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Meta-Analysis of the Association Between Cognitive Abilities and Everyday Functioning in Bipolar Disorder

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Abstract

Objectives—Neurocognitive deficits are common in bipolar disorder and contribute to functional disability. However, the degree to which general and specific cognitive deficits affect everyday functioning in bipolar disorder is unknown. The goal of this meta-analysis was to examine the magnitude of the effect of specific neurocognitive abilities on everyday functioning in bipolar disorder.

Methods—We conducted a comprehensive meta-analysis of studies that reported associations between performance on objective neuropsychological tasks and everyday functioning among individuals with bipolar disorder. From an initial pool of 486 papers, 22 studies met inclusion criteria, comprising a total of 1344 participants. Correlation coefficients were calculated for 11 cognitive domains and four measurement modalities for functioning. We also examined effect moderators, such as sample age, clinical state, and study design.

Results—The mean Pearson correlation between neurocognitive ability and functioning was 0.27, and was significant for all cognitive domains and varied little by cognitive domain. Correlations varied by methods of everyday functioning assessment, being lower for clinician and self-report than performance-based tasks and real-world milestones such as employment. None of the moderator analyses were significant.

Conclusions—Overall, the strength of association between cognitive ability and everyday functioning in bipolar disorder is strikingly similar to that seen in schizophrenia, with little evidence for differences across cognitive domains. The strength of association differed more so according to functional measurement approach.

Keywords

Bipolar disorder; disability; quality of life; functioning; neuropsychology; cognition

INTRODUCTION

Bipolar disorder is among the most disabling illnesses in the world(1). Over the past decade, a number of studies have identified neurocognitive deficits in bipolar disorder as an

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important determinant of this disability(2). Previous meta-analyses (3, 4) have suggested medium to large effect sizes for the neuropsychological differences between people with bipolar disorder and healthy comparison subjects, particularly in the domains of episodic memory, attention/concentration, and executive functioning. Notably, these deficits persist in the absence of acute symptoms, and thus cognitive deficits are not solely a result of mood symptoms in bipolar disorder(2, 3). As a result, it has been suggested that cognitive deficits are a potential treatment target for functional rehabilitation in bipolar disorder(1, 5).

Nevertheless, unlike in schizophrenia(5, 6), there has been no formal meta-analysis of the relationship between cognitive ability measured with standard tests and everyday functioning in bipolar disorder. As such, the magnitude of the impact of cognitive impairment on functioning in bipolar disorder is unclear, in particular whether effects vary across different cognitive domains or functional indicators. Although the general structure of the relationships between symptoms, neurocognitive abilities, and functioning in bipolar disorder appears to be similar to that seen schizophrenia(7), there are several unique aspects of bipolar disorder that could influence the impact of cognitive impairment on functioning. Cognitive impairments in bipolar disorder are less severe than among patients with schizophrenia, with a meta-analysis of 24 studies estimating that bipolar disorder is associated with better performance on neuropsychological testing than schizophrenia, with the magnitude of this difference between groups equivalent to a medium effect size(8). Bipolar patients may have higher levels of premorbid functioning than do people with schizophrenia(9), and unlike the generalized neurocognitive deficits seen in schizophrenia, the deficits associated with bipolar disorder are thought to be more selective. Verbal memory, executive functioning, and sustained attention found to be consistently impaired in bipolar disorder, whereas premorbid IQ and vocabulary appear to be grossly intact(3, 4).

An additional concern is the potential confounding effect of mood symptoms on the relationship between cognitive ability and functioning, as depressive or manic symptoms are associated with both cognitive performance(10, 11) and functioning(12). As such, some reports have restricted samples of patients with bipolar disorder to those in euthymic states, while other studies have statistically adjusted for the effect of symptoms on functioning, and others included patients regardless of clinical state. Additionally, there is some suggestion that bipolar disorder follows a deteriorating course in regard to cognitive abilities(13), and thus factors such as the age of the sample or duration of illness may alter the magnitude of cognitive and functional impairment, and, in turn, their association. Finally, different strategies have been employed to measure everyday functioning. Although there is no consensus definition of everyday functioning, in this review we refer to capacity or performance on daily tasks that are essential for maintenance of social and occupational roles(14). It is unclear whether differences among measurement approaches, such as self-report, clinician-reported instruments, performance-based tests, and functional milestones such as employment, are differentially sensitive to the effects of cognitive impairment, a concern for clinical trials targeting cognitive abilities(15).

To address these gaps in the literature, we conducted a meta-analysis of studies reporting associations between performance-based assessment of neuropsychological functioning and different measures of functional abilities and outcomes in samples of patients with bipolar disorder. We included both cross-sectional and longitudinal studies, and we examined the associations of 11 cognitive domains (e.g., executive functioning, verbal memory) and four different approaches to the measurement of everyday functioning (e.g., clinician-report, performance-based). We sought to address the following questions: 1) What is the average association between cognitive ability and functioning? 2) Which cognitive domains are associated with the greatest impact on functioning? 3) Which everyday functioning assessment methods are associated with the strongest relations relationship with cognitive

ability? And; 4) What moderating effects do sample characteristics and demographics (e.g., euthymic samples vs. all patients, sample age) have on the relationship between cognition and functioning?

MATERIALS AND METHODS

Study Selection

Articles were identified through searches in Pubmed and PSYCINFO databases, restricting inclusion to studies published between 1990 and 2010. Studies were included if they were published in peer-reviewed English-language journals and reported data from adults (aged 18 and older) who were diagnosed with bipolar disorder I or II (DSM III, DSM-IV, ICD). The search terms employed were a combination of the following three sets of terms: a) bipolar disorder, manic depression, b) cogniti*, neuropsych*, and c) disability, function*, independent living skills, quality of life, social or community adjustment, or employment/ occupational status. We also examined reference sections of identified articles as well as previous reviews on cognitive functioning and disability in bipolar disorder(3, 5).

This initial search strategy yielded approximately 486 articles, from which 64 articles were selected for possible inclusion (See Figure 1 for Study Ascertainment Diagram). Two studies reported data from two unique sub-samples and so we included these as separate studies. We included both cross-sectional and prospective follow-up studies that assessed the relationship between cognitive ability at baseline and functioning at follow up, and we examined study design as a moderator. We further excluded articles due to overlapping samples, and, in such cases, we selected the paper with the largest sample size. The search strategy was completed independently by two of the authors, and disagreements were resolved through consensus meetings.

Neurocognitive Functioning

We used a two-stage procedure to categorize neuropsychological tests into domains. Our main goal was to be consistent with a recent meta-analysis in schizophrenia that examined the relationship between various cognitive abilities and functioning (6). The purpose of doing so was to enable qualitative comparisons of effect sizes to those identified in schizophrenia. Therefore, tests were categorized first according to their placement into domains according to Fett et al. Secondly, if the test was not reported in that meta-analysis, we based categorization on standard neuropsychological texts and adjudicated domain placement by way of consensus among authors(5, 6, 16). The domains were: Verbal Ability, Verbal Learning and Memory, Attention/Vigilance, Processing Speed, Working Memory, Visual Learning and Memory, Visuospatial Ability, Verbal Fluency, Reasoning/Problem Solving, Executive Control. An additional domain, Global Cognitive Ability, was also included, so that the total number of domains was 11. We separated the tests typically subsumed under the “executive functioning” domain into two different domains (executive control and abstraction/problem-solving), because recent work suggests that “executive functions” include a heterogeneous set of skills that may only be partially related. Executive control skills have certain characteristics in common, i.e., cognitive flexibility, suppression of automatic responses and conscious allocation of cognitive resources to the successful completion of the task. On the other hand, reasoning/problem-solving skills refer to the ability to discern underlying relationships on a conceptual rather than superficial, sensory-perceptual level, which may be necessary to also successfully navigate and complete a novel task.

Most studies reported relationships between individual cognitive tests and functioning. However, total of 5 studies reported associations between cognitive domains rather than

individual tests, and as expected, there were discrepancies among studies as to how tests were categorized into domains (e.g., Trail Making Test, Part B was classified as any one of executive functions, working memory, or processing speed). Additional studies reported only statistically significant correlations. In such cases, we requested bivariate correlations for specific tests from authors. If studies did not include correlations in the manuscript and authors did not respond to requests for the missing correlations (3 studies), we excluded them from our analyses. For those studies that reported an association at the domain level, rather than among individual tests, we categorized the association into the domain in which the majority of tests were classified (e.g., if 3 of 4 measures were in the Executive Control Domain, the association contributed to the Executive Control Domain). Similarly, some neuropsychological measures include subscales that are comprised of multiple measures that address different constructs (e.g., RBANS Attention includes a processing speed component). In such cases, we held consensus meetings to clarify which domain best fit that particular subscale. Additionally, we re-analyzed the data without these studies to determine whether the inclusion of these measures affected the results.

Next, we calculated the mean effect size within domains in cases where studies reported several tests subsumed under a domain. In order to be included in the meta-analysis, we only included cognitive domains that were reported in at least 2 different studies. Tests included in each of the domains are included in Table 1.

Everyday Functioning Measurement Approaches

In cases where multiple everyday functioning measurement types were presented in the same study, we calculated a global effect size across functional measures as well as for the individual everyday functioning measurement approaches. We classified functional measurement types by the methods used into four categories: Clinician-rated, self-reported, performance-based, and functional milestone. We elected to divide functional measures by measurement strategy rather than outcome domain (e.g., social functioning vs. employment) because the delineation between outcome domains was widely inconsistent across measures – therefore we addressed the sensitivity of functional assessment *methods* to cognitive deficits. As in prior meta-analyses(6), we found that the correlation between performance-based measures of functional skills and other functional measures was rarely assessed, even though the skills examined by these performance-based measures are often conceptualized as mediators between neurocognition and outcome(7). Therefore, we considered performance-based measures as an additional measurement type of functioning.

Moderators

Several potential moderators were considered. Studies were dichotomized into those that restricted their sample inclusion to euthymic patients, statistically adjusted for symptom severity in analyses, or those that included patients regardless of clinical state. Age of the sample and duration of illness (calculated as age minus age of onset) were included as a moderators because there is some suggestion that older age may be associated with worse cognitive performance than would be expected from normal aging(17), while the severity of symptoms during manic episodes may decline(18, 19); as a result, cognition may account for a greater proportion of variance in functioning in samples with older mean ages and/or longer duration of illness. Additional exploratory moderators were study design (cross-sectional or longitudinal), mean age of onset, years of education, sex, and the proportion of the sample that was diagnosed with bipolar disorder I (versus bipolar disorder II).

Statistical Analysis

All bivariate relationships between individual neurocognitive tests and everyday functioning were converted to correlation coefficients. Coefficients were standardized in the direction

such that better cognitive performance was associated with higher functioning. For studies that reported associations embedded in multivariate regressions in which multiple neurocognitive tests were entered into a model, we used the formulas developed by Peterson and Brown(20)to derive bivariate correlation estimates.

To assess the relationship between cognitive domains and everyday functioning, we calculated a pooled effect size (r) for functional measures reported in each study for each cognitive measure, and we then calculated a pooled r for each cognitive domain when multiple tests were included in domain within a given study as well as an overall pooled mean correlation. Correlation coefficients were subjected to r-to-z transformation and weighted using inverse variance weights. Zr was then back-transformed into a r using the inverse Zr formula(21) Heterogeneity was examined using the Q statistic using a random effects model estimated via the method of moments procedure. The “fail safe n” was calculated to assess the robustness of the resulting correlation. To assess for publication bias, we performed Eggers regression test (standard normal deviates regressed on precision)(22). We elected not to conduct statistical comparisons among dependent correlations, because correlations between cognitive tests or domains or functional measurement approaches were rarely provided. Finally moderator analyses were conducted by way of random effects models, using meta-regression for continuous variables and ANOVA for categorical moderators. All analyses were conducted with SPSS Version 18 using macros published by Wilson(23) and MIX Version 2.0(24).

RESULTS

Characteristics of the Studies (Table 3)

Of 22 studies included, the total number of subjects included in the meta-analysis was 1344, and the mean sample size of the studies was 61.1 (sd=48,6, range 13–213). A total of 19studies were cross-sectional, and, of the 3 studies that were longitudinal, the median follow up period was 12 months (range 6 months to 15 years). The sample-weighted mean age of sample participants was 43.9 years (sd=9.5, range 22.7–73.6). The mean proportion of females in the studies was 49.6% (sd=22.2, range 0–100). Mean educational attainment was 13.8 years (sd=1.7, range 9.8–16.3). In regard to clinical characteristics, the mean proportion of the sample that was comprised of patients with bipolar I disorder was 80.9% (sd=19.9, range 18–100). The mean age of onset was 25.2 years (sd=4.5, range 15.0–31.0) and the mean duration of illness was 18.1 years (sd=7.3, range 3.3–34.0). The studies were split between 12 that included only euthymic patients or adjusted for symptoms (55%) and the remainder included patients in various states and did not adjust for symptoms in analyses.

Mean Correlations Across Different Cognitive Domains and Everyday functioning Measurement Approaches (Table 4, Figure 2)

The overall mean correlation pooling both cognitive functioning and everyday functioning was significant (mean r=0.27, 95% CI=0.22–.32, p<0.001, See Figure 2 for a Forest Plot of individual studies). “Fail safe N” for this effect was 88, meaning that 88 additional studies with anon-significant correlation would be needed to make this effect non-significant. Egger’s regression test to identify potential publication bias was not significant (B=−1.63, s.e.=.72, t=−2.27, p=0.151). In regard to heterogeneity, the overall effect was not found to be heterogeneous across studies, as the Q-statistic was not significant (Q=15.1, df=21, p=0.582). As seen in Table 4, all of the cognitive domains were significantly associated with functioning (Bonferroni adjustment for 11 tests, p<0.0045). The range of strength of association among domains was narrow; the lowest correlation was r=0.21 for Visual Learning and Memory domain and the highest was r=0.29 for Working Memory. The

Composite Cognitive Functioning domain had a higher correlation (r=0.33). There was also little evidence of heterogeneity within domains, as none of the domains were associated with a significant Q statistic. Given that some studies included domains rather than individual tests (or amalgamated measure), we re-analyzed the pooled correlation within domains without these studies; the estimated pooled correlations were nearly identical.

In contrast to cognitive domains, everyday functioning measurement approaches were slightly more varied in their relationship to cognition, although all were significantly associated with cognitive ability after adjustment for multiple testing (Bonferroni adjustment for 4 tests, $p<0.0125$). The strongest correlations, pooling effects across cognitive domains, were seen with Performance-based (r=0.32) and Functional Milestone (r=0.33) measures of functioning. Weaker correlations were evident in Clinician-reported (r=0.23) and Self-reported functioning (r=0.20). None of the everyday functioning measurement approaches was associated with significant heterogeneity.

Moderator Analyses

Consistent with the lack of variability seen with the Q-statistic, none of the putative moderators impacted the relationship between cognitive ability and functioning. The only moderators to approach significance were the mean age of the sample(B=0.07, S.E.=0.004, z=1.7, p=0.093), percent of the sample Bipolar I (B=0.002, S.E.=0.001, z=1.8, p=0.071), and year of publication (B=−0.020, S.E.=0.01, z=−1.87, p=0.061). Other non-significant moderators were Age of Onset (B=−0.002, S.E.=0.006, z=−.26, p=0.793), Duration of Illness (B=0.0054, S.E.=0.0041, z=1.3, p=0.191), Education (B=−0.0007, S.E.=0.02, z=0.3, p=0.973), Percent Female (B=−0.002, S.E.=0.001, z=−.1.6, p=0.104), Euthymic Sample (Q=0.212, df=1,20, p=0.631), and Longitudinal Study Design (Q=0.665, df=1,20, p=0.415).

DISCUSSION

The primary findings from this meta-analysis of 22 studies and 1344 patients with bipolar disorder were that 1) cognitive abilities account for a significant, albeit moderate, proportion of variation in everyday functioning, 2) all but one cognitive domains were significantly related with everyday functioning and there was modest effect size variation among these relationships, 3) somewhat more variation was seen among functional measurement approaches, and 4) no sample or study design characteristics significantly modified effect sizes. Overall these findings support that cognitive deficits represent a target for functional rehabilitation in bipolar disorder, yet do not support a specific pathway from individual elements of cognitive impairment to functional disability.

The effect of cognitive ability on functioning can be interpreted as small to moderate in magnitudesuggesting that a great deal of everyday functioning is explained by other factors (e.g., symptoms, motivation, or opportunities for functional attainment). However, the magnitude of the effect of cognitive ability is remarkably consistent with that seen in schizophrenia. The mean correlation in this meta-analysis (r=0.27, 95% CI: 0.22–0.31) is nearly identical to that reported in a recent meta-analysis in schizophrenia, Fett et al. (6) between overall neurocognitive ability and community functioning. Thus, even though patients with bipolar disorder may have lesser impairment in cognitive ability and functioning when compared to patients with schizophrenia(8), the impact of cognitive impairment on everyday functioning appears quite similar(7). Although we hypothesized that selective deficits would be more likely in bipolar disorder, another parallel to schizophrenia is the lack of differential effect of cognitive domains on everyday functioning(25, 26). Decisions regarding the assignment of individual tests to domains was challenging, particularly in cases where domain composite scores or amalgamated tests were provided. Therefore, it is conceivable that alternative categorization of tests into domains

may have yielded different distribution of effect sizes across domains; however, we believe it is unlikely that alternative categorization of tests to domains would have changed the conclusion that variation in effect sizes among domains was minimal, given the small spread in correlations among domains. Thus, similar magnitude and pattern of correlation between cognitive ability and functioning in bipolar disorder and schizophrenia is consistent with the evidence suggesting shared areas of cognitive deficit (e.g., processing speed)(8).

There was somewhat greater variability across measurement approaches to functioning in their sensitivity to cognitive deficits. Due to the limited reporting of reliability coefficients and inter-correlations between functional measurement types, we were not able to conduct formal statistical comparisons across functional domains. Nevertheless, real world outcomes (e.g., employment) were associated with greater association with cognitive abilities, as were performance-based measures of functioning. Clinician rated and self-reported measures of functioning were the least related to cognitive abilities (small effect sizes and the relative variance shared was approximately half for this method compared to performance-based assessments (9% vs 4%). Despite their poor sensitivity to cognitive impairments, the majority of studies employed clinician-rated measures, particularly the Global Assessment of Functioning in the estimation of everyday functioning.

None of the putative moderators impacted the relationship between cognitive ability and functioning. It is important to note that a number of moderators (e.g. substance abuse, presence of psychosis) could not be assessed because they were often either exclusion criteria or defined too inconsistently across studies. It is notable that the lack of difference in effect sizes between studies that included only euthymic patients versus those regardless of clinical state suggests contribution of cognitive impairment to disability is at least somewhat independent from symptoms, and do not imply a need to restrict samples to euthymic patients if the goal of a study is identify a relationship between cognitive ability and functioning. Moreover, the consistency across cross-sectional and longitudinal studies implies that the functional impact of cognitive impairments is relatively stable over time, as the effects were not diminished over time, although the within-person stability of the relationship of cognitive and functional domains remains unstudied. Further, as there were no differential effects by demographic or clinical variables other than age, these findings suggest that the functional impact of cognitive impairments may be reasonably universal across patient demographic subgroups. However, our analyses did not consider non-linear relationships (e.g., the potential for adolescent age of onset to interfere with skill acquisition). Finally, it should be noted that the absence of impact of moderators on the pooled cognitive ability- functional outcome correlation does not mean that these variables are not impactful on the relationship, given the methodological limitations described above.

This meta-analysis pointed toward a number of gaps in the literature as well as areas in need of methodological improvement. In regard to study design, the modal study had a modest sample size (n~60), was cross-sectional, and examined the relationship between multiple cognitive tests and a single clinician-reported measure of functioning. Due to inconsistent or failure to reporting, some important moderators were unable to be examined, such as diagnostic heterogeneity (e.g., presence of psychosis) or comorbid factors (e.g., substance abuse). In light of the between- and within-person instability that characterizes bipolar disorder, little is known about the short-term trajectories of cognitive impairment and functional disability, nor the mechanisms by which cognitive abilities impact functioning. Although cognitive ability and symptoms may be somewhat independent contributors to functioning, study designs that model dynamic interactions between symptoms and cognitive impairments may account for greater variation in functioning(7). Thus, longitudinal designs with repeated administration of *both* neurocognitive and functional

measures may better inform the manner in which these aspects of bipolar disorder influence each other.

Improvement in the measures used to quantify cognitive impairment and everyday functioning are necessary. Although we conformed to standard conceptualization of grouping individual neurocognitive tests into domains, it is could be possible that different categorization of neurocognitive tests may have produced greater variability across domains. The lack of a consistent battery of cognitive tests and domain categorization produces significant cross-study comparison problems, an issue that is the focus of productive initiatives in schizophrenia (i.e., MATRICS, CNTRICS). There is recent movement toward a developing a consensus neurocognitive battery in bipolar disorder, which will be a welcome improvement. Given the joint influence of symptoms and cognitive abilities on functioning on bipolar disorder, the inclusion of instruments that bridge cognitive and affective domains (e.g., impulsivity, theory of mind) may predict greater proportion of variation in everyday functioning. Nevertheless, only one study included in this review utilized such a measure.

Perhaps the greatest area of need would be to improve the measurement of functioning. Extant clinician- or self-report measures were less sensitive to cognitive impairment than relatively gross indicators of functional status (e.g., working or not), and yet the majority of studies only reported clinician-rated assessments of functioning. An unexplored question is to what degree cognitive impairments or symptom states impact the validity of clinician- and self-rated functional assessment approaches(27). There was also little information presented on the reliability of measures of functioning, which made interpretation of the quality of measurement or convergence with other measurement modalities impossible. In addition, because the functional domains that were addressed varied widely across measures, there is no understanding of which arenas of functioning are most impacted by cognitive abilities. Performance-based measures were comparable to functional milestones in their relationship to cognitive ability, and are sensitive to change in schizophrenia, yet only two studies employed these measures and more work is needed to establish their utility in bipolar disorder. Thus, a priority for future work will be in optimizing functional measurement across domains and measurement strategies with respect to validity and sensitivity to cognitive impairments.

In conclusion, the primary clinical implication of this review is that, because cognitive impairments account for a significant degree of disability experienced by people with bipolar disorder, cognitive remediation would, if effective, be likely to impact everyday functioning. The magnitude and specificity of impact of cognitive ability on functioning is similar to that seen schizophrenia, as there does not appear to be evidence for any specific cognitive impairments impacting disability more than others. Longitudinal research characterizing the potentially dynamic influences of clinical factors and symptoms, cognitive ability, and everyday functioning will be needed, as well as better understanding of the validity and utility of cognitive-affective instruments and performance-based functioning measures is helping to explain the immense disability that so often accompanies bipolar disorder.

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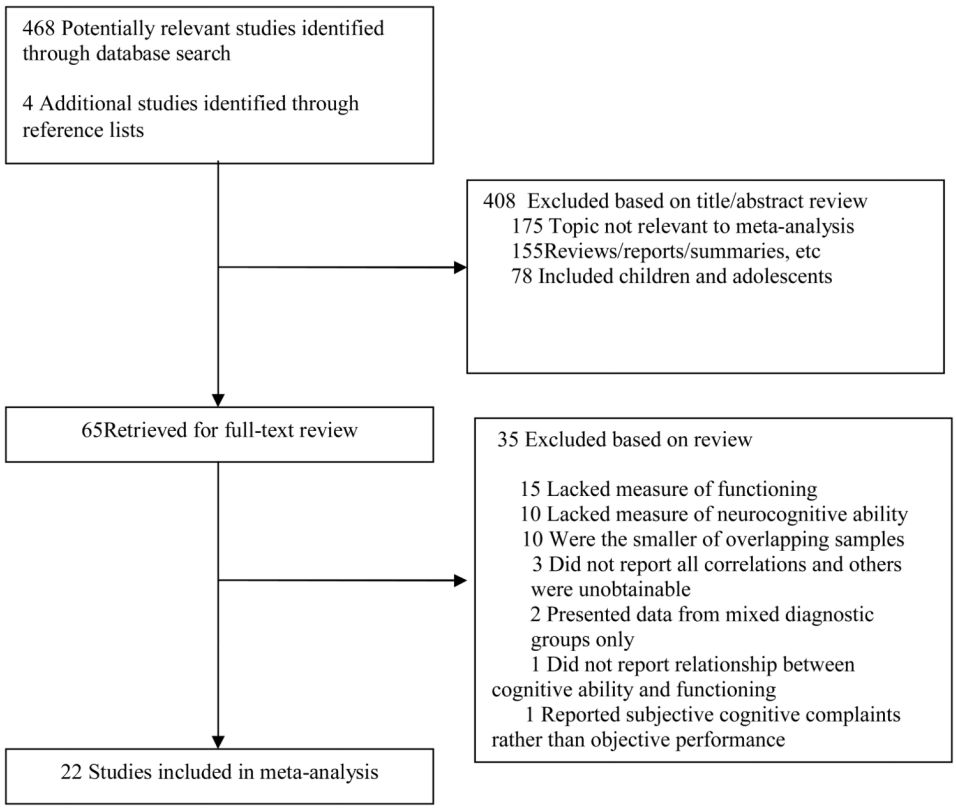

Figure 1.
Study Ascertainment Diagram

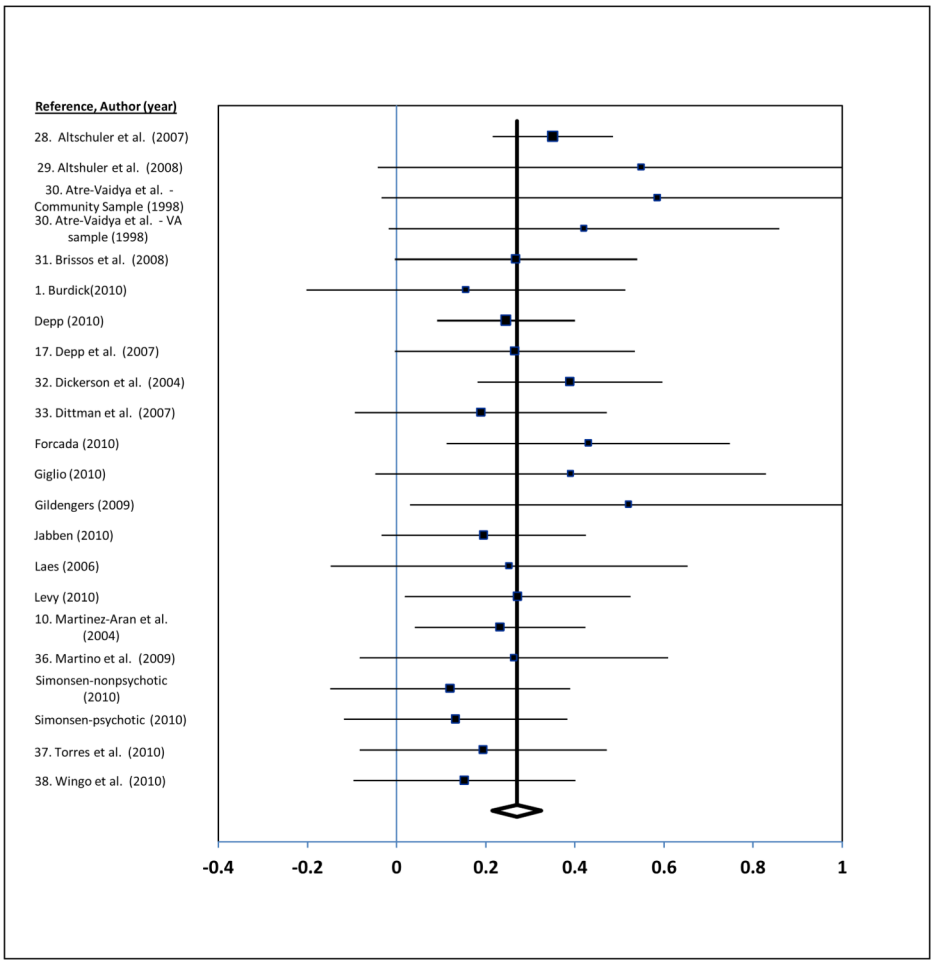

Figure 2.
Forest Plot of the Mean Correlation between Cognitive Ability and Functioning

Table 1

Cognitive Domains and Individual Neurocognitive Tests

Cognitive Domain	Neurocognitive Test
1. Verbal Knowledge	Boston Naming Test Spot the Word Test WAIS Comprehension WAIS Information WRAT Reading WAIS Vocabulary ANART Kaufman Verbal
2. Verbal Learning and Memory	CVLT Trial 1 CVLT Total 1–5 CVLT Short Delay CVLT Long Delay CVLT Recognition Word-list learning Word-list delayed recall WMS Logical Memory Immediate Recall WMS Logical Memory Delayed WMS Paired Associates RAVLT Learning RAVLT Immediate Recall RAVLT Delayed Recall RBANS Verbal Memory Immediate RBANS Verbal Memory Delayed Memory Battery of Signoret
3. Attention/Vigilance	Flanker CPT Reaction Time Neutral Flanker CPT Reaction Time Congruent Flanker CPT Reaction Time Incongruent CPT Correct CPT Time CPT d prime WMS Mental Tracking DRS Attention RBANS Attention Test of Everyday Attention
4. Processing Speed	Stroop Color Task Stroop Word Task Rapid Visual Information Processing Symbol Digit Modalities Test Trailmaking Test, Part A WAIS Digit Symbol Symbol & Letter Cancellation Task
5. Working Memory	Digit Span Letter-Number Sequencing Spatial Working Memory
6. Visual Learning and Memory	Rey-Osterrieth Immediate Rey-Osterrieth Delayed Rey-Osterrieth Recognition WMS Visual Reproduction Immediate WMS Visual Reproduction Delayed Pattern Recognition Spatial Recognition
7. Visuospatial Ability/	Rey-Osterrieth Copy Judgment of Line Orientation Task Simple Drawings Ruff Design Fluency DRS Construction RBANS Visuospatial Construction Kaufman – Non-Verbal
8. Verbal Fluency/Language	Halstead-Wepman Aphasia Phonological Fluency (e.g., Controlled Oral Word Association Test) Semantic Fluency (e.g., Animal

Cognitive Domain	Neurocognitive Test
	Naming)
9. Abstraction and Cognitive Flexibility	WCST Categories Similarities Tower of Hanoi/London DRS Conceptualization Stockings of Cambridge Ideational Fluency WCST Preservative Errors WCST Non-Preservative Errors DRS Initiation/Preservation Stroop Interference/Color Word Task Intra-Extradimensional task EXIT Test Trails B
10. Global Cognitive Ability	Global Neurocognitive Composite Score Dementia Rating Scale RBANS Total German WAIS-R WAIS-III IQ

Table 2

Functional Assessment Method Groups and Individual Functional Measures

Functional Assessment Method Group	Functional Measure
1. Clinician Rating	Global Assessment of Functioning Social Adjustment Scale Multi-dimensional Scale for Independent Functioning Scaled Interview for Maladjustment Social and Occupational Functioning Assessment Scale Functional Assessment Short Test Specific Level of Functioning Scale Strauss-Carpenter Scale
2. Self Report Measure	SF-36 Mental Composite Score SF-36 Physical Composite Score WHO-Quality of Life Scale WHO-Disability Assessment Scale
3. Performance-Based Measure	Social Skills Performance Assessment Performance Assessment of Self-Care Skills
4. Functional Milestone	Employment Status Return to Premorbid Residential Status Return to Premorbid Occupational Status Disability Status

Table 3

Sample Characteristics of Studies Included in the Meta-Analyses

Study	First Author (Year)	N	Mean Age (Yrs)	% Fem	Mean Educ (Yrs)	% Bipolar I	Mean Age of Onset of Illness (Yrs)	Adjusted for Symptom Severity	Cross-Sectional or Longitudinal (Duration of F/U)	Cognitive Domains	Functional Assessment Type (Measure)
1	Altshuler et al (2007) (28)	213	43.3	9	---	---	19.82	No	Cross-Sectional	EC	FM (Employment Status)
2	Altshuler et al (2008) (29).	14	49.7	0	16.3	100	27.70	Yes	Cross-Sectional	VerbLM; EC; Abstract	CL (GAF)
3	Atre-Vaidya et al. (1998)(30) Community Sample	13	47.5	100	13.36	---	29.30	Yes	Cross-Sectional	VerbLM VerbFL;	CL (Scaled Interview for Maladjustment)
4	Atre- Vaidya et al. (1998) (30) Veterans Sample	23	51.9	69	13.46	---	29.50	Yes	Cross-Sectional	VerbLM	CL (Impairment Rating Scale)
5	Brissos et al. (2008) (31)	55	37.1	60	11.20	100	24.69	Yes	Cross-Sectional	VerbLM; EC; VerbFL; PS; A; VA; WM; VisAb; Abstract	SR (WHO-QOL)
6	Burdick et al. (2010) (32)	33	40.2	46	15.3	100	---	Yes	Longitudinal	VerbLM; PS	CL (Global Outcome; Strauss Carpenter)
7	Depp et al. (2007) (17)	67	57.6	28.4	13.9	97	31	Yes	Cross-Sectional	VA; WM; PS; VisLM; VerbLM; EC; VF; VisAb	SR (QWB)
8	Depp et al. (2010) (33)	164	47.6	49.8	14.9	100	19.5	Yes	Cross-Sectional	GC	CL (SLOF); PB (SSPA)
9	Dickerson et al. (2004)(34)	92	41.4	70	14.3	89	20	Yes	Cross-Sectional	VerbLM; PS; GC; A; VisLM; VA; WM	FM (Employment Status)
10	Dittman et al. (2007) (35)	51	42.3	52.7	11.7	71	26.51	Yes	Cross-Sectional	EC; VerbLM; PS; GC; A; VisLM; VA; WM	CL (SAS)
11	Forcada et al. (2010) (36)	41	44.3	51.2		100	24.6	Yes	Cross-Sectional	GC	CL (GAF)
12	Giglio et al. (2010) (37)	81	43.5	71.6	9.8	---	27.5	Yes	Cross-Sectional	EC	CL (FAST)
13	Gildengers et al. (2007)(38)	19	73.6	60	15.7	70	---	No	Cross-Sectional	EC; PS; VisAb	PB (PASS)
14	Jabben et al. (2010) (39)	76	44.4	46		75	---	No	Cross-Sectional	VerbLM; A	CL (GAF)

Study	First Author (Year)	N	Mean Age (Yrs)	% Fem	Mean Educ (Yrs)	% Bipolar I	Mean Age of Onset of Illness (Yrs)	Adjusted for Symptom Severity	Cross-Sectional or Longitudinal (Duration of F/U)	Cognitive Domains	Functional Assessment Type (Measure)
15	Laes (2006)(40)	27	44.2	18.5	15.3	18	---	No	Cross-Sectional	VerbLM; VerbFL; GC; A; Abstract	CL (SAS)
16	Levy (2010)	63	37.5	44	14.6	100	27	No	Cross-Sectional	EC; VerbLM; VerbFL; PS; VisLM; WM; VisAb; Abstract	FM (Disability Status); CL (GAF)
17	Martinez-Aran et al. (2004)(41)	108	41.5	47	11.9	---	25.9	Yes	Cross-Sectional	EC; VerbLM; VerbFL; PS; VisLM; WM	CL (GAF)
18	Martino et al. (2009) (42)	35	43.0	---	13.6	---	30	Yes	Longitudinal, 12 mo.	EC; VerbLM; PS; A; VA; WM; Abstract	CL (GAF; FAST)
19	Simonsen (2010) Nonpsychotic sample	56	36.4	63.6	14.3	29	29.3	No	Cross-Sectional	EC; VerbLM; VerbFL; PS	CL (GAF); SR (SFS)
20	Simonsen (2010) Psychotic sample	64	36.6	53	13.4	82	27.3	No	Cross-Sectional	EC; VerbLM; VerbFL; PS	CL (GAF); SR (SFS)
21	Torres et al. (2010) (43)	53	22.7	53	13.6	100	19.4	No	Longitudinal, 6 mo.	EC; VerbLM; VerbFL; PS; VA; WM; VisAb; Abstract	CL (MSIF; GAF)
22	Wingo et al. (2010) (44)	65	40.1	49.05	15.8	65	15	Yes	Cross-Sectional	EC; VerbLM; VerbFL; PS; VA; WM	FM (Residential Status Index; Vocational Status Index)

Adjustment for Symptom Severity: No=No restriction; Yes=Inclusion of only euthymic patients or Statistical adjustment of symptoms; Cognitive Domain Codes: VA) Verbal Ability, VerbLM) Verbal Learning and Memory, A) Attention/Vigilance, PS) Processing Speed, WM) Working Memory, VisLM) Visual Learning and Memory, VisAb)Visuospatial Ability, VF) Verbal Fluency, Abstract) Reasoning/Abstraction, EC) Executive Control), GC) Global Cognitive Ability; Functional MeasurementCodes:CL) Clinician-Rating; SR) Self-Report; PB) Performance-Based Measure; FM) Functional Milestone; Functional Measure Codes: GAF) Global Assessment of Functioning; MSIF) Multidimensional Scale for Independent Functioning; WHO-DAS) World Health Organization – Disability Assessment Schedule; FAST) Functioning Assessment Short Test; QWB) Quality of Well-Being Scale; SFS) Social Functional Scale; SSPA) Social Skills Performance Assessment

Table 4

Meta-Analyses of Correlation Coefficients Between Cognitive Performance and Everyday Functioning

	k	Mean r	95% Confidence Interval	p-value	Q-Statistic (p-value)
Neurocognitive Domain					
1. Verbal Learning and Memory	17	0.23	0.14–0.31	p<0.001	24.1 (p=0.088)
2. Processing Speed	12	0.23	0.16–0.30	p<0.001	8.0 (p=0.710)
3. Executive Control	11	0.26	0.19–0.33	p<0.001	8.8 (p=0.545)
4. Verbal Fluency	10	0.22	0.13–0.30	p<0.001	5.0 (p=0.833)
5. Reasoning/Problem-Solving	10	0.23	0.14–0.32	p<0.001	3.9 (p=0.686)
6. Working Memory	9	0.29	0.20–0.38	p<0.001	11.4 (p=0.177)
7. Attention/Vigilance	9	0.22	0.13–0.30	p<0.001	4.3 (p=0.833)
8. General Verbal Ability	8	0.24	0.14–0.33	p<0.001	4.6 (p=0.762)
9. Global Cognitive Ability	6	0.34	0.20–0.47	p<0.001	10.7 (p=0.057)
10. Visual Learning and Memory	5	0.26	0.16–0.35	p<0.001	2.7 (p=0.597)
11. Visuospatial Ability	4	0.26	0.12–0.39	p<0.001	1.5 (p=0.656)
Functional Measure Type					
1. Clinician Rated Instrument	16	0.23	0.16–0.29	p<0.001	9.8 (p=0.851)
2. Self-Report Measure	4	0.20	0.07–0.33	p=0.002	1.3 (p=0.795)
3. Functional Milestone	4	0.33	0.24–0.41	p<0.001	4.3 (p=0.432)
4. Performance-Based Task	2	0.32	0.15–0.48	p<0.001	1.2 (p=0.289)