The Relationship Between Neurocognitive and Psychosocial Functioning in Major Depressive Disorder: A Systematic Review

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ABSTRACT

Objective: Neurocognitive deficits are demonstrated in major depressive disorder (MDD) and most likely contribute to the functional impairment experienced by affected individuals. We systematically reviewed the evidence on neurocognitive deficits and their relationship(s) to psychosocial functioning in MDD.

Data Sources: English-language literature was searched in MEDLINE, EMBASE, Science Direct, and PsycInfo databases for the years 1980–October 15, 2013, with the following terms: (*depressive disorder* or *depressive disorder*, *major*) and permutations of (*cognitive*, *neurocognitive*, *neuropsych**) with (*impairment*, *deficit*, *performance*, *test*) and (*quality of life*; *functional outcomes; outcome assessment*, *health care)* or *(assessment*, *outcomes*; *assessment*, *patient outcomes*; *outcomes assessment*; *outcomes assessments*, *patient*).

Study Selection: Inclusion criteria were (1) nongeriatric adults (< 60 years) with a primary diagnosis of MDD by *DSM-IV*, *ICD-9,* or *ICD-10* criteria; (2) use of neuropsychological tests; and (3) use of a specific measure of social, occupational, or daily functioning. Of 488 articles identified in the initial search, 10 met the inclusion criteria.

Data Extraction: Two independent appraisers assessed eligibility of the studies. Substantial heterogeneity in the samples and methods precluded a quantitative meta-analysis, so we performed a narrative descriptive review.

Results: The included studies employed a variety of neurocognitive tests and assessments of psychosocial functioning. Overall, depressed samples had neurocognitive deficits in various domains that were associated with different measures of psychosocial functioning. However, these findings were constrained by methodological limitations of studies.

Conclusions: The limited evidence base suggests that neurocognitive functioning appears to be broadly associated with functional impairment in individuals with MDD, but the quality of evidence is weak. Further studies to clarify the relationship(s) between neurocognitive and psychosocial functioning in MDD will benefit from larger and more homogeneous samples, prospective designs with multivariate analyses, and use of comprehensive assessments of psychosocial functioning that are validated in depressed populations.

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Major depressive disorder (MDD) is a leading cause of functional disability worldwide, especially for young and middle-aged adults.[1] Interestingly, psychosocial functioning in individuals with MDD is not always strongly correlated with symptom severity, and functional impairments may persist even when patients are in symptom remission from a major depressive episode.[2–5] These findings have prompted research into additional causes of functional impairment in patients with MDD, with an aim to develop interventions to improve functioning.

Individuals with MDD usually have cognitive complaints, and neurocognitive deficits are likely to contribute to their functional impairment. Much research has focused on profiling MDD-related neurocognitive impairments, but their prevalence, etiology, and severity are still not well understood. Rather than a consistent profile of neurocognitive impairments, research to date has generated at least some evidence of diminishment or impairment across most domains of cognitive function, including (1) information processing speed,[6] (2) sustained and selective attention,[7,8] (3) different aspects of learning and memory,[8,9] and (4) executive functioning.[10–14] There is also evidence that cognitive deficits may persist even following the remission of a depressive episode.[15–17]

In other chronic psychiatric illnesses such as schizophrenia and bipolar disorder, neurocognitive impairments have been identified as an important component of the illness and have been shown to predict both clinical and functional outcomes.[18–22] Poorer neurocognitive functioning is also associated with worse clinical and functional outcomes in late-life depression.[23,24] The objective of this work was to systematically review studies on neurocognitive deficits and their impact on aspects of psychosocial functioning in working-age adults with MDD.

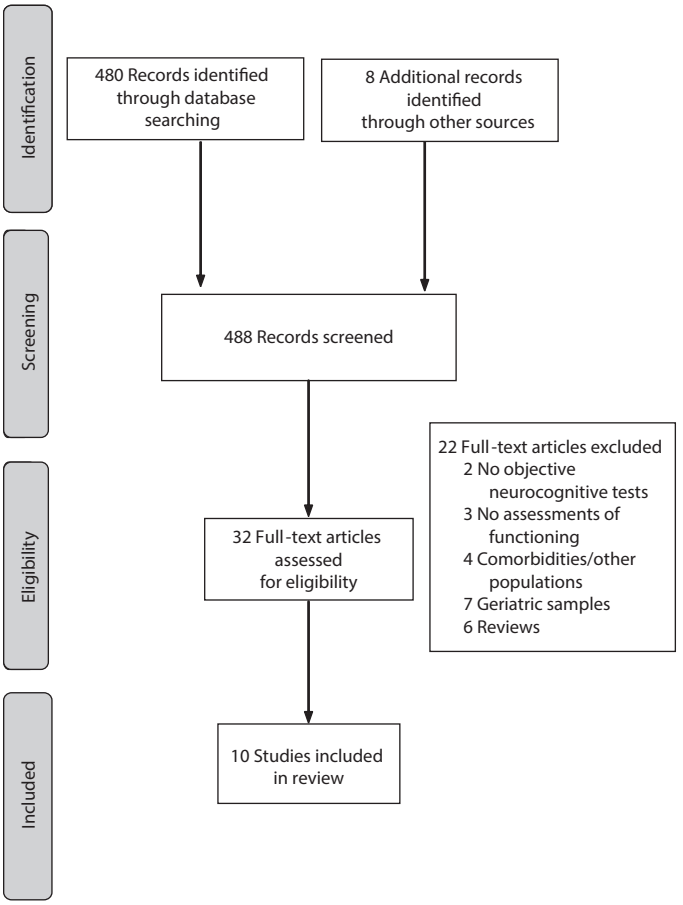
DATA SOURCES

The English-language literature up to and including October 15, 2013, was searched through the MEDLINE, EMBASE, ScienceDirect, and PsycInfo databases (Figure 1). Three main sets of general and Medical Subject Headings (MeSH) search terms (combined within each set with an OR operator) were combined with an AND operator: *depressive disorder/* or *depressive disorder*, *major/*; permutations of *cognitive*, *neurocognitive*, and *neuropsych** with *impairment*, *deficit*, *performance*, and *test*; and *quality of life or functional outcomes or outcome assessment* (*health care*) OR *assessment*, *outcomes* OR *assessment*, *patient outcomes* OR *outcomes assessment* OR *outcomes assessments*, *patient*. When appropriate, results were limited to articles on human adult populations, with the search terms as major subjects, or with *neuropsychological tests* as a keyword. Previously identified articles were also reviewed for inclusion. After all relevant publications were collected, their references were searched for additional articles.

Clinical Points

- Neurocognitive deficits are associated with impairment in psychosocial functioning in individuals with major depressive disorder, although the existing scientific literature on this topic is still limited.
- Intervention research should focus on effects of treatment in improving both neurocognitive and psychosocial functioning.
- Clinicians should monitor both psychosocial functioning and cognitive symptoms as important aspects of depression treatment.

Figure 1. PRISMA[a] Flow Diagram for Study Selection



[a]Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org).

Study Selection

Studies were selected for the review if they included the following: (1) subjects meeting validated diagnostic criteria for unipolar MDD (eg, defined according to the *DSM-IV*, *ICD-9*, or *ICD-10*), (2) a nongeriatric adult population (aged < 60 years), (3) an objective measure of neurocognitive functioning (ie, neuropsychological tests), and (4) a specific assessment of psychosocial functioning (eg, social or work functioning scale).

Data Extraction

Two reviewers (V.C.E., R.W.L.) independently examined the studies to determine eligibility, and conflicts were resolved by consensus. Because this study consisted of a review of published, publicly available research data, institutional review board approval was not needed.

RESULTS

The systematic search process is illustrated in Figure 1. The initial database search yielded 488 articles (MEDLINE = 136, EMBASE [1990–current] = 39, ScienceDirect [all years] = 148, PsycINFO [1998–2002] = 157, other = 8). Of those, 32 had titles and/or abstracts that suggested they might be eligible for inclusion in the review; all other articles were clearly off topic, most likely identified in the initial search because of the comprehensive set of search terms. These 32 articles were examined independently by 2 reviewers. Articles were excluded due to a focus on a geriatric population, qualitative reviews, a focus on samples with significant comorbidities or samples without MDD as a primary diagnosis (eg, bipolar disorder, traumatic brain injury), and a lack of assessments of either functional outcomes or objective neurocognitive deficits.

Ten articles met the inclusion criteria. Two of these studies[25,26] had been identified and summarized in detail in a previous review of neurocognitive functioning and occupational functioning.[27] Because the studies used varied methodologies and different assessments of cognition and psychosocial functioning, we conducted a narrative descriptive review instead of a quantitative meta-analysis.

Sample Characteristics and Assessments

Sample demographic and clinical characteristics, neurocognitive tests, and assessments of functioning for the 10 studies are summarized in Table 1. Patient samples were demographically and clinically heterogeneous. Although most studies excluded participants with neurologic or neurodegenerative illness (eg, dementia), history of moderate to severe traumatic brain injury, severe learning disabilities, psychotic disorders, and other conditions that could affect neurocognitive functioning, they varied considerably in whether they included, excluded, or controlled for other psychiatric and general medical conditions and other clinical factors that could affect both neurocognition and psychosocial functioning, such as psychotic symptoms and medications. Patient samples also varied considerably in depression severity, ranging from outpatients in remission[28] to hospitalized patients awaiting electroconvulsive therapy,[29] although most samples consisted of outpatients with MDD who were at least moderately depressed. Two studies examined treatment-resistant samples.[29,30] Five studies included a comparison sample of matched healthy subjects or a normative population sample.[25,26,28,31,32]

Studies used a variety of neuropsychological tests and test batteries to assess cognitive functioning (Table 1). To facilitate comparisons across studies, we focused on

Table 1. Sample Characteristics and Assessments for Included Studies

Study (country)	Patients/Healthy Subjects (if applicable), N	Age, Range, Mean (SD), y[a]	Employment Status	Depression Diagnosis	Depression Severity, Mean (SD)	No. of Depressive Episodes, Mean (SD)	Psychiatric Comorbidity	Psychosis	Medication Status	Neurocognitive Tests	Assessments of Functioning[b]
Cross-sectional design											
Baune et al[25] (Australia)	70 Outpatients Current MDD, 26 Past MDD, 44 206 Age- and gender-matched healthy subjects	20–77; Current MDD: 46.0 (12.1) Past MDD: 44.2 (15.9)	Not reported	MDD by *DSM-IV* criteria (MINI)	HDRS-17 Current MDD, 18.0 (5.9) Past MDD, 6.8 (4.3)	Not reported	Yes Current MDD, 69% Past MDD, 48% Across all MDD subjects GAD, 49% Dysthymia, 41% Panic disorder, 29% Alcohol dependence, 7%	Excluded	Current MDD: 85% taking medications SSRI, 42% SNRI, 27% Other antidepressant, 15% Past MDD: 86% taking medications SSRI, 48% SNRI, 18% TCA, 5% Other antidepressant, 14%	Repeatable Battery for the Assessment of Neuropsychological Status,[33] including Attention: Digit Span, Coding Tests Immediate memory: List Learning, Story Memory Tests Delayed memory: List Learning Free Recall, List Learning Recognition, Story Memory Free Recall, Figure Free Recall Tests Visuospatial/constructional: Figure Copy, Line Orientation Tests Verbal fluency/language: Picture Naming, Semantic Fluency Tests	Medical Outcomes Study Health Survey Short-Form, 36 item (SF-36)[34]; Activities of Daily Living (ADL)[35]; Instrumental Activities of Daily Living (IADL)[36]; Employment status
Godard et al[26] (Canada)	16 Outpatients 30 Age- and education-matched healthy subjects	18–65, 49.5 (12.3)	Not reported	MDD by *DSM-IV* criteria (MINI)	MADRS, 28.5 (5.1) HDRS-29, 31.2 (5.1)	Not reported	Yes Personality disorders, 38% Anxiety disorders, 19% Substance use disorders, 6% Other, 12%	3/16 (19%) had either current or past psychotic symptoms	69% Taking medications Antidepressants, 25% Benzodiazepines, 44% Mood stabilizers, 25% Antipsychotics, 19%	CogitEx II[37] and Delis-Kaplan Executive Function System (D-KEFS)[38] test batteries and others, including Executive function: Sequential Memorization Test, Verbal Fluency Test, Design Fluency Test, Tower Test, Twenty Questions Test Attention/Processing speed: Simple Reaction Time Test, Divided Attention Test, Conditional Reaction Time Test, Choice Reaction Time Test, Continuous Performance Test (CPT), Color-Word Interference Test Verbal learning and memory: California Verbal Learning Test (CVLT) Visuospatial: Block Design Test	Longitudinal Interval Follow-Up Evaluation—Range of Impaired Functioning Tool (LIFE-RIFT)[39]
Gupta et al[30] (Canada)	33 Outpatients	18–74, 45.8 (13.0)	Employed: 30% Unemployed: 70%	MDD by *DSM-IV* criteria (MINI), with treatment resistance[c]	MADRS, 25.1 (8.1)	Not reported	Yes Anxiety disorders, 33% Alcohol dependence/abuse, 6% Other substance dependence/abuse, 6% Borderline personality disorder, 6%	2/33 (6%) had past psychotic symptoms	Not reported, but sample most likely taking medications due to treatment-resistant depression and comorbidities	Executive function: Stroop Color-Word Test (response inhibition), Trail-Making Test (TMT) Part B Attention: CPT-Identical Pairs Version Processing speed: Symbol Coding Task, TMT Part A Verbal learning/(working) memory: Hopkins Verbal Learning Test, Letter Number Sequencing Test (LNS) Verbal fluency: Controlled Oral Word Association Test (COWAT) and Animal Naming Tests Composite score (NCS): Equally weighted average of all domains' *z* scores	LIFE-RIFT, Social Skills Performance Assessment,[40] Advanced Finances Task (AFT)[41]

(continued)

Table 1 (continued). Sample Characteristics and Assessments for Included Studies

Study (country)	Patients/Healthy Subjects (if applicable), N	Age, Range, Mean (SD), y[a]	Employment Status	Depression Diagnosis	Depression Severity, Mean (SD)	No. of Depressive Episodes, Mean (SD)	Psychiatric Comorbidity	Psychosis	Medication Status	Neurocognitive Tests	Assessments of Functioning[b]
McCall and Dunn[29] (United States)	77 Inpatients awaiting electroconvulsive therapy	56.5 (15.8)	Not reported; all were inpatients and thus not working	MDD by *DSM-IV* criteria (SCID), 81% with treatment resistance[d]	HDRS-21, 28.9 (5.0)	2.6 (1.7)	Not reported	12/77 (16%) had current psychotic symptoms	Not reported, but all were inpatients and thus most likely treated with medications	Global cognition: Mini-Mental Status Examination Verbal memory: Delayed recall on Rey Auditory Verbal Learning Test (RAVLT) Nonverbal memory: Rey Figure Test	Personal Self-Maintenance Scale[36] (measure of ADL), IADL,[36] Daily Living and Role Functioning,[42] Relation to Self and Others[42]
Naismith et al[32] (Australia)	21 Outpatients 21 Age-, sex-, and education-matched healthy subjects	25–69, 53.9 (11.8)	Not reported	MDD by *DSM-IV* criteria (MINI)	HDRS-17, 21.7 (4.4)	3.6 (3.3)	Not reported	Excluded	90% Taking medications SSRI, 38% SNRI, 33% Lithium, 14% TCA, 10% MAOI, 5% Other antidepressant, 5% Atypical antipsychotic, 5%	Executive functioning: TMT Part B, Stroop Color Word Test, computerized Tower of London test Processing/psychomotor speed: Choice Reaction Time Test and TMT Part A Initial learning: logical memory subtest of Wechsler Memory Scale-Revised (WMS-R), RAVLT Memory retention: RAVLT Premorbid functioning: National Adult Reading Test (NART)	Medical Outcomes Study Health Survey Short-Form, 12 item,[43] Brief Disability Questionnaire (BDQ)[44]
Shimizu et al[28] (Japan)	43 Outpatients in remission 43 Age- and education-matched healthy subjects	20–59, 38.3 (8.9)	All patients on long-term disability from work	MDD by *DSM-IV* criteria (MINI), currently in remission	HDRS-17, 2.9 (2.2)	2.3 (1.4)	Comorbid Axis I and II diagnoses excluded	Excluded	95% Taking medications; specific medications not reported	Executive function: Wisconsin Card Sorting Test (WCST), TMT Attention/processing speed: CPT omissions/commissions and response time Immediate and delayed memory: Auditory Verbal Learning Test (AVLT) Verbal fluency: Word Fluency Test	SF-36

(continued)

Table 1 (continued). Sample Characteristics and Assessments for Included Studies

Study (country)	Patients/Healthy Subjects (if applicable), N	Age, Range, Mean (SD), y[a]	Employment Status	Depression Diagnosis	Depression Severity, Mean (SD)	No. of Depressive Episodes, Mean (SD)	Psychiatric Comorbidity	Psychosis	Medication Status	Neurocognitive Tests	Assessments of Functioning[b]
Prospective design											
Jaeger et al[45] (United States)	48 Inpatients	18–59, 39.6 (12.7)	Not reported; all were inpatients at initial assessment and thus not working	MDD by *DSM-IV* criteria (SCID)	HDRS-17 At initial assessment, 16.5 (7.1) At 6-mo follow-up, 11.7 (6.6)	Not reported	Not reported	10/48 (21%) had current psychotic symptoms	At initial assessment: Antidepressants, 63% Antipsychotic, 35% Anticonvulsants, 29% Anxiolytics, 19% Mood stabilizers, 6% Hypnotics/sedatives, 6% At 6-mo follow-up: 88% Taking medications; specific medications not reported	Executive functioning: WCST perseveration errors, Ruff Figural Fluency Test unique designs, COWAT correct, Animal naming Attention/processing speed: Concentration-Endurance Test (D2) Errors, Stroop Words, Stroop Colors, Trails A Time, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol (Raw) Motor speed: Finger tap preferred, nonpreferred, Grooved Peg preferred, nonpreferred Verbal/visual learning/memory: WMS-R Verbal paired I, II, Visual Paired I, II Working memory: D2 Fluctuation, WAIS-R Digit Span (Forward), LNS Total Correct, LNS Longest Span, WAIS-R Arithmetic (Raw), WAIS Digit Span (Back), WMS-R Logical/Memory Verbal fluency: COWAT correct, Animal naming Nonverbal functioning: WAIS-R Block Design (Raw), WAIS-R Picture Comprehension (Raw), WAIS-R Similarities (Raw) Verbal knowledge: WAIS-R Vocabulary (Raw), WAIS-R Comprehension (Raw), WAIS-R Similarities (Raw)	Multidimensional Scale of Independent Functioning (MSIF)[46]
Withall et al[47] (Australia)	48 Inpatients at initial assessment	20–60 38.0 (10.6)	At initial assessment: Unemployed or pension/retired, 35% Part-time, 31% Full-time, 33% At 3 months after discharge: Unemployed or pension/retired, 33% Part-time, 21% Full-time, 46%	MDD by *DSM-IV* criteria	HDRS-17 At initial assessment, 28.3 (5.7) At 3-mo after discharge, 10.7 (6.0)	Not reported	Comorbid Axis I diagnoses excluded	Not reported	At initial assessment, 56% taking medications SSRI/SNRI, 56% Benzodiazepines, 2% Atypical antipsychotic, 2% At 3 mo after discharge: SSRI/SNRI, 90%	Executive function: WMS-R Digit-Span subtest (Forward and Backward), Stroop Color Word Test, Shortened WCST, Modified Six Elements Test Attention: WMS-R Digit-Span subtest Motor speed: Computerized Simple Reaction Time test Verbal learning and memory: CVLT Delayed free recall, event-based prospective memory: Prospective Memory Task Verbal fluency: COWAT Premorbid functioning: NART	Social and Occupational Functioning Assessment Scale[48]; Employment status

(continued)

Table 1 (continued). Sample Characteristics and Assessments for Included Studies

Study (country)	Patients/Healthy Subjects (if applicable), N	Age, Range, Mean (SD), y[a]	Employment Status	Depression Diagnosis	Depression Severity, Mean (SD)	No. of Depressive Episodes, Mean (SD)	Psychiatric Comorbidity	Psychosis	Medication Status	Neurocognitive Tests	Assessments of Functioning[b]
Airaksinen et al[49] (Sweden)	76 Currently depressed persons selected from a sample of 125 depressed participants in a population-based longitudinal study on mental health At 3-year follow-up: 41 still depressed, 35 recovered	20–64 At 3-year follow-up: Still depressed, 46.0 (10.9) Recovered, 45.4 (11.8)	Not reported	MDD, dysthymic disorder, or mixed anxiety depressive disorder by *DSM-IV* criteria	Not reported	Not reported	Only anxiety symptoms reported At initial assessment: Still depressed, 61% Recovered, 69% At 3-y follow-up: Still depressed, 63% Recovered, 6%	Not reported	At initial assessment, 52% taking medications: Depressed, 32% Recovered, 20% At 3-y follow-up, 72% taking medications: Depressed, 46% Recovered, 26%	Delayed and verbal memory: Free recall, cued recall, utilization of retrieval support	BDQ–5-item Role Disability Scale
Godard et al[31] (Canada)	13 Outpatients 30 Age- and education-matched healthy subjects	49.3 (12.0)	Not reported	MDD by *DSM-IV* criteria (MINI)	MADRS At initial assessment, 26.5 (7.3) At 12-mo follow-up, 13.3 (9.4)	2.2 (1.5)	Yes Personality disorders, 31% Anxiety disorders, 15% Substance use disorders, 8% Other, 14%	1/13 (8%) had current psychotic symptoms; 1/13 (8%) had past psychotic symptoms	At initial assessment: Antidepressants, 100% Benzodiazepines, 92% Mood stabilizers, 54% Antipsychotics, 54% Hypnotics/sedatives, 8% At 12-mo follow-up: Not reported	CogitEx II and D-KEFS test batteries and others, including Executive function/verbal fluency: Sequential Memorization Test, Verbal Fluency Test, Design Fluency Test, Tower Test, Twenty Questions Test Attention/processing speed: Simple Reaction Time Test, Divided Attention Test, Conditional Reaction Time Test, Choice Reaction Time Test, CPT, Color-Word Interference Test Verbal learning and memory: CVLT Visual functions: Block Design Test General intelligence: WAIS Vocabulary and Matrix Reasoning	LIFE-RIFT

[a]For patient groups only.
[b]Assessments of functioning are described in greater detail in Table 2.
[c]Patients had at least Stage I treatment resistance according to criteria defined by Thase and Rush.[50]
[d]Treatment resistance was assessed by a modified rating scale.[51]
Abbreviations: ECT = electroconvulsive therapy, HDRS-17 = 17-item Hamilton Depression Rating Scale, HDRS-21 = 21-item Hamilton Depression Rating Scale, HDRS-29 = 29-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, MINI = Mini-International Neuropsychiatric Interview, NCS = Neurocognitive Composite Score, SCID = Structured Clinical Interview for *DSM-IV*, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 2. Assessments of Psychosocial Functioning in Included Studies

Assessment	Type	Brief Description
Brief Disability Questionnaire[44]	Self-report	Assesses disability in everyday activities, with physical and mental health, and functional domains, eg, "Have your personal problems decreased your motivation for work?"
Daily Living and Role Functioning (DLRF)[42] and Relation to Self and Others (RSO)[42]	Self-report	Subscales of the Behavior and Symptom Identification Scale (BASIS-32) assessing satisfaction with daily living and role functioning (DLRF) and interpersonal functioning, relationships, and self-regulation (RSO) Considered assessments of quality of life
Index of Activities of Daily Living (ADL),[35] Instrumental Activities of Daily Living (IADL)[36]	Clinician rated	Assesses independence in basic life activities, with categories bathing, dressing, toileting, transferring, continence, and feeding (ADLs), as well as activities including shopping, housekeeping, handling finances, and taking medications (IADLs)
Longitudinal Interval Follow-Up Evaluation—Range of Impaired Functioning Tool (LIFE-RIFT)[39]	Clinician rated	Assesses impairment in work (maximum of employment, household, student items), interpersonal (maximum of family, friends), life satisfaction, and recreation subscales; subscale scores can then be summed to yield a global score
Medical Outcomes Study Health Survey Short-Form, 12- and 36-item versions[34,43]	Self-report	Assesses physical and psychological health and quality of life, including physical functioning, role physical functioning, bodily pain, general health perceptions, vitality, social functioning, role emotional functioning, and mental health
Multidimensional Scale of Independent Functioning[46]	Clinician rated	Assesses degree of (1) role responsibility, (2) role support, and (3) performance in work, education, and residential domains
Physical Self-Maintenance Scale[36]	Clinician rated	An adapted version of the Index of Activities of Daily Living[35]
Social and Occupational Functioning Assessment Scale[48]	Clinician rated	Assesses social, occupational, and interpersonal functioning with a single global score from 0 to 100
Social Skills Performance Assessment (SSPA)[40] and Advanced Finances Task (AFT)[41]	Performance based (laboratory tasks)	Assesses competence through role-playing in 2 different social situations (SSPA) and adaptive skills through a series of mock financial tasks (AFT)

patients' performance in the cognitive domains purportedly assessed by the neurocognitive tests in each study. These included attention, psychomotor speed, processing speed, verbal and visual learning, immediate and delayed memory, visuospatial abilities, verbal/ideational fluency, executive functioning, and global cognition.

Studies also employed a variety of self-report, clinician-rated, and laboratory assessments to assess functioning and disability (summarized in Table 2). The majority of assessments were self-report questionnaires and interview-based rating scales; 2 studies[25,47] also examined employment status. Three studies[25,28,32] used versions of the Medical Outcomes Study Health Survey Short-Form, 36 item (SF-36)[34] and 12-item (SF-12)[43] versions, which are considered measures of health-related quality of life rather than specific measures of social or occupational function. Two studies[25,29] used assessments of Activities of Daily Living (ADL) (the Katz Index of Activities of Daily Living[35] and the Personal Self-Maintenance Scale [PSMS][36]) and Instrumental Activities of Daily Living (IADL),[36] which are measures designed for patient populations and conditions other than MDD. Only 1 study[30] used controlled laboratory tasks as well as clinician-rated (interview-based) assessments of functioning, thereby assessing both functional competence ("what one can do") in a controlled setting and functional performance ("what one actually does") in everyday life.

Is Neuropsychological Performance Related to Psychosocial Functioning in MDD?

Studies used various methodological and statistical approaches to explore the relationship between neurocognitive and functional assessments (summarized in Table 3). Two studies[26,45] examined only correlational relationships, and 5 studies[28–30,32,47] used multivariate regression analyses. Two prospective studies[31,49] did not assess this relationship directly, but instead conducted separate analyses to examine how each independently changed over time.

Despite their demographic, clinical, and methodological heterogeneity, all studies found that depressed patients were impaired in at least 1 cognitive domain, and all 8 studies that directly assessed the relationship between cognition and psychosocial functioning found that performance in at least 1 cognitive domain (most commonly executive function, attention, psychomotor speed, and certain aspects of memory) was associated with a functional outcome (Table 3). In cross-sectional studies, cognitive domains associated with psychosocial functioning were executive function and attention,[25,26,30] psychomotor and processing speed,[26,32] and verbal and visual memory, both immediate and delayed.[25,26,28] In the study using laboratory performance testing for psychosocial functioning,[30] sustained attention was associated with both social competence (assessed with the Social Skills Performance Assessment[40]) and recreational functioning (assessed with the Longitudinal Interval Follow-Up Evaluation—Range of Impaired Functioning Tool,[39] recreation subscale), whereas executive function was associated with adaptive competence (assessed with the Advanced Finances Task[41]).

However, the quality of this evidence base is limited. For example, 1 cross-sectional study[28] found a significant relationship only between delayed verbal memory and the general health perceptions subscale of the SF-36, which is not a measure of psychosocial functioning. Other studies found significant correlations between neurocognitive and functioning assessments that, on subsequent multivariate analyses, were no longer significant. For example, McCall and Dunn[29] found several significant correlations between neurocognitive tests of verbal learning and delayed memory and functional measures (IADL and the relation to self and others subscale of the Behavior and Symptom Identification Scale[42]), but regression analyses showed that the only significant cognition predictor of psychosocial functioning was a global measure (the Mini-Mental Status Examination[52]).

Table 3. Summary of Studies Exploring Relationships Between Neurocognitive and Psychosocial Assessments[a]

			Neurocognitive Domains									Psychosocial Assessments				
Study	N (MDD)	Healthy Controls	Executive Function	Attention	Processing Speed	Psychomotor Speed	Verbal/ Visual Memory	Immediate/ Delayed Memory	Verbal Fluency/ Language	Visuo-Spatial Abilities	Global Cognition	Activities of Daily Living	Health-Related Quality of Life	General Functioning	Other	Comments
Cross-sectional design																
Baune et al[25]	70	Yes		X[1]			O[1] Verbal Visual	X[1] Immediate delay	X[1]	X[1]		ADL; IADL	SF-36		Employment status[1]	Clinical heterogeneity, including high rates of comorbidity and medications; ADL/IADLS, may not be sensitive for MDD
Godard et al[26]	16	Yes	X[2,3,5]	X[2,3]	X[3]		X[2,4,5] Verbal	O[4,5] Immediate O[2] Delay		X				LIFE-RIFT: work,[2] interpersonal,[3] and life satisfaction[4] subscales and global score[5]		Clinical heterogeneity, including high rates of comorbidity and extensive medications; small sample size; correlational analyses only; cognitive tests selected for demonstrated sensitivity to impairments in depressed samples
Gupta et al[30]	33	No	X[6]	X[7]	X		X Verbal		X		X			LIFE-RIFT: recreation[7] subscale only	SSPA[7] AFT[6]	Treatment-resistant sample; controlled laboratory tasks of functioning; small sample size; cognitive tests selected for demonstrated sensitivity to impairments in depressed samples; multivariate analyses
McCall and Dunn[29]	77	No					X Verbal Visual	X Delay			X[8]	PSMS (ADL); IADL[8];		DLRF; RSO		Assessments of functioning, especially PSMS, may not be sensitive for MDD; older, treatment-resistant sample; multivariate analyses
Naismith et al[32]	21	Yes	X		O[9]	X[9]	X Verbal Visual	X Delay					SF-12 mental subscale	BDQ: physical disability only[9]		Assessments of functioning may not be sensitive for MDD; older sample; small sample size; multivariate analyses
Shimizu et al[28]	43	Yes	X	X	X		O[10] Verbal	X Immediate X[10] Delay	X				SF-36: general health perceptions only[10]			Remitted depression sample; controlled for other psychiatric and medical comorbidities; multivariate analyses
Prospective design																
Jaeger et al[45]	48	No	X	X[11]		X[11]	X verbal/ visual[11]		X[11]	X[11]				MSIF global score[11]		Comorbidities not reported; correlational analyses only
Withall et al[47]	48	No	X[12]	X	X		X[12] Verbal	X[12] Delay	X					SOFAS[12]	Employment status	SOFAS scores may have been inflated as patients transitioned from inpatient to outpatient during follow up; variable time to follow up; multivariate analyses

[a]An X indicates cognitive domains that were assessed in each study as categorized by the authors, whereas an O indicates other possible categorizations of assessed cognitive domains, according to the specific tests used. A shaded cell indicates that performance in that neurocognitive domain was significantly related to a functional outcome, denoted by a superscript number and underlined.

Abbreviations: ADL = Activities of Daily Living; AFT = Advanced Finances Task; BDQ = Brief Disability Questionnaire; DLRF = Daily Living and Role Functioning; IADL = Instrumental Activities of Daily Living; LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation—Range of Impaired Functioning Tool; MSIF = Multidimensional Scale of Independent Functioning; PSMS = Personal Self-Maintenance Scale; RSO = Relation to Self and Others; SF-12 = Medical Outcomes Study Health Survey Short-Form, 12 item; SF-36 = Medical Outcomes Study Health Survey Short-Form, 36 item; SOFAS = Social and Occupational Functioning Assessment Scale; SSPA = Social Skills Performance Assessment.

Table 4. Summary of Prospective Studies With Only Separate Analyses of Neurocognitive and Psychosocial Functioning[a]

			Neurocognitive Domains								Psychosocial Assessments			
Study	MDD, N	Healthy Controls	Executive Function	Attention	Processing Speed	Psychomotor Speed	Verbal/ Visual Memory	Immediate/ Delayed Memory	Verbal Fluency/ Language	Visuo-Spatial Abilities	Global Cognition	Activities of Daily Living	Health-Related Quality of Life	General Functioning	Other	Comments
Airaksinen et al[49]	76	No					X Verbal	X Delay						BDQ: Role Disability Scale		Limited assessments of cognitive domains; separate analyses of cognition and functioning only
Godard et al[31]	13	Yes	X	X	O		X Verbal		O	X				LIFE-RIFT		Small sample size; separate analyses of cognition and functioning only

[a]An X indicates cognitive domains that were assessed in each study as categorized by the authors, whereas an O indicates other possible categorizations of assessed cognitive domains, according to the specific tests used.

Abbreviations: BDQ = Brief Disability Questionnaire, LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation—Range of Impaired Functioning Tool, MDD = major depressive disorder.

Similarly, Naismith et al[32] found that memory retention significantly correlated with the functional disability subscale of the Brief Disability Questionnaire[44] but, in multivariate analyses, no longer remained a significant predictor. In these analyses, psychomotor speed was a predictor of physical disability but not functional disability.

Prospective studies can provide stronger evidence for a direct relationship between neurocognitive and psychosocial functioning by showing that 1 variable (ie, neurocognitive deficits) at baseline predicts the outcome of another (psychosocial functioning) at follow-up. Only 2 prospective studies examined the relationship between cognition and functioning directly. In 1 study of 48 inpatients with MDD,[47] aspects of executive functioning (ie, cognitive flexibility and error monitoring) and memory predicted scores at 3-month follow-up on the Social and Occupational Functioning Assessment Scale.[53] In the other prospective study,[45] coincidently also of 48 inpatients with MDD, nonverbal reasoning, visual memory, and fine motor dexterity and speed at baseline were correlated with scores from the Multidimensional Scale of Independent Functioning[46] at 6-month follow-up, even after controlling for depression severity.

Two other prospective studies (Table 4) conducted analyses on cognitive and psychosocial functioning separately, and so cannot address the direct relationship between cognition and functioning. One small study[31] (n = 13 outpatients) found that both cognition and psychosocial functioning (as assessed by the Longitudinal Interval Follow-up Evaluation) improved over 12 months, whereas the other[49] (n = 76 depressed persons with various diagnoses of MDD, dysthymia, and mixed anxiety depressive disorder) found that functional outcomes (on a 5-item subscale of the Brief Disability Questionnaire) improved at 3-year follow-up, but the verbal episodic memory of both the still-depressed and recovered groups remained unchanged. The latter findings are limited by the various depression diagnoses (the number of subjects with MDD was not reported) and the limited number of neuropsychological tests.

Because most assessments of functioning consisted of a combination of basic personal, occupational, and social domains, it is difficult to draw conclusions about neurocognitive effects on specific areas of psychosocial functioning. Nevertheless, functioning in areas such as employment and education, recreation, social skills, financial planning, and domestic responsibilities, and quality of life in mental health and perceptions of health, were implicated across studies.

DISCUSSION

An extensive body of research suggests that MDD is associated with neurocognitive deficits; these deficits are likely to contribute to the social and occupational impairments observed in patients diagnosed with depression.[54] We systematically and critically reviewed existing studies on neurocognitive deficits and their impact on psychosocial functioning in adults with MDD. Ultimately, only 10 studies met the inclusion criteria, and all had methodological limitations that temper the findings. Most had small sample sizes, ranging from 13 to 77 participants with MDD. They employed a wide range of neurocognitive test batteries and assessments of psychosocial functioning, several of which may not be optimal for the young- to middle-aged adult samples studied. Studies also varied in their design and analyses (prospective versus cross-sectional, time of data collection in the course of illness, multivariate versus correlational analyses, and comparisons with healthy subjects or normative data). Only 5 studies investigated multivariate models (thus controlling for intercorrelations among variables) of the relationship between cognitive and psychosocial functioning, and only 1 of these did so prospectively.

Notwithstanding these limitations, these studies provide some limited evidence that neurocognitive deficits are significant and clinically important factors related to the quality of life and level of social and occupational functioning of individuals with MDD. All studies that directly assessed the relationship between cognition and functioning found that performance in at least 1 cognitive domain was broadly associated with or predicted a functional outcome.

Several factors may contribute to the inconsistent functional outcomes for specific neurocognitive domains across studies. These include differences in patient

demographics such as age, education, and socioeconomic status[55]; illness severity (including severity of current symptoms,[56,57] as well as age at onset, number of episodes,[58] and chronicity[59]); general medical and psychiatric comorbidity[60,61]; concomitant medications; timeframe for data collection; and, importantly, the reliability, validity, and sensitivity of the assessments of neurocognitive and psychosocial functioning used. It may be especially important to use adequately sensitive and validated assessments of functioning in higher-functioning samples, such as depressed patients who are maintaining stable employment, to ensure that any subtle but important changes in functioning are captured. Indeed, some studies included in this review used assessments of functioning that most likely lack the appropriate sensitivity for a depressed, nongeriatric adult sample. For example, the ADL (including the PSMS) and IADL questionnaires were developed specifically for use in older adults who may be unable to care for themselves due to aging-related physical and mental disabilities, and they assess quite basic aspects of functioning.[35,36] It is therefore unsurprising that these scales were not associated with neurocognitive functioning in MDD studies.

There are other challenges in assessing mental health–related functional impairments. One important distinction is that between patients' functioning and patients' perceptions of their quality of life. Both are important and related outcomes that were included under the umbrella of "psychosocial functioning" in this review. Another important consideration is whether assessments of functioning are subjective (self-report or interview-based, which rely on patients' perceptions of his or her level of functioning) or more quantifiable, objective, and separate from self-perception (eg, employment status, number of hours scheduled and worked, observation-based assessments, laboratory tasks). Subjective measures of functioning are often simpler, easier, and less time-consuming to use than observation-based and laboratory assessments, but they may be vulnerable to patients' biases and thus may provide less accurate information about true levels of functioning. On the other hand, objective measures of functioning may also be influenced by external factors, such as patients' degree of social support; the nature of their work; educational, social, and domestic responsibilities; and the institutional supports (such as sick leave, disability, and unemployment insurance) available to them. Measures that take into account contextual factors might help avoid these pitfalls. For example, the Multidimensional Scale of Independent Functioning assesses not only patients' level of role performance but also their role position and the presence and degree of role support, allowing for distinctions between, for example, patients who are higher functioning with much social or institutional support and those who are lower functioning but independent.[46] Finally, laboratory tasks are another possible solution, both to subjectivity in self-report and interview-based assessments and to the influence of external factors in objective measures of functioning. However, laboratory measures must demonstrate ecological validity or risk similarly misrepresenting patients' true levels of functioning. Ultimately, any assessment modality will have both strengths and weaknesses that are important to consider when selecting measures and interpreting results.

Some research has suggested that measurable neurocognitive impairments are present only in a minority of patients with depression, albeit a sizable minority.[62] It may be fruitful to examine more specifically the impact of cognitive impairment on psychosocial functioning in this subset of depressed patients. Interestingly, recent research has suggested that neurocognitive functioning, particularly executive function, in patients with major mood disorders predicts clinical outcomes and prognosis, perhaps even more so than the specific psychiatric diagnosis itself.[63] Thus, neurocognitive impairments are emerging as relevant both for traditional clinical outcomes such as symptom remission and for functional outcomes.

Similarly, higher severity of depressive symptoms is generally associated with both greater cognitive impairments[56,57] and poorer psychosocial functioning.[64] However, it is unclear to what degree cognitive deficits mediate the relationship between depressive illness and psychosocial outcomes within varying levels of symptom severity. For example, in milder depression, persistent cognitive deficits may be responsible for a greater proportion of psychosocial impairment than in severe depression, in which other symptoms (eg, lack of motivation, hopelessness, somatic symptoms) may be the more significant contributors to functional disability. To our knowledge, no research has yet examined the mediating role of both cognitive deficits and depression severity on psychosocial outcomes.

To date, there are very few published studies that have examined the relationship between cognitive, social, and occupational functioning, and these studies have some significant methodological limitations. Given these limitations, it is difficult to draw definitive conclusions about the relationship(s) between neurocognitive impairment, psychosocial functioning, and other factors in MDD. Further research is clearly necessary and warranted. Future studies should include larger and more homogeneous samples, prospective study designs, and multivariate statistical methods. They should also employ more extensive and higher quality assessments of psychosocial and occupational functioning, specifically, those that have been developed and validated for use in depressed and/or psychiatric populations (for examples of some available assessments, see recent reviews[5,65]). Similarly, the neuropsychological tests employed should have demonstrated sensitivity to detect cognitive deficits in depressed populations. Finally, because cognitive impairment may be present only in a minority of depressed patients and may be especially difficult to detect in educated and/or high-functioning depressed samples (such as those with stable employment), it is important to include a matched, healthy subject comparison sample. If normative data are used, it is important to try to match, control, or adjust for important variables such as education and level of intelligence. Ultimately, future clinical research should also address interventions to improve neurocognitive functioning

in individuals with MDD, with the ultimate objective of optimizing psychosocial functioning.

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REFERENCES

1. *The World Health Report 2004: Changing History*. Annex Table 3: Burden of Disease in DALYs by Cause, Sex, and Mortality Stratum in WHO Regions, Estimates for 2002. Geneva, Switzerland: World Health Organization; 2004.
2. McKnight PE, Kashdan TB. The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. *Clin Psychol Rev*. 2009;29(3):243–259.
3. Dewa CS, Thompson AH, Jacobs P. The association of treatment of depressive episodes and work productivity. *Can J Psychiatry*. 2011;56(12):743–750.
4. Harvey PD. Mood symptoms, cognition, and everyday functioning: in major depression, bipolar disorder, and schizophrenia. *Innov Clin Neurosci*. 2011;8(10):14–18.
5. Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional recovery from depression. *CNS Drugs*. 2010;24(4):267–284.
6. Tsourtos G, Thompson JC, Stough C. Evidence of an early information processing speed deficit in unipolar major depression. *Psychol Med*. 2002;32(2):259–265.
7. Landrø NI, Stiles TC, Sletvold H. Neuropsychological function in nonpsychotic unipolar major depression. *Neuropsychiatry Neuropsychol Behav Neurol*. 2001;14(4):233–240.
8. Porter RJ, Gallagher P, Thompson JM, et al. Neurocognitive impairment in drug-free patients with major depressive disorder. *Br J Psychiatry*. 2003;182(3):214–220.
9. Preiss M, Kucerova H, Lukavsky J, et al. Cognitive deficits in the euthymic phase of unipolar depression. *Psychiatry Res*. 2009;169(3):235–239.
10. Gohier B, Ferracci L, Surguladze SA, et al. Cognitive inhibition and working memory in unipolar depression. *J Affect Disord*. 2009;116(1–2):100–105.
11. Henry J, Crawford JR. A meta-analytic review of verbal fluency deficits in depression. *J Clin Exp Neuropsychol*. 2005;27(1):78–101.
12. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull*. 2013;139(1):81–132.
13. Wagner S, Doering B, Helmreich I, et al. A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment. *Acta Psychiatr Scand*. 2012;125(4):281–292.
14. Langenecker SA, Bieliauskas LA, Rapport LJ, et al. Face emotion perception and executive functioning deficits in depression. *J Clin Exp Neuropsychol*. 2005;27(3):320–333.
15. Hasselbalch BJ, Knorr U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect Disord*. 2011;134(1–3):20–31.
16. Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropathology. *Br J Psychiatry*. 2001;178(3):200–206.
17. Paelecke-Habermann Y, Pohl J, Leplow B. Attention and executive functions in remitted major depression patients. *J Affect Disord*. 2005;89(1–3):125–135.
18. Martinez-Aran A, Vieta E, Torrent C, et al. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord*. 2007;9(1–2):103–113.
19. Martino DJ, Marengo E, Igoa A, et al. Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. *J Affect Disord*. 2009;116(1–2):37–42.
20. Torres IJ, DeFreitas CM, DeFreitas VG, et al. Relationship between cognitive functioning and 6-month clinical and functional outcome in patients with first manic episode bipolar I disorder. *Psychol Med*. 2011;41(5):971–982.
21. Wingo AP, Harvey PD, Baldessarini RJ. Neurocognitive impairment in bipolar disorder patients: functional implications. *Bipolar Disord*. 2009;11(2):113–125.
22. Mur M, Portella MJ, Martinez-Aran A, et al. Influence of clinical and neuropsychological variables on the psychosocial and occupational outcome of remitted bipolar patients. *Psychopathology*. 2009;42(3):148–156.
23. Sanders JB, Bremmer MA, Comijs HC, et al. Cognitive functioning and the natural course of depressive symptoms in late life. *Am J Geriatr Psychiatry*. 2011;19(7):664–672.
24. Yen YC, Rebok GW, Gallo JJ, et al. Depressive symptoms impair everyday problem-solving ability through cognitive abilities in late life. *Am J Geriatr Psychiatry*. 2011;19(2):142–150.
25. Baune BT, Miller R, McAfoose J, et al. The role of cognitive impairment in general functioning in major depression. *Psychiatry Res*. 2010;176(2–3):183–189.
26. Godard J, Grondin S, Baruch P, et al. Psychosocial and neurocognitive profiles in depressed patients with major depressive disorder and bipolar disorder. *Psychiatry Res*. 2011;190(2–3):244–252.
27. Evans VC, Chan SSL, Iverson GL, et al. Systematic review of neurocognition and occupational functioning in major depressive disorder. *Neuropsychiatry*. 2013;3(1):97–105.
28. Shimizu Y, Kitagawa N, Mitsui N, et al. Neurocognitive impairments and quality of life in unemployed patients with remitted major depressive disorder. *Psychiatry Res*. 2013;210(3):913–918.
29. McCall WV, Dunn AG. Cognitive deficits are associated with functional impairment in severely depressed patients. *Psychiatry Res*. 2003;121(2):179–184.
30. Gupta M, Holshausen K, Best MW, et al. Relationships among neurocognition, symptoms, and functioning in treatment-resistant depression. *Arch Clin Neuropsychol*. 2013;28(3):272–281.
31. Godard J, Baruch P, Grondin S, et al. Psychosocial and neurocognitive functioning in unipolar and bipolar depression: a 12-month prospective study. *Psychiatry Res*. 2012;196(1):145–153.
32. Naismith SL, Longley WA, Scott EM, et al. Disability in major depression related to self-rated and objectively-measured cognitive deficits: a preliminary study. *BMC Psychiatry*. 2007;7(1):32.
33. Randolph C. *The Repeatable Battery for Neuropsychological Status*. Austin, TX: Harcourt Brace & Co; 1999.
34. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36), 2: conceptual framework and item selection. *Med Care*. 1992;30(6):473–483.
35. Katz S, Downs TD, Cash HR, et al. Progress in development of the index of ADL. *Gerontologist*. 1970;10(1):20–30.
36. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9(3):179–186.
37. Laplante L, Baruch P. *Manuel de CogitEx II*. Shawinigan-Sud, CA: Recherche Pragma Research; 1999.
38. Delis DC, Kaplan E, Kramer JH. *The Delis-Kaplan Executive Function System: Technical Manual*. San Antonio, TX: The Psychological Corporation; 2001.
39. Leon AC, Solomon DA, Mueller TI, et al. The Range of Impaired Functioning Tool (LIFE-RIFT): a brief measure of functional impairment. *Psychol Med*. 1999;29(4):869–878.
40. Patterson TL, Moscona S, McKibbin CL, et al. Social skills performance assessment among older patients with schizophrenia. *Schizophr Res*. 2001;48(2–3):351–360.
41. Heaton RK, Marcotte TD, Mindt MR, et al; HNRC Group. The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc*. 2004;10(3):317–331.
42. Eisen SV, Dill DL, Grob MC. Reliability and validity of a brief patient-report

instrument for psychiatric outcome evaluation. *Hosp Community Psychiatry*. 1994;45(3):242–247.
43. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220–233.
44. Von Korff M, Ustun TB, Ormel J, et al. Self-report disability in an international primary care study of psychological illness. *J Clin Epidemiol*. 1996;49(3):297–303.
45. Jaeger J, Berns S, Uzelac S, et al. Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Res*. 2006;145(1):39–48.
46. Jaeger J, Berns SM, Czobor P. The multidimensional scale of independent functioning: a new instrument for measuring functional disability in psychiatric populations. *Schizophr Bull*. 2003;29(1):153–168.
47. Withall A, Harris LM, Cumming SR. The relationship between cognitive function and clinical and functional outcomes in major depressive disorder. *Psychol Med*. 2009;39(3):393–402.
48. Goldman HH, Skodol AE, Lave TR. Revising Axis V for *DSM-IV*: a review of measures of social functioning. *Am J Psychiatry*. 1992;149(9):1148–1156.
49. Airaksinen E, Wahlin Å, Larsson M, et al. Cognitive and social functioning in recovery from depression: results from a population-based three-year follow-up. *J Affect Disord*. 2006;96(1–2):107–110.
50. Thase ME, Rush AJ. Treatment Resistant Depression. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress*. New York, NY: Raven Press; 1995:1081–1097.
51. Prudic J, Haskett RF, Mulsant B, et al. Resistance to antidepressant medications and short-term clinical response to ECT. *Am J Psychiatry*. 1996;153(8):985–992.
52. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
53. Bosc M. Assessment of social functioning in depression. *Compr Psychiatry*. 2000;41(1):63–69.
54. McIntyre RS, Cha DS, Soczynska JK, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety*. 2013;30(6):515–527.
55. Daly EJ, Trivedi MH, Wisniewski SR, et al. Health-related quality of life in depression: a STAR*D report. *Ann Clin Psychiatry*. 2010;22(1):43–55.
56. McClintock SM, Husain MM, Greer TL, et al. Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. *Neuropsychology*. 2010;24(1):9–34.
57. McDermott LM, Ebmeier KP. A meta-analysis of depression severity and cognitive function. *J Affect Disord*. 2009;119(1–3):1–8.
58. Bhardwaj A, Wilkinson P, Srivastava C, et al. Cognitive deficits in euthymic patients with recurrent depression. *J Nerv Ment Dis*. 2010;198(7):513–515.
59. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev*. 2011;35(3):804–817.
60. Brieger P, Ehrt U, Bloeink R, et al. Consequences of comorbid personality disorders in major depression. *J Nerv Ment Dis*. 2002;190(5):304–309.
61. Mittal D, Fortney JC, Pyne JM, et al. Impact of comorbid anxiety disorders on health-related quality of life among patients with major depressive disorder. *Psychiatr Serv*. 2006;57(12):1731–1737.
62. Iverson GL, Brooks BL, Langenecker SA, et al. Identifying a cognitive impairment subgroup in adults with mood disorders. *J Affect Disord*. 2011;132(3):360–367.
63. Lee RS, Hermens DF, Redoblado-Hodge MA, et al. Neuropsychological and socio-occupational functioning in young psychiatric outpatients: a longitudinal investigation. *PLoS ONE*. 2013;8(3):e58176.
64. Judd LL, Akiskal HS, Zeller PJ, et al. Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch Gen Psychiatry*. 2000;57(4):375–380.
65. Lam RW, Filteau MJ, Milev R. Clinical effectiveness: the importance of psychosocial functioning outcomes. *J Affect Disord*. 2011;132(suppl 1): S9–S13.