic state had magnified deficits in visual scanning relative to more clinically stable patients. Third, patients with depression also showed greater phonemic fluency deficits relative to euthymic patients. There was no difference between manic and euthymic patients on measures of problem-solving (WCST), sustained visual vigilance, long-delay free recall of

verbal information, or verbal fluency, or between manic or depressed and euthymic patients on a measure of set-switching (Trails B). To our knowledge this is the first meta-analysis to investigate the degree to which acute clinical state may modify the pattern or magnitude of neurocognitive impairment evident in patients with bipolar disorder evident in stable phases of the illness.

Moderator Analyses

Results of moderator analyses of studies of euthymia revealed that bipolar patient samples with higher mean levels of education showed diminished impairment on measures of working memory and executive-function (but, paradoxically, greater impairment on measures of verbal learning), suggesting that education may have a protective effective against deficits in working memory and executive-function in the illness. It remains unclear why higher mean education was linked to poorer verbal memory in the current meta-analysis, particularly when literature on age-related memory disorders suggests that education usually plays a protective role in terms of disease and age-related memory decline (e.g., Scarmeas et al., 2006).

The results from euthymic patients demonstrate clearly that neurocognitive deficits are evident in this disorder relative to healthy controls, and that deficits in attention and memory are stable across illness phase. These findings, in combination with findings from unaffected first-degree relatives showing attenuated deficits across a variety of neurocognitive measures (e.g., Arts et al., 2007) provide further support for the idea that these neurocognitive deficits reflect genetic liability to the disease. The increased magnitude of neurocognitive impairment in verbal memory and phonemic fluency in acute mood states also shows that state factors may moderate the level of performance on neurocognitive measures, at least in some domains.

Effect of Symptoms

We note that these findings do not rule out the role of symptoms in the production of neurocognitive deficits in euthymia. Several studies have revealed that controlling for symptoms in patients ostensibly in a euthymic state reduced differences in neurocognitive test performance between patients and controls (Ferrier et al., 1999; Clark et al, 2002; Thompson et al., 2005). A review of the criteria for determining euthymia in the current analysis indicated large inter-study differences for classifying patients as euthymic with many samples including patients with substantial residual symptoms. However, differences in types of symptom scales selected and reporting methods for symptoms across studies made it impossible to quantify effects of symptoms on observed effects-sizes in our moderator analyses of patients in a euthymic state.

Another important methodological issue is the degree to which samples of depressed and manic/mixed patients analyzed in the current paper possess equivalent levels of symptoms. As the scales used to assess depressed and manic symptoms have distinct psychometric characteristics it remains unclear to what degree differences in impairment in observed neurocognitive test performance between samples of depressed and manic patients represent differences in clinical state per se versus differences in magnitude of symptoms. A related issue is the degree to which differences in magnitude of symptoms of patients in manic and depressed states produce less engagement with neurocognitive testing procedures relative to patients in stable phases of the illness. We do note, however, that our results suggest a specific pattern of accentuation of neurocognitive deficits in each mood state, rather than an overall reduction in neurocognitive test performance, arguing against a non-specific reduction in engagement with the test procedures in acute illness states.

Effects of Medication Status

Differences evident between clinical samples and controls on neurocognitive tests could also reflect differences in medication status between groups. Three lines of evidence argue against this possibility. First, studies comparing euthymic patients on or off mood stabilizing medication have found no (Joffe et al, 1998) or modest (Goswami et al., 2002) effects of medication on neurocognitive test performance. Second, patients assessed during a first-episode of illness, before exposure to mood-stabilizing medications, also show evidence of neurocognitive deficits that are similar, or even more severe than those patients who have been chronically medicated (e.g., Nehra et al., 2006). Lastly, unaffected first-degree relatives of people with bipolar illness, who have never been treated with mood stabilizing medication, show similar, albeit attenuated deficits to those evident in patients (e.g., Arts et al., 2007). Nonetheless, only 55% of studies of euthymia even detailed the number of patients treated with lithium, and only 29% described the number of patients on anticonvulsants (see Table 3), with even fewer reporting daily dosage. More precise description of medication status in future studies of neurocognition in bipolar illness will be crucial for calrifying how medications most commonly prescribed for the illness influence the pattern of deficits observed in this analysis.

Evidence for Selective Neurocognitive Deficits

Results from the current meta-analysis suggest evidence of large effect-size impairment in verbal learning and verbal and non-verbal memory in patients in a euthymic state against a background of widespread moderate effect-size decrements in other neurocognitive areas. Results of fail-safe N analyses suggest that findings for verbal learning were particularly robust, with 55 negative findings necessary to reduce this finding to a small effect. Nonetheless, we acknowledge that establishing differential deficits across a background of generalized impairment is complicated by inter-test psychometric differences in task complexity, difficulty, and floor and ceiling effects that may have influenced differences in observed mean effect-sizes (e.g., Chapman & Chapman, 1973, 1978). It also remains unclear to what degree much of the impairment on these measures may represent a common impairment in elementary neurocognitive function that cuts across different neuropsychological measures or whether this widespread pattern represents multiple distinct sources of impairment. For example, recent studies in schizophrenia have suggested that impairment across a variety of standardized neuropsychological instruments thought to represent distinct neurocognitive domains can actually be explained by a single common cognitive factor using hierarchical modeling (e.g., Dickinson et al., 2008). These findings suggest the potential value of similar research approaches utilizing large samples of patients with bipolar illness to help elucidate the mechanism of neurocognitive impairment demonstrated in this meta-analysis. Lastly, the comparison of neurocognitive function between bipolar patients and healthy controls (a criteria for entry into this meta-analysis) leaves open the question of whether this observed pattern of deficits is specific to bipolar illness, or represent the effects of psychopathology more generally. Studies that compare neurocognitive deficits in bipolar illness and other psychiatric disorders, such as schizophrenia, will shed light on this issue (e.g., Schretlen et al., 2007; Seidman et al., 2002).

Limitations

Caveats to the current findings should be noted. First, the sample of studies for several domains of neurocognitive functioning in euthymia (e.g., verbal prose recall, non-verbal memory) were small and observed mean effect-sizes will need to be confirmed in future meta-analyses as increasing numbers of studies employing those specific measures are published. Second, the number of studies documenting neurocognitive impairment in acute disease states in bipolar disorder remains small and findings of exaggerated neurocognitive deficits in verbal learning and fluency in the current analysis will need to be confirmed as larger numbers of studies are

published. Third, we note that that some of the strongest findings in the analysis were unstable as measured by our heterogeneity statistic (e.g., verbal learning). As can be seen in Table 2, this instability may represent the grouping of very different samples of bipolar patients into the same analysis. Nearly half of studies of euthymia did not explicitly exclude bipolar II patients, while the other half did exclude on this basis, and over 60% of studies of euthymia did not exclude patients with comorbid psychiatric disorders, while the remainder did exclude on this basis. Differences in residual symptoms between samples may also contribute to these heterogenous findings. Fourth, some neurocognitive domains (e.g., working memory) are not well-represented in terms of the number of measures evaluated in the meta-analysis and thus will require replication with larger groups of tests assessing the same construct. Fifth, only a subset of neurocognitive measures studied in euthymia assessing a limited number of domains (attention, verbal learning and memory, language and executive-function) were evaluated in manic/mixed and depressed phases of the illness. Sixth, a significant portion of studies analyzed may represent atypical samples by using any history of substance abuse as exclusionary criteria (see Table 3). Seventh, as is common to all meta-analyses, it is unknown the degree to which our findings may represent publication bias. Inclusion of unpublished negative findings would affect our overall results, and their absence may have led us to overestimate our reported effect-sizes.

Future Research

The results of this meta-analysis suggest several avenues for future study. First while several studies have demonstrated a link between neurocognitive impairment and psychosocial function (Martinez-Aran et al., 2004; Atre-Vaidya et al., 1998) additional research is needed to identify which features of this profile of neurocognitive dysfunction are most closely linked to psychosocial status. Such information can help guide the development of novel pharmacologic or behavioral interventions targeted at improving neurocognitive deficits and the associated psychosocial impairment that is well-documented in this population. Second, few studies, to our knowledge, have investigated the effects of acute disease process and only one study (Malhi et al., 2007) followed patients longitudinally to evaluate the impact of differing mood states on observed neurocognitive dysfunction. More powerful longitudinal studies following patients across mood cycles will be crucial for clarifying the relationship between neurocognitive impairment and mood state. Third, a rapidly emerging area of research has identified differences in neuropsychological function of patients with bipolar illness with and without a history of psychosis (Glahn et al., 2007, Bora et al., 2007). However, only 12% of studies in this meta-analysis measured the number of patients in their sample with a history of psychosis. Thus, it will be crucial for future studies of neurocognition in bipolar illness to stratify patients according to this dimension of illness. As data in this area of research accumulates, future meta-analyses can utilize this clinical feature as an additional moderating variable potentially influencing the neurocognitive signature of the disorder described in the current study. Fourth, a very important implication of the current study is that future research studies should ensure that mood status remains consistent within, and is compared across, patients in different states. Careful and consistent definitions of euthymic, manic and depressed symptom states across bipolar research centers will also be crucial in this endeavor. Fifth, more detailed reporting of sample characteristics such as co-morbid diagnoses, age-of-onset, hospitalizations, estimated IQ and medication status will be crucial for future study comparisons. Sixth, future studies that evaluate the effects of state on neurocognitive impairment should include measures of effort for bipolar patients assessed in highly varied symptomatic states will be crucial for determining whether state-related differences in the magnitude of specific neurocognitive impairment are not an artifact of differences in global levels of effort. Lastly, limiting future meta-analyses to samples that are diagnostically homogenous in terms of bipolar I vs. II, and exclude samples on the basis of comorbid

psychiatric diagnoses will provide a more precise assessment of the signature of neurocognitive impairment in bipolar disorder.

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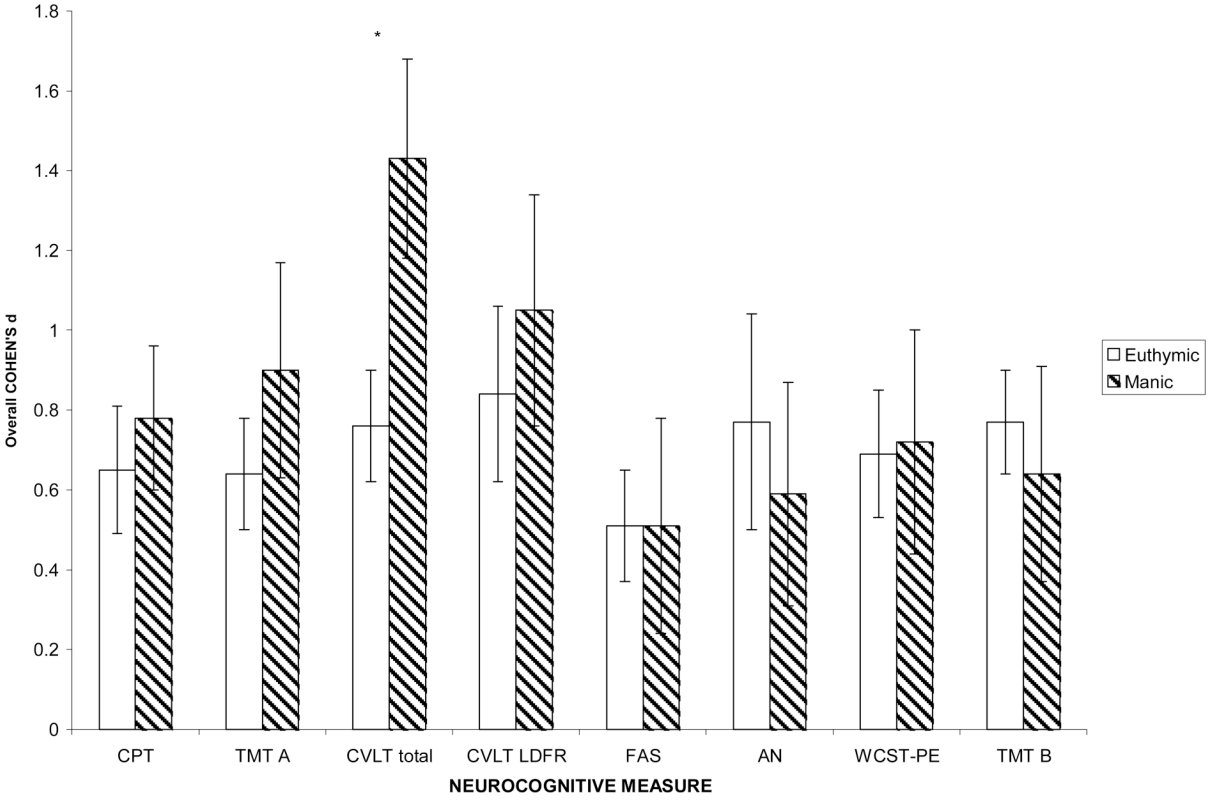

Figure 1.
Overall effect-size comparison (+/− 95% confidence interval) of patients with bipolar disorder in a manic/mixed state versus euthymic state on standardized measures of neurocognition. *=p<.05.

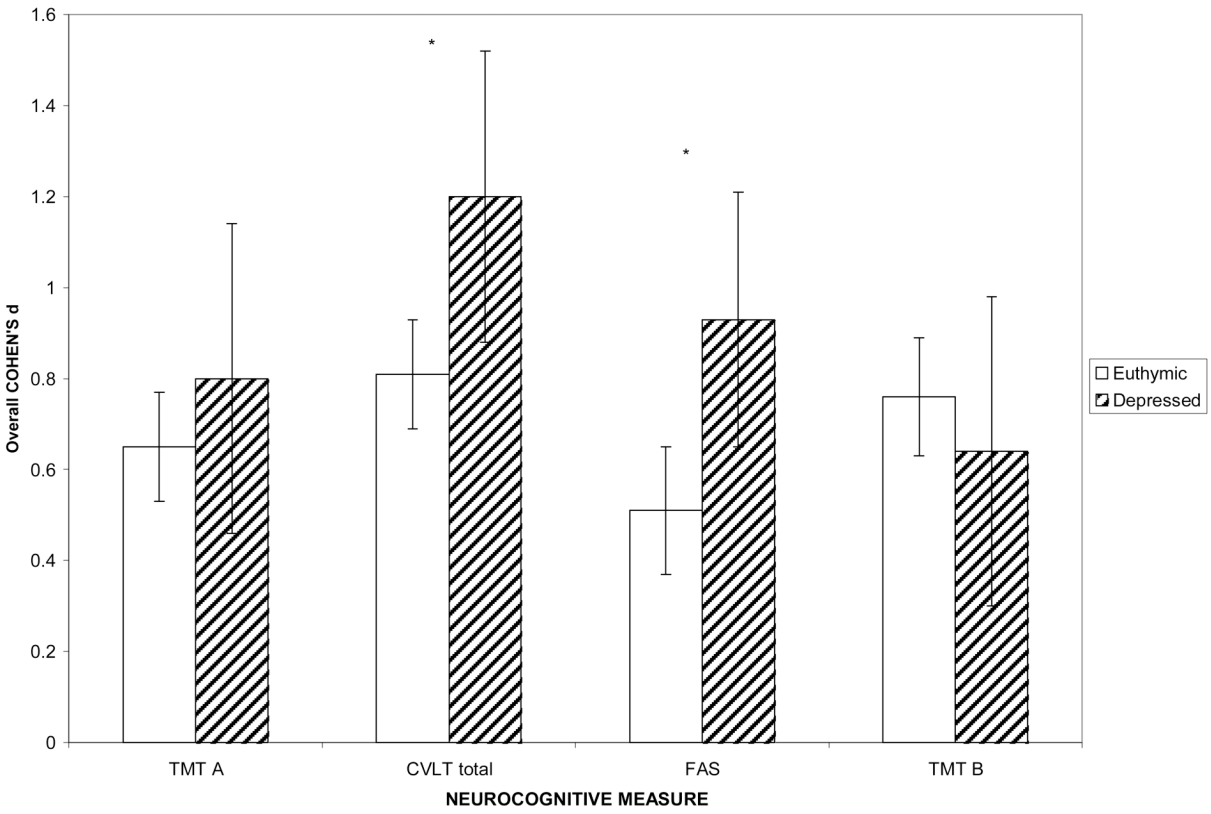

Figure 2.
Overall effect-size comparison (+/− 95% confidence interval) of patients with bipolar disorder in a depressed versus euthymic state on standardized measures of neurocognition.*=p<.05.

Table 1

Neuropsychological measures studied in the meta-analysis

Attention
Continuous Performance Test
Digits Forward
Trails A
Working Memory
Digits Backward
Verbal Memory
Rey Auditory/California Verbal Learning Test—Total Recalled, Long Delay Free Recall
Wechsler Memory Scale-Logical Memory (WMS-LM)
Non-verbal Memory
Rey Complex Figure Test (RCFT)—Immediate and Delayed Recall
Wechsler Memory Scale-Visual Reproduction (WMS-VR)
Visuospatial Function
Block Design
Rey Complex Figure Test (RCFT)-Copy
Language
Controlled Oral Word Association Test (COWA-FAS)
Animal Naming (AN)
Psychomotor Speed
Digit Symbol Substitution Test (DSST)
Executive Function
Wisconsin Card Sorting Test (WCST)-Categories Achieved and Perseverative Errors
Stroop Color Word Test (SCWT)
Trails B

Table 2

Demographic and clinical characteristics of studies included in the meta-analysis.

Variable	Euthymia	Mania/Mixed	Depression
Sample Size	28.50 (14.82)	24.15 (9.60)	19.2 (7.85)
% reporting	100	100	100
Age (years)	38.91 (8.39)	31.11 (7.81)	40.2 (6.84)
% reporting	95	92	80
% Male	48.2 (19.12)	48.4 (15.37)	54.5 (31.64)
% reporting	93	92	80
Education (years)	13.86 (1.67)	12.93 (1.34)	12.78 (1.28)
% reporting	71	77	80
IQ (estimate or full-scale)	106.08 (8.09)	107.12 (4.09)	105.6
% reporting	48	38	20
Illness Duration (years)	14.93 (6.01)	11.48 (2.50)	11.57 (5.15)
% reporting	67	38	60
Age of Onset	24.20 (5.08)	23.93 (3.01)	26.33 (2.11)
% reporting	57	46	60
No. Hospitalizations	3.52 (2.44)	2.25 (.87)	1.70
% reporting	36	31	20
% History of Psychosis	63.04 (22.25)	53.10	75.00
% reporting	12	8	20
Lithium (%-treated)	62.48 (22.63)	53.83 (36.51)	65.00 (7.07)
% reporting	55	31	40
Anticonvulsants (%-treated)	34.67 (15.73)	NR	NR
% reporting	29	0	0

Table 3

Participant inclusion criteria for studies included in the meta-analysis (% of studies).

Inclusion Criteria	Euthymic	Manic/Mixed	Depressed
Bipolar I only	57	70	50
No Psychiatric Comorbidities	33	50	20
No drug or alcohol misuse in past year or less	45	50	20
No lifetime history of drug or alcohol misuse	21	20	60

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Table 4

Mean effect sizes for neuropsychological measures for patients with bipolar illness during euthymia as compared to healthy controls. Measures are organized by neurocognitive domain.

Measure	K	N (patient/control)	d	95% CI	Z	p	Q_w	p	N_{fs}
Attention									
CPT	13	401/404	.69	.54/.83	9.16	<.0001	64.80	<.0001	32
Digits Forward	8	326/275	.41	.24/.57	4.82	.0001	10.55	.16	8
Trails A	17	638/514	.65	.58/.77	10.40	<.0001	18.48	.30	38
Working Memory									
Digits Backward	10	367/414	.65	.50/.81	8.30	<.0001	44.09	<.0001	23
Verbal Memory									
R/CVLT Total	18	642/645	.81	.69/.93	13.31	<.0001	33.54	.01	55
R/CVLT Long Delay Free Recall	9	347/267	.78	.61/.95	8.95	<.0001	15.78	.05	26
WMS-LM-Imm.	3	85/159	.74	.44/1.03	4.89	<.0001	.40	.82	8
WMS-LM-Del.	3	85/159	.83	.53/1.13	5.47	<.0001	.38	.83	9
Non-verbal Memory									
RCFT-Imm.	3	94/93	.73	.43/1.03	4.83	<.0001	.64	.73	8
RCFT-Del.	3	110/92	.80	.51/1.10	5.38	<.0001	.32	.85	9
WMS-VR-Imm.	3	85/159	.63	.33/.92	4.19	<.0001	2.44	.30	6
WMS-VR-Del.	3	85/159	.92	.62/1.22	6.03	<.0001	2.81	.25	11
Visuospatial Function									
Block Design	5	169/139	.55	.31/.79	4.52	<.0001	4.41	.35	9
RCFT Copy	4	131/89	.26	−.02/.53	1.84	.07	1.62	.66	1

Measure	K	N (patient/control)	d	95% CI	Z	p	Q_w	p	N_{fs}
Language									
FAS	15	543/462	.51	.38/.64	7.73	<.0001	19.24	.16	23
AN	8	299/196	.75	.56/.94	7.75	<.0001	9.40	.23	23
Psychomotor Speed									
DSST	10	279/411	.66	.50/.83	7.91	<.0001	18.15	.03	22
Executive-Function									
WCST-CAT	16	565/511	.54	.41/.66	8.15	<.0001	61.46	<.0001	27
WCST-PE	15	510/514	.61	.48/.74	9.09	<.0001	34.65	.0017	31
SCWT	15	460/395	.75	.60/.89	10.22	<.0001	29.78	.008	41
Trails B	18	663/530	.73	.61/.85	11.70	<.0001	58.76	<.0001	48

Note: AN=Animal Naming, AVLT=Auditory Verbal Learning Test, BD=Block Design, CPT=Continuous Performance Test, CVLT=California Verbal Learning Test, DS=Digit Span, DSST=Digit Symbol Substitution Test, FAS=Controlled Oral Word Association Test, RAVLT=Rey Auditory Verbal Learning Test, RCFT=Rey Complex Figure Test, SCWT=Stroop Color Word Test, WCST=Wisconsin Card Sorting Test, CAT=Categories, PE=Perseverative Errors, WMS-LM=Wechsler Memory Scale, Logical Memory subtest, WMS-VR=Wechsler Memory Scale-Visual Reproduction subtest. *k*, number of studies; N, number of participants; ES, weighted effect-size between-groups; 95% CI, 95% confidence interval; Z significance statistic between the groups, Q_W within-group homogeneity statistic, N_{fS}, indicates the number of null findings that would need to be found to reduce the mean effect size to .20.

Table 5

Mean effect sizes for neuropsychological measures in patients with bipolar illness during a manic/mixed phase as compared to healthy controls. Measures are organized by neurocognitive domain.

Measure	*k*	N (patient/control)	d	95% CI	Z	p	Q_w	p	N_{fs}
Attention									
CPT	4	107/103	.79	.50/1.06	5.49	<.0001	.06	>.99	12
Trails A	4	111/117	.90	.62/1.18	6.40	<.0001	.71	.87	14
Verbal Memory									
R/CVLT Total	6	140/157	1.43	1.17/1.68	11.09	<.0001	8.188	.15	37
R/CVLT Long Delay Recall	4	91/128	1.05	.76/1.35	7.02	<.0001	1.115	.77	17
Language									
FAS	4	109/119	.51	.24/.77	3.70	.0002	2.78	.43	6
AN	4	100/113	.59	.31/.87	4.11	<.0001	2.69	.44	8
Executive-Function									
WCST-PE	4	98/123	.72	.45/1.00	5.10	<.0001	5.27	.15	10
Trails B	4	111/117	.64	.37/.91	4.62	<.0001	4.61	.20	9

Note: AN=Animal Naming, AVLT=Auditory Verbal Learning Test, CPT=Continuous Performance Test, CVLT=California Verbal Learning Test, DS=Digit Span, FAS=Controlled Oral Word Association Test, RAVLT=Rey Auditory Verbal Learning Test, WCST=Wisconsin Card Sorting Test, PE=Perseverative Errors. *k*, number of studies; N, number of participants; ES, weighted effect-size between-groups; 95% CI, 95% confidence interval; Z significance statistic between the groups, Q_W within-group homogeneity statistic, N_{fS}, indicates the number of null findings that would need to be found to reduce the mean effect size to .20.

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Table 6

Mean effect sizes for neuropsychological measures in patients with bipolar illness in a depressed phase as compared to healthy controls. Measures are organized by neurocognitive domain.

Measure	K	N (patient/control)	d	95% CI	Z	p	Q_w	p	N_{fs}
Attention									
Trails A	3	69/89	.80	.46/1.13	4.64	<.0001	6.73	.04	9
Verbal Memory									
R/CVLT Total	4	81/109	1.20	.88/1.53	7.23	<.0001	5.85	.12	20
Language									
FAS	5	96/124	.93	.65/1.22	6.47	<.0001	1.77	.78	18
Executive-Functioning									
Trails B	3	69/89	.64	.3/.97	3.77	.0002	4.27	.19	7

Note: CVLT=California Verbal Learning Test, FAS=Controlled Oral Word Association Test, RAVLT=Rey Auditory Verbal Learning Test. *k*, number of studies; N, number of participants; ES, weighted effect-size between-groups; 95% CI, 95% confidence interval; Z significance statistic between the groups, Q_W within-group homogeneity statistic, N_{fs}, indicates the number of null findings that would need to be found to reduce the mean effect size to .20.