Association Between Depression Severity and Neurocognitive Function in Major Depressive Disorder: A Review and Synthesis

Shawn M. McClintock  
University of Texas Southwestern Medical Center at Dallas and Columbia University  
Mustafa M. Husain, Tracy L. Greer, and C. Munro Cullum  
University of Texas Southwestern Medical Center at Dallas

The effects of major depressive disorder (MDD) on neurocognitive function remain poorly understood. Results from published studies vary widely in terms of methodological factors, and very little is known about the effects of depression severity and other clinical characteristics on neurocognitive function. The purpose of this review was to synthesize prior research findings regarding neurocognitive functioning in patients with MDD and varying levels of depression severity and to provide recommendations for future directions. Overall, this review suggests that MDD has been inconsistently associated with neurocognitive functioning and there is limited understanding regarding the relationship between depression severity and neurocognitive sequelae. There was much heterogeneity on depression severity-related factors across studies assessing neurocognitive function in MDD, as well as substantial variability in the consideration of depression severity among studies, which suggests a need to further explore this important issue.

Keywords: major depressive disorder, neuropsychology, depression severity, neurocognitive function

It has long been noted that major depressive disorder (MDD) can negatively affect neurocognitive function (Schatzberg, 2002; Shenal, Harrison, & Demaree, 2003; Zakzanis, Leach, & Kaplan, 1999). The majority of studies have focused on MDD collectively in relation to cognitive functioning, and in addition to sampling differences, many do not comment on unique or additional depression characteristics such as symptom severity at the time of assessment. Of clinical relevance, some patients with MDD show cognitive difficulties whereas others do not. The emphasis on MDD collectively has left a gap in the research, and in turn clinical practice, concerning the relationship between magnitude of depression severity and neurocognitive function (Zakzanis et al., 1999). The result of this gap is significant, as cognitive impairments associated with MDD can significantly reduce function, impair quality of life, and contribute to disability (Jaeger, Berns, Uzelac, & Davis-Conway, 2006; Naismith, Longley, Scott, & Hickie, 2007).

Major depression has been negatively associated with the neuropsychological domains of executive function (Harvey et al., 2004), attention and concentration (Kampf-Sherf et al., 2004), memory (Fossati, Amar, Raoux, Ergis, & Allilaire, 1999), and processing speed (Nebes et al., 2000). In a meta-analysis of 22 studies, Zakzanis and colleagues (1999) showed that declarative or episodic memory (mean effect size, Cohen’s $d = 0.73$) and attention (mean effect size $= 0.59$) were the cognitive domains that tended to be most affected by depression. Moreover, neurophysiological studies have implicated the role of the prefrontal cortex and the hippocampus in MDD (Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Schatzberg, 2002). However, there has been considerable variability in methodologies across studies thereby contributing to some of the inconsistencies in the neurocognitive associated effects of depression.

The purpose of this review was to synthesize prior research findings regarding associations between depression severity and neurocognitive functioning in MDD, and further to provide recommendations for future directions. To accomplish a systematic literature review (Wright, Brand, Dunn, & Spindler, 2007), we searched the PsychInfo and Medline databases (English language literature, 1980 to 2008; OvidSP, Ovid Technologies, Inc.) with the following terms (e.g., OvidSP subject headings): major depressive disorder and neuropsychology. To control for duplicate information and redundancy, the results were imported and managed with EndNote (Version $\times 2$ for Mac, The Thomson Corp., New York, NY). When we encountered studies with overlapping participant samples, the studies with the smaller sample sizes were excluded from consideration. A total of 35 studies (see Table 1) that focused on depression severity were included in this review. These studies were published between 1991 and 2007, from multiple countries of origin (Australia, Belgium, Canada, Denmark, France, Germany, Israel, New Zealand, Norway, Sweden, United Kingdom, United States), and the sample sizes ranged from 40 to 420 ($M = 113.4$, $SD = 85.2$).

MDD

Depression has been found to be the fourth leading cause of disability worldwide (Moussavi et al., 2007), and those with depression have a higher mortality rate relative to those persons not (text continues on page 25)
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<tr>
<td>1991</td>
<td>Martin, Oren, &amp; Boon</td>
<td>MDD (n = 13); dysthymics (n = 17); controls (n = 18)</td>
<td>Age range not reported, but mean ages ranged from 38.1 to 40.7 between groups; participants were not medicated</td>
<td>WCST, WAIS-R</td>
<td>DSM-III-R diagnoses established by SCID-I; depression severity assessed with BDI and 21-item HAM-D</td>
<td>MDD group performed significantly worse on the Digit Span subtest of the WAIS–R; no group differences on WCST; however, BDI score significantly predicted WCST Total Errors, Perseverative Responses, and Failure to Maintain Set</td>
<td>Symptom severity scores indicated depressed groups did not significantly differ from one another, with mean HAM–D scores of 19.0 ± 8.88 in MDD group and 16.4 ± 6.31 for dysthymics (both moderate range); BDI scores were in moderate range for depressed group (22.23 ± 11.16) and mild for dysthymic (16.35 ± 7.91); control scored in normal range</td>
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<td>1997</td>
<td>Paradiso, Lamberty, Garvey, &amp; Robinson</td>
<td>History of MDD (n = 20) or bipolar disorder (n = 11) who were currently euthymic, and nonpatient group (n = 19)</td>
<td>Age range not reported, but mean ages ranged from 49.8 to 55.9 between groups; medication status varied, but most were on medications</td>
<td>TMT–A, TMT–B, CERAD Word List Memory Test, Stroop, and Digit Symbol subtest of WAIS–R</td>
<td>DSM-III-R diagnoses established by SCID-I; symptom severity assessed with 23-item HAM–D (score of 14 or less required), Manic Behavior Rating Scale (score of 16 or less required)</td>
<td>MDD group performed significantly worse than controls on TMT–A, TMT–B, Stroop, Digit Symbol, and the CERAD word list memory test</td>
<td>Inclusion criteria required hospitalization and/or two or more MDEs within a 2-year period (i.e., all were chronic)</td>
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<td>1998</td>
<td>Kessing et al.</td>
<td>MDD with three or more depressive episodes (n = 68); MDD with one depressive episode (n = 50); bipolar disorder with more than one episode (n = 28) (all patient groups were in euthymic phase); controls (n = 58)</td>
<td>Age range: &gt; 40; patients were identified through Danish psychiatric case registry who had received psychiatric hospitalization; controls had same access to care; medication status varied</td>
<td>CAMCOG, MDTRS, GBS, GDS, MMSE</td>
<td>Diagnosis established with ICD–10 criteria; depression severity assessed with 17-item HAM–D and BDI</td>
<td>On all cognitive measures, patients with recurrent depressive episodes were significantly more impaired than those with one episode; number of depressive episodes was significantly associated with cognitive decline as measured by the CAMCOG and MDTRS; patients with recurrent depressive episodes were significantly more impaired on all measures than controls</td>
<td>Groups were compared on the basis of number of episodes (one vs. three or more)</td>
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<td>1999</td>
<td>Beblo, Baumann, Bogerts, Wallesch, &amp; Herman</td>
<td>MDD inpatients ($n = 41$); normal controls ($n = 20$); MDD patients treated with pharmacotherapy, psychotherapy or both for 4.5 months and retested ($n = 27$)</td>
<td>Age range: 31 to 68 years</td>
<td>RAVLT Versions A and B, WMS–R, Corsi Block Tapping Test, Five-Point Test, COWAT, Block Design, Go/No-Go</td>
<td>DSM–III–R diagnoses established by SCID–I; symptom severity assessed with BDI, CSD, and MADRS</td>
<td>MDD group performed significantly worse on all tasks compared to controls at first examination; treated patients at follow-up showed significant improvements on visual paired association test, Block Design, Corsi Block-Tapping, COWAT, design fluency, and reaction times in the flexibility task; responders showed better improvements than nonresponders</td>
<td>Although all participants were inpatients, there was a wide range of severity based on symptom scores—median MADRS was 16 (mild range), with a range from 5 (no depression/ remission) to 43 (severe-very severe range)</td>
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<td>1999</td>
<td>Fossati, Amar, Raoux, Ergis, &amp; Allilaire</td>
<td>MDD inpatients ($n = 20$); schizophrenic inpatients ($n = 14$); normal controls ($n = 20$)</td>
<td>Age range: 18 to 45 years</td>
<td>Verbal fluency, MCST, Delis test; WAIS–Digit Span Forward and Backward and Visuomotor Span Forward and Backward, Grober and Buschke’s Verbal Learning Test</td>
<td>DSM–IV diagnoses established by checklist; symptom severity assessed with MADRS and SRRS (MDD required scores of 20 or more); schizophrenics required score of 60 or more on PANSS</td>
<td>MDD and patients with schizophrenia significantly worse compared to controls on: Digit Span Forward, Visuospatial Backward, semantic fluency, and spontaneous and structured sorting on the Delis test; MDD significantly worse compared to controls on Verbal Span Backward; no correlation between symptom severity ratings and cognitive performance</td>
<td>All were inpatients with moderate level of severity required at entry (mean MADRS = 23.7 ± 4.3)</td>
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<td>2000</td>
<td>Burt, Prudic, Peyser, Clark, &amp; Sackeim</td>
<td>Young adult with MDD ($n = 29$), older group with MDD ($n = 24$), young adult with bipolar ($n = 13$) and older group with bipolar ($n = 13$)</td>
<td>Inpatient sample referred for treatment with ECT; older group defined as 60 or greater; no medications except lorazepam for 5 days prior to testing; psychotic symptoms allowed</td>
<td>SRT; paired-word and paired-face tasks; randomization to Rey–Osterrieth, Taylor, or Richie Figure, Randt Memory Test</td>
<td>Diagnoses established with SADS; symptom severity assessed with 24-item HAM–D (score of 18 or more required)</td>
<td>Older group with MDD had poorer performance on delayed reproduction of complex figures than young MDD or young bipolar; greater depression severity was associated with greater impairment on delayed recognition memory</td>
<td>Although sample was inpatients referred for ECT, HAM–D score required for entry was at upper end of mild range (18)</td>
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<td>2000</td>
<td>McBride &amp; Abeles</td>
<td>One group of adults recruited for aging project (n = 50)</td>
<td>PASAT; TMT-B; WAIS–R Digit Span</td>
<td>Depression severity assessed with BDI and GDS</td>
<td>Significant positive correlations were found between the TMT–B and both depression severity measures; total BDI score accounted for 18% of the variance on TMT–B</td>
<td>Mean symptom severity scores were not reported, but were used to correlate with neuropsychological performance</td>
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<td>2000</td>
<td>Nebes et al.</td>
<td>Older group MDD (n = 39); normal older controls (n = 19)</td>
<td>n back test; WAIS–R Digit Symbol Substitution test; Block Design subtest of WAIS–III, Logical Memory subtest of WMS–III, CVLT, and CFT</td>
<td>DSM–IV diagnosis established by SCID–I; depression severity assessed with 17-item HAM–D (required score of 15 or more)</td>
<td>Patients performed significantly worse than controls on working memory and processing speed tasks; processing reductions appear to mediate impairments on episodic memory tasks; baseline HAM–D and age of onset of illness did not affect results</td>
<td>Inclusion required HAM–D in moderate range—mean was 23.3 ± 4.5; 20 participants were recurrent, 19 were experiencing first episode; 15 were early onset (before age 59), 24 were late onset (age 60 or later)</td>
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<td>2000</td>
<td>Sweeney, Kmiec, &amp; Kupfer</td>
<td>Inpatients with bipolar (n = 35; 21 in depressed state, 14 in mixed or manic state) or MDD (n = 58); healthy controls (n = 51)</td>
<td>CANTAB</td>
<td>DSM–IV diagnosis established by SCID–I; symptom severity assessed with 17-item HAM–D, BPRS, BRMS, SAPS</td>
<td>MDD performed significantly worse on measures of episodic memory (Delayed Matching to sample); MDD reaction times were relatively fast, suggesting a speed/accuracy trade-off; severity of depression and psychosis severity correlated with performance on many of the tasks</td>
<td>All were inpatients, but level of symptom severity was varied—mixed bipolar group had mean HAM–D score consistent with mild depression (12.93 ± 9.09), bipolar depressed group was in moderate range (17.30 ± 5.46), and nonbipolar depressed was in severe range (21.64 ± 4.30)</td>
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<td>2001</td>
<td>Grant, Thase, &amp; Sweeney</td>
<td>MDD ( (n = 123) ); healthy controls ( (n = 26) )</td>
<td>Nonbipolar, nonchronic outpatients; the mean age of MDD group was 39.0 ± 10.4, and mean age of the healthy control group was 40.2 ± 9.7</td>
<td>TMT–A, Digit Span, CPT, Hopkins Verbal Learning Test, WMS–R–Visual Reproduction Scale, Halstead-Reitan Category Test, COWAT, WCST, TMT–B, CANTAB</td>
<td>DSM–IV diagnosis established by SCID–I; depression severity assessed with 17-item HAM–D (required score of 15 or more)</td>
<td>MDD group performed significantly worse than healthy controls on WCST (categories, perseverative responses and errors, and failure to maintain set); clinician-rated depression severity was related to performance on two executive function tasks (ID/ED task), motor skill and reaction time from CANTAB; patients who did not improve after 28 days of treatment were more impaired on the WCST and the ID/ED task from CANTAB; age of onset of first episode significantly negatively correlated with measures of attention, psychomotor speed, and executive function; longer depressive episodes were associated with poorer performance on WCST failure to maintain set</td>
<td>Moderate symptom severity required at entry ( (M = 16.7 ± 5.4) ); sample was nonchronic (episode less than 2 years duration); number of episodes varied with 42 having single episode, 38 having 1–2 episodes, and 43 having 3 or more episodes; mean age of onset was 27.9 ± 12.5 years</td>
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<td>2001</td>
<td>Kiosses, Klimstra, Murphy, &amp; Alexopoulos</td>
<td>Older MDD ( (n = 126) )</td>
<td>Age range: 60 or greater; both outpatients and inpatients; medication status was varied</td>
<td>DRS</td>
<td>DSM–IV and RDC diagnoses established with SADS; symptom severity assessed with 24-item HAM–D</td>
<td>Impairment on the initiation and perseveration subscale was associated with more functional impairment and disability than severity of depression (using a HAM–D cut-off score of 27)</td>
<td>Severity was varied, with inclusion of both outpatients and inpatients; mean HAM–D was 27.29 ± 5.88, but ranged from 18 to 44 (mild to very severe)</td>
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<td>2001</td>
<td>Landro, Stiles, &amp; Sletvold</td>
<td>MDD ($n = 22$); healthy controls ($n = 30$)</td>
<td>Age range not specified, but mean age was $40$ for both groups; no medications (antidepressants, lithium or neuroleptics) for at least 1 month prior to testing</td>
<td>APT (Tasks a to d), APT Choice Reaction Time, difference between TMT–B and TMT–A, Digit Symbol Test, PASAT, Digit Span Forward, Randt Memory Test, Kimura Recurring Recognition Figures Test, COWAT, WAIS Block Design</td>
<td>$DSM-III-R$ diagnosis established by $SCID-I$; depression severity assessed with BDI</td>
<td>MDD group scored significantly lower than controls on selective attention, working memory, verbal long-term memory, and verbal fluency; selective attention and working memory met criteria for selective or differential deficits in the MDD group; BDI scores did not correlate with neuropsychological test performance</td>
<td>Majority ($n = 16$) of patients were recurrent; mean BDI score was $23.0 \pm 6.7$ (moderate range); controls scored in normal range</td>
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<td>2001</td>
<td>Neu et al.</td>
<td>Inpatient group ($n = 80$) comprised of MDD, bipolar disorder, dysthymia, and schizoaffective disorder, depressive type; healthy controls ($n = 62$); patients tested at admission and discharge</td>
<td>Age range: $30$ to $60$ years; medication status varied—about two thirds were medicated and one third was not at time of admission</td>
<td>RAVLT Animal Naming, WMS Visual Memory subscale, TMT–A</td>
<td>$DSM-IV$ diagnoses established with clinical interview; depression severity assessed with BRMS</td>
<td>Group with depression (all patient group) performed significantly worse than controls on verbal memory, psychomotor speed, and verbal fluency at admission; MDD group performed significantly worse on verbal memory only at admission and showed significant improvements on verbal memory and verbal fluency at discharge; BRMS score was used as covariate, but did not influence any of the results</td>
<td>Group with depression had median of $3.0$ episodes of illness and $2.0$ inpatient hospitalizations; mean age at onset of MDD was $41.38 \pm 12.96$; mean BRMS score was $19.74 \pm 4.86$</td>
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<td>2002</td>
<td>Fossati, Coyette, Ergis, &amp; Allilaire</td>
<td>Group with depression ($n = 49$) comprised of both MDD ($n = 36$) and bipolar disorder ($n = 16$); normal controls ($n = 70$)</td>
<td>Age range: 19 to 72 years; inpatients; sample divided into 4 subgroups with an age cut-off of 45 years to assess the effect of age on memory performance</td>
<td>Free and cued selective reminding procedure, MCST</td>
<td>DSM–IV diagnoses established by checklist; depression severity assessed with MADRS and SRRS (MDD required scores of 20 or more)</td>
<td>Patients showed significant impairments compared to controls on free recall that was not attributed to age effects; patients with mild executive impairment based on the MCST had significantly lower recall scores that those with no executive impairment, which was again not associated with age</td>
<td>All were inpatients with at least moderate severity required at inclusion; mean MADRS score was slightly greater than 25 for both older and younger depressives, indicating moderate severity; older depressed had greater age at first episode ($45.7 \pm 13.21$) compared to younger ($25.3 \pm 6.71$), but longer duration of illness; groups were similar with respect to number of episode and hospitalizations</td>
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<td>2002</td>
<td>Rohling, Green, Allen, &amp; Iverson</td>
<td>Patients with a variety of health issues ($n = 420$) who were divided into two groups based on BDI score quartiles: low depression group (bottom quartile; $n = 115$) and high depression group (highest quartile; $n = 112$)</td>
<td>Age range not reported, but mean age = 42.4; medication status not reported, but likely varied based on treatments for different medical diagnoses; patients who failed symptom validity tests were excluded</td>
<td>WCST, Thurstone Word Fluency Test, Ruff Figural Fluency Test, Category Test; CVLT, RMT–W, CSRT; CFT, RMT–F; WAIS–R Digit Span, TMT; Finger Tapping Test, Grip Strength, Grooved Pegboard, Finger Tip Number Writing</td>
<td>Depression severity assessed with BDI, MMPI–2 (Depression Scale), and SCL–90–R (Depression Scale)</td>
<td>No significant differences were noted between high and low depressed groups on effortful or automatic tasks; the high depressive group performed significantly worse on two tasks from the psychomotor and sensory-perceptual category: the Grooved Pegboard and Finger Tip Number Writing (left hand)</td>
<td>Low depression group had a mean BDI score consistent with no depression; high depressed group was consistent with severe depression; difference between groups was verified with MMPI–2 and SCL–90–R scores; groups differed significantly on all three measures</td>
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<td>2002</td>
<td>Taylor, Wagner, &amp; Steffens</td>
<td>Older patients with depression ($n = 52$), were diagnosed with mild cognitive impairment at baseline</td>
<td>Age range: 60 or greater; medication status varied, but all participants were in a treatment program; patients tested at baseline, 6 months, and 12 months</td>
<td>MMSE</td>
<td>Depression severity assessed with MADRS (score of 15 or greater required)</td>
<td>Both symptom severity and cognitive status improved over time; a higher baseline MADRS was associated with a lower baseline MMSE and less improvement in MMSE over time</td>
<td>Inclusion required mild depression; mean MADRS score was in moderate range (30.3 ± 8.7) decreasing to mild range at 12 months (10.1 ± 9.2)</td>
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<td>2003</td>
<td>Farrin, Hull, Unwin, Wykes, &amp; David</td>
<td>Mildly depressed ($n = 43$); nondepressed ($n = 59$)</td>
<td>All male U.K. military personnel; age range: 22 to 58 years</td>
<td>SART, PASAT, Stroop; WMS–R Logical Memory and Paired Associates subtests</td>
<td>Mild depression defined as BDI score &gt; 10; nondepressed defined as BDI &lt; 10</td>
<td>Mildly depressed scored significantly lower on Logical Memory immediate recall, made significantly more errors of commission on the SART, and had a slower reaction time following an error on the SART</td>
<td>Mean BDI = 18.19 ± 6.50, consistent with mild range; nondepressed mean in normal range</td>
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<td>2003</td>
<td>Hammar, Lund, &amp; Hugdahl</td>
<td>MDD ($n = 21$) tested at two time points—inclusion and 6-month follow-up; healthy controls ($n = 21$)</td>
<td>Age range: 20 to 56 years; patients received antidepressant treatment; both inpatients and outpatients, but majority were inpatients ($n = 18$)</td>
<td>Visual search paradigm examining automatic and effortful processing</td>
<td>DSM–IV criteria met for recurrent MDD; depression severity assessed with HAM–D (required score of 18 or more)</td>
<td>MDD significantly differed from healthy controls on effortful processing at both testing sessions, despite improvements in depressive severity</td>
<td>All participants had recurrent depression; mean HAM–D = 21.9 ± 3.7; did not include information on duration of illness, but suggested that this could have impacted results</td>
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<td>2003</td>
<td>F. C. Murphy, Michael, Robbins, &amp; Sahakian</td>
<td>MDD (n = 27); healthy controls (n = 23)</td>
<td>Age range: 26 to 59 years; mixture of inpatients and outpatients; all but one patient was taking at least one antidepressant or mood stabilizer</td>
<td>Probability Reversal task; CANTAB Spatial Working Memory task; groups were divided such that half received negative feedback and half did not</td>
<td><em>DSM–IV</em> diagnoses established with clinical interview; depression severity assessed with HAM–D, MADRS, CID; control participants assessed with BDI (score or 9 or less required)</td>
<td>Patients had significantly worse performance on maintenance failure and matching on the Probability Reversal task and between-search errors on the Spatial Working Memory task; feedback improved performance in both MDD and controls; no relationship between symptom severity scores and neuropsychological test performance</td>
<td>Symptom severity was in moderate to severe range—mean HAM–D score was 23.6 ± 4.2, MADRS was 34.3 ± 5.4</td>
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<td>2003</td>
<td>Naismith et al.</td>
<td>MDD (n = 55); healthy controls (n = 22)</td>
<td>Age range: 30 to 82 years (MDD), 40 to 74 years (controls); medication status varied; both inpatients and outpatients included; both nonpsychotic and psychotic features included; 12 participants diagnosed with bipolar disorder</td>
<td>TMT–B, RAVLT, Raven’s Colored Progressive Matrices, WAIS–R Block Design and Vocabulary subtests, Benton Visual Retention Test (Form D, Administration A), Phonetic and Semantic Fluency, computerized WCST, simple and choice reaction time, computerized version of the Tower of London</td>
<td><em>DSM–IV</em> diagnoses established with <em>SCID–I</em>; depression severity assessed with 21-item HAM–D</td>
<td>MDD patients performed significantly worse on all tests except WAIS–R Vocabulary and WCST; higher HAM–D scores were significantly associated with lower z scores on semantic fluency and WCST (perseverations); no association between length of episode or lifetime diagnoses and neuropsychological test performance; inpatients were significantly worse on RAVLT percentage retention; later age of onset (≥50 years) performed worse than early onset on WAIS–R Block Design, CPT, TMT–B, Tower of London, and Raven’s Matrices, although only Tower of London remained significant when age was added as a covariate</td>
<td>Mean HAM–D was in severe range; average duration of illness was 45 weeks</td>
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<tr>
<td>2003</td>
<td>Porter, Gallagher, Thompson, &amp; Young</td>
<td>MDD ($n = 44$); healthy controls ($n = 44$)</td>
<td>Age range: 18 to 65 years; free of all psychotropic medications at least 6 weeks prior to recruitment</td>
<td>Digit Symbol Substitution Test; RAVLT; Visuospatial CANTAB Paired-Associates Learning, Pattern Recognition, Spatial Recognition and Simultaneous/Delayed Matching to Sample subtests; COWAT, ELFT, Vigil CPT, and CANTAB Spatial Working Memory and Tower of London subtests</td>
<td>DSM–IV criteria were met; depression severity assessed with 17-item HAM–D, MADRS, BDI</td>
<td>MDD performed significantly worse than controls on the RAVLT (list-learning and distractor list); all CANTAB visuospatial tasks; all sustained attention and executive function tasks except the Tower of London task; HAM–D scores were significantly correlated with performance on RAVLT (retroactive interference, long-term recall, and retroactive interference), pattern recognition (percentage correct), Delayed Matching to Sample and Paired-Associates Learning (total trials); illness characteristics were provided but were not related to neuropsychological test performance</td>
<td>Most were first episode ($n = 30$); mean symptom severity scores were in the moderate range, but range was—mean HAM–D = 21.1 ± 4.4 (range 15 to 30), MADRS = 28.9 ± 5.5 (range 18 to 38); BDI = 27.9 ± 10.2 (range 8 to 47)</td>
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<td>2004</td>
<td>Airaksinen, Larsson, Lundberg, &amp; Forsell</td>
<td>MDD ($n = 68$); dysthymia ($n = 28$); mixed anxiety-depressive disorder ($n = 25$); minor depression ($n = 66$); controls ($n = 175$)</td>
<td>Age range: 20 to 64 years; 47 participants across the four depressed groups were treated with psychotropic medications</td>
<td>Episodic memory task consisting of 32 words in eight categories; Word Association Test, TMT–A, TMT–B</td>
<td>DSM–IV diagnoses established by SCAN</td>
<td>MDD group recalled fewer words on free and cued recall compared to controls; mixed anxiety-depressive disorder group recalled fewer cued recall words than controls; combined depressed group (i.e., all four subgroups) had a longer TMT–B completion time compared to controls, only the dysthymic subgroup independently differed from controls on the TMT–B</td>
<td>Severity was based on categorical psychiatric diagnosis; Symptom severity at time of testing was not assessed</td>
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<td>2004</td>
<td>Baudic, Tzortzis, Barba, &amp; Traykov</td>
<td>Older MDD ($n = 21$); normal control ($n = 19$)</td>
<td>MDD age range: 53 to 93 years; control age range: 61 to 85 years; no medications, no psychotic features</td>
<td>COWAT, CET, Hayling Test, SCIT, TMT–A, TMT–B, Graphic Sequences of Luria, MCST, Logical Memory I, Digit Span Forward, Corsi Block Tapping Test</td>
<td><strong>DSM–IV</strong> diagnosis established by clinical interview, MADRS, GDS, and ERD; must have MADRS $&gt; 20$</td>
<td>MDD group performed significantly worse than controls on Logical Memory I and all executive function measures except Hayling Test; severity (MADRS) was significantly correlated with performance on many executive function measures (COWAT, MCST, TMT–B [time], Hayling test [Section B])</td>
<td>Moderate level of severity required for entry; group with depression had mean MADRS of 33.3 ± 6.3, which falls in the moderate severity range; control group scores consistent with no depression</td>
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<td>2004</td>
<td>Biringer et al.</td>
<td>Recurrent MDD ($n = 50$) tested before and after ($n = 30$) a 26-month test–retest interval</td>
<td>Age range: 20 to 50 years; majority on psychotropic medication</td>
<td>WCST (categories completed, perseverative errors, failure to maintain set, nonperseverative errors), PASAT (2- and 3-s subtests), WAIS–R–Backward Digit Span, Stroop, COWAT (phonemic and semantic categories)</td>
<td><strong>DSM–IV</strong> diagnoses established with MINI; depression severity assessed with 17-item HAM–D and MADRS (minimum scores of 18 on both)</td>
<td>HAM–D change scores (reverse scaled) were significantly positively correlated with a composite change score of executive function based on all measures; the only significant correlation on individual tasks was between HAM–D and COWAT (number of words in semantic categories); recovered patients (HAM–D $&lt; 8$, i.e., remitted) showed greater mean improvements on 8 of the 10 measurements than nonrecovered patients; course of illness characteristics were not related to neuropsychological test performance</td>
<td>Mean HAM–D in severe range; all had long duration of disease, but those who did retest differed significantly from those who did not (mean years 13.6 ± 9.3 vs. 6.1 ± 5.1, respectively)</td>
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<td>2004</td>
<td>Harvey et al.</td>
<td>MDD inpatients ($n = 22$); healthy controls ($n = 22$)</td>
<td>Age range: 22 to 53 years; medication status varied, but most were on tricyclic antidepressants</td>
<td>(<em>DSM–IV</em>) diagnoses established with MINI; depression severity assessed with MADRS (score of 20 or higher required) and BDI</td>
<td>MDD group scored significantly lower than controls on all complexity levels of the <em>n</em>-back test, the TMT–B test, number of perseverative errors on the WCST, number and speed of response on the Stroop (color and interference); those with multiple hospitalizations performed lower on <em>n</em>-back test compared to those hospitalized for the first time</td>
<td>Moderate level of severity was required; mean MADRS score was in the moderate range (27.7 ± 4.3); mean years of illness was $8.2 ± 11.3$ years; mean number of depressive episodes was $2.8 ± 2.4$; mean number of hospitalizations for depression was $1.9 ± 1.2$</td>
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<td>2004</td>
<td>Kampf-Sherf et al.</td>
<td>MDD ($n = 55$)</td>
<td>Age range not reported; participants were tested at baseline and again following 6 weeks of SSRI treatment</td>
<td>TMT–A, TMT–B, Purdue Pegboard, CFT, RAVLT, BVRT, WAIS–R Arithmetic, Block Design and Similarities subtests, HVOT, modified verbal fluency measure, VFOT</td>
<td><em>DSM–IV</em> diagnosis of MDD established with <em>SCID–I</em>; depression severity assessed with HAM–D</td>
<td>SSRI responders performed more poorly than nonresponders on more complex tasks WAIS–R subtests, HVOT, BVRT ‘correct responses and perseverations, and CFT strategy and performed better than nonresponders on verbal fluency and VFOT</td>
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<td>2004</td>
<td>Leuchter et al.</td>
<td>MDD ($n = 51$); NP testing occurred at baseline and was included to determine whether it might predict participants who were likely to respond to placebo</td>
<td>Age range: &gt; 21; treatment with either fluoxetine, venlafaxine, or placebo +15 to 20 min of brief supportive psychotherapy</td>
<td>TMT–A, Stroop A and B, Digit Symbol Test, TMT–B, WCST, Auditory Consonant Trigrams, COWAT, Stoop Trail, Language: Boston Naming Test, verbal learning: RAVLT, WMS–R Visual Reproduction, CFT Figure, Digit Span, WAIS–R Block Design, CFT Copy, Benton Facial Recognition</td>
<td><em>DSM–IV</em> diagnosis of MDD established with <em>SCID–I</em>; depression severity assessed with 17-item HAM–D (required score $\geq 16$)</td>
<td>Placebo responders performed significantly faster on the Digit Symbol Test than placebo nonresponders, medication responders, and medication nonresponders</td>
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<td>2004</td>
<td>Majer et al.</td>
<td>MDD or bipolar disorder inpatients in depressive episode (n = 73) tested before and after admission to hospital (mean time = 12 weeks); recovered (n = 19) retested 6 months later</td>
<td>Age range: 18 to 69 years; all but four were receiving pharmacological treatment at time of first testing; 10 had psychotic features</td>
<td>German assessments of alertness, divided attention, two selective attention tasks, German equivalents of the TMT and Stroop tests, verbal and short-term memory: WMS–R Digit Span Forward and Backward, computerized version of WCST</td>
<td><em>DSM–IV</em> diagnoses established with clinical interview; depression severity assessed with 21-item HAM–D, MADRS, BDI</td>
<td>Patients were impaired on all cognitive tests at admission except Digit Span Forward and Stroop; impairments remained at discharge with the exception of performance on the letter cancellation task assessing selective attention; nonresponders and nonremitters performed significantly worse on the divided attention task at admission; significant positive correlations between lifetime duration of illness and reaction time on alertness and divided attention tasks; divided attention was significantly associated with course of disorder</td>
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<td>2004</td>
<td>Stordal et al.</td>
<td>Recurrent MDD (n = 45); healthy controls (n = 50)</td>
<td>Age range: 19 to 51 years; mix of inpatients and outpatients; medication status varied</td>
<td>COWAT, Tower of London, PASAT, WAIS–R Digits Backward, Stoop, WCST; simple reaction time from the California Computerized Assessment Package</td>
<td><em>DSM–IV</em> diagnoses established with <em>SCID–I</em>; depression severity assessed with 17-item HAM–D (score of 18 or greater required) and MADRS</td>
<td>MDD patients performed significantly worse compared to controls on the COWAT (phonemic and categorical verbal fluency), Stroop (Color–Word subtest), WCST (failure to maintain set and perseverative errors), PASAT, and Digits Backward; psychomotor speed accounted for approximately one fourth of the observed impairments</td>
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<td>2005</td>
<td>Alexopoulos et al.</td>
<td>Nondemented older patients with MDD (n = 112)</td>
<td>Age ≥ 60 years; MDD of moderate severity (HAM–D score 24.33 ± 4.70); all participants treated with 40 mg citalopram for 8 weeks; NP testing was used to predict response to citalopram</td>
<td>MDRS–IP, Stroop</td>
<td><em>DSM–IV</em> diagnoses established with the SADS and parts of the <em>SCID–I</em>, patient version; depression severity assessed with 24-item HAM–D</td>
<td>Citalopram nonresponders performed significantly worse on the MDRS–IP subscale and the Stroop; however, they were older, less educated, and had a greater medical burden</td>
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<td>2005</td>
<td>Rapp et al.</td>
<td>Older MDD (n = 116); two-by-two factorial design—one factor was current MDE (present vs. absent), the other was recurrent MDD (present vs. absent)</td>
<td>Age range: 60 to 97</td>
<td>TMT–A, TMT–B, Digit Symbol Substitution Test, Verbal Fluency, task comprised of list-learning, recognition and delayed recall</td>
<td>DSM–III–R or DSM–IV diagnosis of MDD established with MDS questionnaire; depression severity assessed with GDS</td>
<td>MDD with current MDE performed significantly worse than those not with current MDE on attention/executive function tasks; patients with late-onset MDD performed worse than those with recurrent MDD</td>
<td>Late onset was defined as no previous history of MDD; recurrent was defined as at least one prior MDE; current symptoms on GDS were significantly different for those in versus out of current MDE, irrespective of chronicity</td>
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<td>2006</td>
<td>Elderkin-Thompson, Mintz, Haroon, Lavretsky, &amp; Kumar</td>
<td>MDD (n = 63); minor depression (n = 32); healthy controls (n = 71)</td>
<td>Age ≥ 60</td>
<td>CVLT; WCST, Letter–Number Sequences from WAIS–III, Stroop (Part I)</td>
<td>DSM–IV diagnosis of MDD established with SCID–I and HAM–D &gt; 15; minor depression defined as presence of low mood and/or interest and one additional depressive symptom from DSM–IV checklist and HAM–D between 8–16</td>
<td>Major and minor older participants with depression recalled significantly fewer words on Trial 1 of List A and on List B and were more impaired on semantic and serial clustering compared to controls; mediation analyses conducted with the other tasks showed that performance differences on Trial 5 were secondary to executive dysfunction; while both early and late onset participants’ depression diagnosis mediated CVLT semantic clustering and WCST performance; effects were stronger in late onset participants</td>
<td>Mean HAM–D scores were 10.8 ± 2.0 (mild range) for minor depression, 17.4 ± 4.4 (moderate range) for MDD</td>
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<td>2006</td>
<td>Gualtieri, Johnson, &amp; Benedict</td>
<td>MDD on no psychotropic medications (n = 38); MDD on psychotropic medications who had been successfully treated for at least 4 weeks (n = 31); normal controls (n = 69)</td>
<td>Age range: 18 to 65 years</td>
<td>CNS Vital Signs computerized battery</td>
<td>DSM–IV diagnosis of MDD established with clinical interview; depression severity assessed with HAM–D and BDI</td>
<td>MDD performed significantly worse than normal controls on Stroop errors, number correct on shifting attention test, and reaction time on the continuous performance test; MDD performed significantly worse than treated MDD on complex attention and vigilance tasks; treated MDD did not differ significantly from controls on pairwise comparisons, but summary scores indicated that treated MDD performed worse on four of six domains and 10 of 15 primary scores, suggesting that treatment did not normalize performance</td>
<td>Mean BDI = 16.86, HAM–D = 15 in untreated MDD group; treated group had mean scores in the remitted range (mean BDI = 1.5, HAM–D = 6)</td>
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<tr>
<td>2006</td>
<td>Wang et al.</td>
<td>MDD currently depressed (n = 57); MDD previously depressed (n = 42); healthy controls never depressed (n = 46)</td>
<td>Mean ages ranged from 26.9 to 31.0 between groups; medication status varied, but majority were not medicated</td>
<td>CVLT</td>
<td>DSM–IV criteria were met; depression severity assessed with BDI</td>
<td>No significant performance differences were found</td>
<td>Mean BDI scores were in mild to moderate range for currently depressed (15.8 ± 8.6) and normal range for previously and never depressed (6.4 ± 4.0 versus 1.1 ± 1.7, respectively)</td>
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Participants did not meet criteria for MDD and meansymptom severity scores were within normal range atbaseline; state-positive participantshad significantincreases in symptomseverity scores atfollow-up.

Table 1 (continued)

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<td>2007</td>
<td>Cysique et al.</td>
<td>HIV-infected adult men who did not meet criteria for serious mental illness or current major depressive episode at baseline (n = 227)</td>
<td>Age range not reported; mean age = 32.1; participants were grouped into two groups: those with a history of MDD (trait positive) and those without (trait negative); also grouped based on whether criteria for MDE were met at follow-up (state positive and state negative)</td>
<td>Subtests from WAIS–R and Halstead–Reitan Battery, PASAT, Figure Memory Test, Story Memory Test, Boston Naming Test, Thurstone Word Fluency Test, motor skills: Finger Tapping, Grooved Pegboard</td>
<td>DSM–III–R diagnoses established with the SCID–I; depression severity assessed with the BDI and HAM–D</td>
<td>Neither trait nor state groups significantly differed on neuropsychological test performance; however, state-positive participants at follow-up were more likely to report subjective neurocognitive complaints at both baseline and follow-up</td>
<td>Participants did not meet criteria for MDD and mean symptom severity scores were within normal range at baseline; state-positive participants had significant increases in symptom severity scores at follow-up</td>
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Note. WCST = Wisconsin Card Sorting Test; WAIS–R = Wechsler Adult Intelligence Scale–Revised; DSM = Diagnostic and Statistical Manual of Mental Disorders; SCID–I = Structured Clinical Interview for DSM–IV; BDI = Beck Depression Inventory; HAM–D = Hamilton Rating Scale for Depression; TMT–A = Trail Making Test–Part A; TMT–B = TMT–Part B; CERAD = Consortium to Establish a Registry for Alzheimer’s Disease; Stroop = Stroop Color and Word Test; CAMCOG = Cambridge Cognitive Examination total score; MDRS = Mattis Dementia Rating Scale; GBS = Gottfries-Brane-Steen Dementia Rating Scale; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; ICD–10 = International Classification of Diseases-10; RAVLT = Rey Auditory Verbal Learning Test; WMS–R = Wechsler Memory Test–Revised; COWAT = Controlled Oral Word Association Test; CFT = Rey–Osterrieth Complex Figure Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; BPRS = Brief Psychiatric Rating Scale; BRMS = Bech–Rafaelsen Melancholia Scale; SAPS = Scale for the Assessment of Positive Symptoms; CPT = Continuous Performance Test; ID/ED = Intra-dimensional/Extra-dimensional; DRMT = Dementia Rating Scale; RMT–W = Warrington’s Recognition Memory Test–Words; RMT–F = RMT–Faces; CSRT = CogniSyst Story Recall Test; MMPI–2 = Minnesota Multiphasic Personality Inventory–2; SCL–90–R = Symptom Checklist–90–Revised; SART = Sustained Attention to Response Task; CID = Clinical Interview for Depression; ELFT = Exclude Letter Fluency Test; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; CET = Cognitive Estimates Test; SCIT = Stroop Color Interference Test; ERDT = Scale for the Evaluation of Psychomotor Retardation in Depressed Patients; MINI = Mini International Neuropsychiatric Interview; SSRI = selective serotonin reuptake inhibitor; BVRT = Benton Visual Retention Test; HVOT = Hooper Visual Organization Test; VFOT = Visual Frequency of Occurrence Test; MDRS–IP = Mattis Dementia Rating Scale Initiation-Persistence subtest; MDE = major depressive episode; CNS = CNS vital signs.
depressed (Cuijpers & Smit, 2002). The lifetime prevalence of MDD ranges between 5% and 20% (Hamet & Tremblay, 2005; Kessler et al., 2003). The annual incidence of MDD has been found to be three to five adults per 1,000 (J. M. Murphy, Laird, Monson, Sobol, & Leighton, 2000) and it has been estimated that 5% to 25% of the population will experience depression at some point in their lifetime (Kessler et al., 2003). Women are consistently diagnosed with MDD more frequently than men at a ratio of 2:1 (Kessler, 2003; Marcus et al., 2005), and younger cohorts (50 years and younger) have been found to have higher rates of depression relative to older (51 years and older) cohorts (Husain et al., 2005).

### Defining Depression Severity

Severity of depression, and its potential effects on cognitive function, should be considered both with respect to the level of symptom severity at the time of neuropsychological testing (i.e., state of depressive symptomatology), and with respect to course of illness (i.e., number and duration of depressive episodes, duration of illness, treatment resistance). These different aspects of severity may influence both neuropsychological performance and the potential resolution of cognitive impairments with treatment.

Evaluation of depressive symptoms at a particular time point is typically done with symptom rating scales, such as the Hamilton Rating Scale for Depression (HAMD–D; Hamilton, 1960), or the Inventory of Depressive Symptomatology (IDS; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). Different total scores correspond to various levels of severity. For example, scores ranging between 0 and 11 on the 30-item IDS and 0 to 7 on the 17-item HAM–D represent no depression (or remission), whereas 47 or greater on the IDS and 26 or greater on the HAM–D represent very severe depression (http://www.idsd-qids.org). These symptom severity scores are often correlated with neuropsychological test performance to evaluate the relationship between symptom severity and cognitive function.

The presence or absence of psychotic features is also evaluated when examining depression severity at the symptom level (Fennig, Craig, Lavelle, Kovaszny, & Bromet, 1994). Psychosis, per the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM–IV–TR; American Psychiatric Association, 2000), is an indicator of depression severity rather than a subtype of depression, and is qualified as either mood congruent (e.g., content is consistent with depressive theme) or mood incongruent. Research has suggested that persons diagnosed with psychotic depression are older, have worse premorbid functioning and longer depressive episode duration, and are more prone to future psychotic depressive episodes (Bromet et al., 1992; Craig, Grossman, Bromet, Fochtmann, & Carlson, 2007; Naz et al., 2007).

In addition, aspects about individuals’ course of illness—such as number of depressive episodes and duration of episodes, as well as age at onset of depression—may impact cognitive performance. Treatment resistance is also a relevant consideration, as it contributes to longer episodes, as well as the likelihood for exposure to more types of psychotropic medications and combinations of psychotropic medications for a longer period of time, which is negatively associated with cognitive function (Gibel & Ritsner, 2008; Neumann et al., 2002).

Of note, many studies included both inpatients and outpatients, which contributes to a wide range of severity in study samples being assessed. These patient samples (inpatients or outpatients) are likely to differ on all aspects of severity discussed above. In addition, they are likely to differ with respect to current treatments, as well as past treatment history, both of which may be associated with cognitive performance. Therefore, it is important to consider the distribution of such patients in studies examining cognitive impairment in depression.

### Recurrent and Single Episode Depression

For those persons diagnosed with MDD, between 50% and 75% experience more than one depressive episode (Gold & Chrousos, 2002; Harkness, Monroe, Simons, & Thase, 1999; Kennedy & Paykel, 2004). Typically, the subsequent depressive episode occurs within 6 months after recovering from the first episode, with recurrence increasing proportionally to the number of subsequent episodes (Angst, 1999). Illustrating the high recurrence rate, a longitudinal study following 69 participants with MDD over a 20-year time period showed that over 92% recovered on average by 12 months (median recovery time was 7 months) and 67% of those who recovered later had a recurrence of depression (Kennedy, Abbott, & Paykel, 2003).

Recurrent depression has been suggested to be more severe and disabling than single episode depression (Paradis, Reinherz, Giaconia, & Fitzmaurice, 2006). Those with chronic, recurrent depression have been shown to have more Axis I (i.e., anxiety, substance abuse), Axis II (i.e., personality disorder), and Axis III (i.e., somatic complaints, somatic diseases) comorbidities (Katon, 2003; Vuorilehto, Melartin, & Isometsa, 2005). Moreover, recurrent depression has been associated with increased negative perceptions of social stimuli (i.e., vocal expressions, facial expressions) and self (Bos et al., 2005), as well as poor marital and interpersonal relationships and poor employment functioning (Elinson, Houck, Marcus, & Pincus, 2004; Judd et al., 2000; Kennedy & Paykel, 2004; Kessler, 1997; Wilhelm, Parker, Dewhurst-Savellis, & Asghari, 1999), which suggests recurrent depression, relative to single episode, may be more deleterious. However, in The Netherlands Mental Health Survey and Incidence Study (Kuijshhaar, Hoeymans, Bijl, Spijker, & Essink-Bot, 2003), the severity of the depressive episode was found to be more related to increasing levels of disability as opposed to the number of depressive episodes. Thus, there is conflicting evidence as to whether severity of the depressive episode or the number of depressive episodes may contribute more strongly to the level of functional impairment.

Physiological correlates of recurrent MDD have included increased cortisol (Bos et al., 2005), glucocorticoids (Lampe et al., 2003), and decreased hippocampal volume (Neumeister et al., 2005). The reduction in the hippocampus was found to be most prominent in the posterior region that has specific implications in spatial learning and memory (Porter, Gallagher, Thompson, & Young, 2003). A relationship has been shown to exist between recurrent MDD and increased cortisol and decreased hippocampal volume, as well as reduced cerebral gray matter volume (i.e., decrease in neuron and glial cell density and size; Cotter, Mackay, Landau, Kerwin, & Everall, 2001; Rajkowska, 2000).

There is conflicting information regarding the association between cognitive function and recurrent depression. A major-
pressive episode (MDE) can be conceptualized as a traumatic event that potentially could harm the brain and negatively impact cognitive functioning, with more MDEs causing more harm than one (Altschuler, 1993; Fossati, Coyette, Ergis, & Allilaire, 2002; Rapp et al., 2005). Various researchers (Burt, Prudic, Peyser, Clark, & Sackeim, 2000; Grant, Thase, & Sweeney, 2001) have speculated that there is a cumulative, neurotoxic effect of MDEs on brain physiology, which may be associated with neuropsychological dysfunction. For example, the number of depressive episodes has been associated with a decrease in cognitive performance (Kessing, 1998) on the Cambridge Cognitive Examination total score (CAMCOG; Huppert, Brayne, Gill, Paykel, & Beardall, 1995), a computerized neuropsychological screening tool. Also, those with recurrent depression were found to be more impaired on the Wisconsin Card Sorting Test (Heaton et al., 1993), a measure of problem solving, the Paced Auditory Serial Addition Test (Gronwall, 1977), a measure of attention and working memory, and the Stroop test (Stroop, 1935), a measure of inhibition and executive function, compared to control participants (Stordal et al., 2004).

In contrast, research by Grant et al. (2001) showed no relationship between the number of MDEs and performance on the Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray, Robbins, & Sahakian, 1996), a computerized screening battery that assesses memory, attention, and executive function. The conflicting information regarding the association between the number of MDEs and neurocognitive performance could be attributable to multiple factors including methodological (i.e., different neuropsychological instruments) or sample (i.e., sociodemographic or clinical characteristics) related differences among studies. Also, although the number of MDEs may have a cumulative effect on cognitive function, several investigators suggested that after the depressive episode remits, cognitive functioning often returns to normal. During the euthymic state, it is believed that the brain heals itself, in turn improving and returning cognitive functioning back to normal (Hammar, Lund, & Hugdahl, 2003; Neu et al., 2005). However, other recent studies have suggested that at least certain aspects of neurocognitive dysfunction (e.g., effortful attention) are resistant to antidepressant treatment (e.g., selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitor) and remain even when the depressive episode has remitted (Gualtieri, Johnson, & Benedict, 2006; Paelecke-Habermann, Pohl, & Leblow, 2005).

Neurophysiological and Neurobiological Correlates of MDD

In general, MDD has often been associated with neurophysiological changes (Liotti & Mayberg, 2001). Studies using positron emission tomography (PET) have shown decreased regional cerebral blood flow (rCBF) in areas that have been implicated in affective disorders including the medial prefrontal cortex, anterior cingulate, and the orbital frontal cortex (Dolan, Bench, Brown, Scott, & Frackowiak, 1994; Elderkin-Thompson, Boone, Hwang, & Kumar, 2004). Moreover, in a study of 10 depressed patients assessing mood-congruent processing biases using functional magnetic resonance imaging (fMRI), it was found that abnormal responses were associated with the medial and orbital prefrontal cortices (Elliott et al., 2002). Other neuroimaging studies have shown abnormal functioning in frontal and limbic connections using MRI (Krishnan, Hays, & Blazer, 1997), or increased glucose metabolism in the caudate nucleus (Drevets, 2000), and the limbic regions (Alexopoulos et al., 2005) using PET. In the study by Krishnan et al. (1997), late-life depression was hypothesized to be related to vascular lesions in the frontal and limbic connections that may dysregulate norepinephrine and serotonin circuitry. This concept of “vascular depression” was proposed by Alexopoulos et al. (1997), based on their finding of associations between depression, vascular lesions, and vascular risk factors. Additional research has found that cerebral emboli were greatly associated with depressive symptoms, even after adjusting for demographic factors in a cohort of older patients with vascular dementia (Purandare et al., 2006). Though no investigations have examined the association between vascular lesions and depression severity, this line of investigation could provide useful information particularly with regard to addressing the effects of the number of lesions and depression severity, and then followed by treatment options (for a comprehensive review, see Blazer, 2009).

Neurobiologically, serotonergic and hypothalamic pituitary axis (HPA) dysfunction has been suggested to impact neurocognitive functioning in those persons with depression (McAllister-Williams, Ferrier, & Young, 1998). As identified in PET studies, the serotonergic system is abnormal in depressed patients as there are fewer serotonin receptors (i.e., 5-HT1a) and the serotonin transportation mechanism (5-HTT) is inefficient (Drevets, Frank, & Price, 1999). The above information helps to support the association between MDD, neuroanatomical regions, and neuropsychological processes; however, the nature of that relationship and the potential impact of other factors is unclear.

Pseudodementia

Depression, when very severe, has been reported to cause such significant cognitive impairments in some individuals such that persons may be described as having pseudodementia, which is defined as reversible impairment of memory secondary to depression (Salzman & Guiffreund, 1986). Although it may be difficult in rare cases to differentiate dementia from pseudodementia, in true dementia, cognitive decline progresses over time, whereas in pseudodementia, the cognitive loss follows after the onset of MDD (McBride & Abeles, 2000; Reynolds & Hoch, 1987; Reynolds et al., 1988). Disorders that cause dementia such as Alzheimer’s disease also tend to have characteristic neuropsychological profiles that help distinguish dementia from depression (Kasahara et al., 2006; Naugle, Cullum, & Bigler, 1998). There has been considerable debate as to whether depression serves as a prodromal stage (Broe et al., 1990) or a risk factor for dementia (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006; Devanand et al., 1996; Geda et al., 2006). For example, in a large cohort (N = 1,070) of community living people over the age of 65, pseudodementia showed a 0.6% prevalence rate, and of the six persons diagnosed with pseudodementia, only two developed dementia (Copeland et al., 1988). However, in a separate large cohort (N = 1,070) of persons age 60 years or older who were part of a dementia registry, baseline depressed mood was found to increase the risk of incident dementia (Devanand et al., 1996). Also, Saiz-Fonseca, Lee, and Walker (2007) found a relative risk of 3.929, 95% CI [1.985, 7.775], for the development of dementia in patients with
depression and pseudodementia on a 5- or 7-year follow-up examination. Further, a recent study suggested that patients with late-life depression, even after successful antidepressant treatment, were more likely to be diagnosed with mild cognitive impairment (nonamnestic or amnestic subtype) or dementia, relative to a matched control group (Bhalla et al., 2009). Thus, there is a complex association between depression and dementia (for a comprehensive review of the relationship between depression, pseudodementia, and dementia, see Butters et al., 2008).

Neurocognitive Studies of MDD

Cognitive dysfunction related to MDD (see Table 1 for details of the studies discussed in this section) has been reported in some, but not all studies (Gorlyn et al., 2006; F. C. Murphy, Michael, Robbins, & Sahakian, 2003; Shenal et al., 2003) that examined varying degrees of depression severity (Landro, Stiles, & Sletvold, 2001). In a study comparing 22 patients with nonpsychotic MDD to 30 healthy normal participants, Landro and colleagues (2001) found that those with MDD performed significantly worse in the domains of attention, working memory, verbal long-term memory, and verbal fluency. The depressed group scored more than 1.5 standard deviations lower in attention and working memory, 1.0 standard deviation lower in verbal long-term memory, and 0.5 standard deviations lower in verbal fluency. This is consistent with other findings indicating impairment in verbal fluency and cognitive flexibility (Beblo, Baumann, Bogerts, Wallewch, & Herrman, 1999; Leuchter et al., 2004). For example, Beblo et al. (1999) found that 41 depressed patients, compared to a control group, performed worse (i.e., 1 standard deviation) on verbal fluency (Controlled Oral Word Association Test; Benton & Hamsher, 1983) and design fluency. Another study comparing patients with bipolar disorder or MD, and controls found the MDD group scored lower on a measure of nonverbal memory from the CANTAB battery (i.e., Match to Sample Task) relative to the control group, but the difference was minimal (Sweeney, Kmiec, & Kupfer, 2000).

Clinically, the relationship between MDD and global cognitive function may be modulated by depression severity. For example, one report noted that patients who required hospitalization for depression were found to have greater cognitive difficulties (Rohling, Green, Allen, & Iversion, 2002). Even during euthymic and remission phases, the effects of depression severity may linger, influencing cognitive effectiveness. It has been postulated that due to the negative effects of the MDE, the brain, during the euthymic phase, is in a period of healing and may not function at its normal level (Kessing, 1998; Paradiso, Lamberty, Garvey, & Robinson, 1997). However, Hammar et al. (2003) found in a cohort of 21 patients (18 hospitalized) with MDD that cognitive functioning returned to normal during remission. Depression severity may particularly impact aspects of memory. In research comparing 26 patients with MDD, 28 with minor depression, and 38 healthy controls, those with MDD were significantly more impaired on tests of verbal recall and set maintenance relative to the other groups. Those with minor depression were found to be mildly impaired on a measure of executive functioning (Elderkin-Thompson et al., 2003), relative to healthy controls. Minor depression, as defined in the DSM–IV–TR (American Psychiatric Association, 2000), is similar to MDD, except it consists of having only two to five depressive symptoms (one symptom must be either sad mood or anhedonia) for a minimum of 2 weeks. In the above study by Elderkin-Thompson et al. (2003), working memory was assessed with the Digit Span subtest of the revised Wechsler Memory Scale (Wechsler, 1987) and executive functioning was assessed with a modified version of the Wisconsin Card Sorting Test. We found it interesting that other research has suggested that those with minor depression perform as well as controls on cognitive measures (Airaksinen, Larsson, Lundberg, & Forsell, 2004).

Even though much of the above information suggests that MDD is negatively associated with cognitive functioning, some research has disagreed with that relationship (Austin, Mitchell, & Goodwin, 2001). Particularly in young adult patients with mild to moderate depression, cognitive compromise seems to be rare. For example, Wang et al. (2006) found no differences in performance on a comprehensive battery of neuropsychological tests including the CANTAB, Trail Making Test Parts A and B, Digit Span, Continuous Performance Test, verbal fluency, the WCST, and the Category Test between mild to moderate depressed (N = 123, based on DSM–IV; American Psychiatric Association, 1994, criteria and the Beck Depression Inventory [BDI]; Beck, 1978) and healthy young adult control (N = 36) cohorts. Gorlyn et al. (2006) examined performance on the Wechsler Adult Intelligence Scale (3rd ed., WAIS–III; Wechsler, 1997) in 121 severely depressed patients (based on DSM–IV criteria and the HAM–D) and 41 healthy controls. The depressed group performed worse on the performance IQ subtests, particularly those that were timed (e.g., Coding, Symbol Search), which also resulted in low scores on the processing speed index. In a longitudinal study (Cysigue et al., 2007) assessing the impact of depression on cognitive functioning in a cohort of HIV positive men (N = 227), no relationship was found between mild trait depression and objective neuropsychological measures, although a relationship was found between trait depression and subjective cognitive complaints. In the Cysigue et al. (2007) study, neuropsychological performance was analyzed using normative adjusted T scores from the revised version of the Wechsler Adult Intelligence Scale (WAIS–R; Wechsler, 1981) and the Halstead–Reitan Battery (Heaton et al., 1991). Moreover, in a study of 30 patients with MDD, executive function was found to improve after remission was achieved (Birlinger et al., 2005). Further research may help elucidate the relationship between depression severity and neurocognitive functioning as well as discern if normalization of function is time dependent postremission.

Attention and Memory

Both automatic and effortful attention can be negatively affected by MDD. In a study (Farrin, Hull, Unwin, Wykes, & David, 2003) of 102 men with MDD compared to 59 controls, the depressed group performed significantly worse on the Sustained Attention to Response Task (SART; Robertson, Manly, & Andrade, 1997), a computer-administered test of visual attention. Also, impairment in divided attention, defined as difficulty in attending to both visual and auditory stimuli, was found to be predictive of the outcome of the depressive course in one study (Majer et al., 2004). In the study by Majer et al. (2004), the analyses controlled for age, gender, years of education, depression severity (as rated on the HAM–D), duration of illness, duration of hospitalization, type of antidepressant treatment, number of previous hospitalizations, and duration of illness. In the above study by Elderkin-Thompson et al. (2003), working memory was assessed with the Digit Span subtest of the revised Wechsler Memory Scale (Wechsler, 1987) and executive functioning was assessed with a modified version of the Wisconsin Card Sorting Test. We found it interesting that other research has suggested that those with minor depression perform as well as controls on cognitive measures (Airaksinen, Larsson, Lundberg, & Forsell, 2004).
sant (activating or sedating), and other psychotropic medications (neuroleptic, mood stabilizer, tranquilizer).

Depression may also negatively impact different types of memory, including explicit, implicit, short term, long term, and working memory (Nitschke, Heller, Etienne, & Miller, 2004; Wang et al., 2006). Performance on verbal memory tasks may result from poor frontal-temporal lobe functioning, preoccupation with negative thoughts, or decreased processing speed (Nebes et al., 2000). In a study examining the relationship of the BDI (Beck, 1978) to various versions of the California Verbal Learning Test (CVLT; e.g., adult, child; Delis, Kramer, Kaplan, & Ober, 1987; Delis, Kramer, Kaplan, & Ober, 1994), once adjusted for age, gender, and intelligence, depression accounted for only 2% of the variance in the CVLT score (O’Jile, Schrimsher, & O’Bryant, 2005). Contrary to the above, persons with MDD have been found to score between 0.5 and 1 standard deviation (corrected for age, education, and gender) below the normative population on the CVLT List A total Trials 1 to 5 (Otto et al., 1994). Behaviorally, MDD may also decrease individuals’ abilities to carry out instrumental activities of daily living, which may affect patients’ abilities to comply with cognitive testing (Kiosses & Alexopoulos, 2005) Thus, there is an indication that those with MDD may not perform as well as those without MDD on measures of attention and/or memory.

Executive Functioning

Executive functioning (EF) has been defined as “the ability to maintain an appropriate problem-solving set for attainment of a future goal” (Welsch & Pennington, 1988, p. 201). Expanding this definition, Welsch, Pennington, and Groisser (1991) added that EF includes the abilities of planning, performing organized searches, and controlling impulses.

EF can be negatively affected by depression as it has been shown to decrease initiation and problem solving (Elderkin-Thompson, Mintz, Haroon, Lavretsky, & Kumar, 2006; Harvey et al., 2004; Kiosses, Klimstra, Murphy, & Alexopoulos, 2001), affect planning (Rogers et al., 2004), impair verbal fluency (Henry & Crawford, 2005), and impede cognitive flexibility (Baudic, Tzortzis, Barba, & Traykov, 2004; Butters et al., 2004). Although there is no consensus on the mechanisms of action, it is believed that depression is associated with frontal cortical impairment, which in turn leads to executive dysfunction because EF is mainly governed by the frontal cortices (Alvarez & Emory, 2006; Bravers et al., 1997; Carpenter, Just, & Reichle, 2000; Dolan et al., 1994; Kaiser et al., 2003).

Research has indicated that depression severity may play a role in the degree of executive impairment (Taylor, Wagner, & Stefens, 2002). Although the Taylor et al. (2002) study included patients who were diagnosed with MCI at baseline, in a small cohort (N = 13) study, depression severity, as measured by the HAM-D (Hamilton, 1960) was found to be an independent predictor of total errors, perseverative responses, and failure to maintain set on the WCST (Martin, Oren, & Boon, 1991). Contrary to this finding, Harvey and colleagues (2004) found no relationship between depression severity and the WCST in 22 depressed patients. Also, in one study, those with MDD were found to perform similarly to those with schizophrenia on the California Card Sorting Test (Delis, Squire, Bihrl, & Massman, 1992). Both groups were found to be impaired in generating spontaneous sorts and they were unable to identify some of the sorting principles in the structured sort. The variable findings between the studies suggest that the relationship between EF and depression severity may be moderated by the EF measure used.

Influence of Medications and Comorbid Illness on Cognitive Function in MDD

It is important to consider not only the positive influence that antidepressant medication may have on cognitive function in depression, but also the potential adverse effects of pharmacotherapy. Here again, the impact of chronicity of depression is important because there is some evidence to suggest that long term and/or repeated exposure to some antidepressant medications may adversely affect cognitive function. For example, tricyclic antidepressants (e.g., amitriptyline, nortriptyline) may worsen some cognitive processes such as reaction time and information processing speed, possibly due to the anticholinergic effects of these medications, whereas it has been noted that Selective Serotonin Reuptake Inhibitor (SSRI) may hold some benefit for cognitive function, particularly in older adults (Brooks & Hoblyn, 2007). Similarly, medications for specific symptoms of depression, such as hypnotics used for insomnia, may independently impair cognitive function.

A related concern is the impact of comorbid diseases and depression. Depression is highly comorbid with many other chronic illnesses that can exert independent adverse effects on cognitive function. Increased age can be a contributing concern because the likelihood of comorbidity increases, as does the likelihood of polypharmacy, which may introduce additional adverse pharmacological effects on cognitive function. Psychiatric comorbidities such as substance abuse and anxiety are important to consider in depressed patients because of their independent potential effects on cognition. For example, substance abuse has been associated with both neurophysiological changes in frontostriatal brain regions, as well as objective cognitive impairments (Bechera & Martin, 2004; Lamers, Bechera, Rizzo, & Ramaekers, 2006; Robbins, Ersche, & Everitt, 2008; Salo, Ursu, Buonocore, Leamom, & Carter, 2009). Furthermore, treatments for substance use disorders, such as methadone and nicotine replacement therapies have also been associated with impaired cognitive function in some studies (Soyka et al., 2008; Spiga, Lintas, & Diana, 2008). Similarly, anxiety, also known to be highly comorbid with depression, can affect cognitive processing in some cases, and is often treated with benzodiazepines, which have known negative effects on cognitive function (Buffett-Jerrott & Stewart, 2002). In these cases, both the disease state and its treatment may contribute to cognitive impairments.

Many other general medical chronic diseases, such as diabetes and vascular illness, are highly comorbid with depression and can also independently impact cognitive function. Diabetes has been associated with some cognitive impairments (Awad, Gagnon, & Messier, 2004; Cukierman-Yaffe et al., 2009), and these deficits may worsen with increasing age and/or the presence of vascular disease or depressive symptomatology (Awad et al., 2004). Vascular illness is another example of a general medical condition that is highly comorbid with depression and associated with independent adverse effects on cognitive function (Roman et al., 2004; Sachdev et al., 2004; Waldstein et al., 2003). The potential cumulative and additive cognitive impairments arising from comorbid psychiatric and medical condi-
tions, as well as their treatments, must be considered when evaluating cognitive function in depression.

Summary of Findings

Depression is a significant clinical disease with varying levels of severity, each associated with degrees of impairment in the areas of social, functional, and interpersonal abilities. However, depression has been inconsistently associated with neurocognitive functioning (Gualtieri et al., 2006) and there is limited understanding regarding the relationship between depression severity and neurocognitive sequelae. Although research has shown detrimental effects in the domains of attention, learning and memory, and EF related to depression, there is disagreement as to the mediators of neurocognitive impairment, and for that matter, the mechanisms underlying the neurocognitive impairment. Several aspects of depression severity have been associated with more pronounced cognitive impairment, such as increased symptom severity at the time of neuropsychological testing. The presence of depression with psychosis may negatively impact neuropsychological domains such as EF, verbal and visual memory, and psychomotor skills to a greater extent relative to depression without psychotic features (Reichenberg et al., 2008). In addition, recurrent depression has been associated with worse cognitive performance compared to single-episode depression (Kessing, 1998), and longer depressive episodes have been associated with greater impairments on some aspects of executive function compared to shorter episodes (Grant et al., 2001). Age of onset of depression (Driscoll et al., 2005) is a more complicated factor, with some evidence suggesting that an early onset depression (i.e., onset before age 55) is associated with poorer cognitive function (Majer et al., 2004), although other evidence suggests that late-onset depression (i.e., onset at age ≥ 55) is associated with poorer cognitive function (Elderkin-Thompson et al., 2006; Rapp et al., 2005). However, many studies have found no relationship between course of illness factors and cognitive performance in depression (Biringer et al., 2005; Naismith et al., 2003; Porter et al., 2003), and still more have not included assessments of such a relationship. It is clear that there is much heterogeneity on severity-related factors (i.e., level of symptom severity, course of illness characteristics) within samples assessing cognitive function in MDD, as well as substantial variability in the consideration of severity among studies, resulting in the need to further explore this important issue.

Future Directions

Individual studies examining cognitive deficits associated with MDD tend to not provide consistent information regarding depression severity (Zakzanis et al., 1999), which has limited the understanding of the relationship between depression and neurocognitive function (Naismith et al., 2003). This may be attributed to many factors such as limitations in quantifying the level of depression severity and deciding how to measure depressive symptoms (Gullion & Rush, 1998). Although there is limited information regarding the cognitive effects associated with depression severity, this paucity in research demonstrates the importance of conducting further research in the relationship between cognitive functioning and intradomain specific depressive factors (Ebmeyer, Donaghey, & Steele, 2006).

Although depression can negatively impact cognitive functioning in some cases (Shen et al., 2003), it is important to understand what specifically about MDD is affecting cognitive abilities. Furthermore, the factors associated with cognitive dysfunction in depression are not well understood. There is considerable variability and not all persons with MDD show reduced cognitive performance, although estimates of dysfunction have been found to range from mild to severe in the depressive population (Elliott, 1998; Veiel, 1997). For example, is the variability in cognitive performance related to the number of depressive episodes, the severity of the major depressive episode, or the MDD subtype (i.e., melancholic, atypical)? Also, factors such as length of the depressive episode, onset of the depressive episode, and individual factors such as age, education, cognitive reserve, or genetic predisposition to depression, could play a role in the development of cognitive impairment secondary to depression.

Prior research has helped increase the understanding of the complex relationship between cognitive function and MDD; however, this understanding has been limited by small sample sizes, limited sociodemographic information (e.g., socioeconomic status, parental education), limited neurocognitive evaluations, and the use of either self-report or clinician-rated depressive instruments as opposed to both.

Table 2

Recommendations for Future Study Directions

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
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<tbody>
<tr>
<td>1. Comprehensively characterize the sociodemographics of the study sample</td>
<td>(a) Provide demographic adjusted neurocognitive scores (b) Allows for study of sociodemographic moderating factors</td>
</tr>
<tr>
<td>2. Include a comprehensive neuropsychological assessment that includes measures of</td>
<td>(a) Learning and memory (both verbal and visual) (b) Visuospatial abilities (c) Working memory (both verbal and visual) (d) Attention/concentration (e) Psychomotor speed (f) Executive functioning (g) Language functions (h) Intelligence or estimate of intellectual functioning (i) Social cognition (j) Subjective cognitive complaints</td>
</tr>
<tr>
<td>3. Base psychiatric diagnoses of depression on standardized, research diagnostic criteria</td>
<td>(a) Allows for establishing universally accepted diagnosis (b) Establishes homogenous groups (c) Collects comorbid psychiatric illnesses (d) Provides general assessment of global functioning</td>
</tr>
<tr>
<td>4. Utilize both clinician-rated and self-rated depression severity instruments that are identical in content</td>
<td>(a) Provides a mechanism to assess the relationship between objective and subjective clinical ratings with neurocognitive functioning (b) Identical clinician-rated and self-rated measures increases confidence of the ratings by reducing confounding and unidentical items</td>
</tr>
<tr>
<td>5. Comprehensively characterize the depressive illness</td>
<td>(a) Specify the depressive episode subtype (i.e., melancholic, atypical) (b) Specify the number of depressive episodes (c) Specify the duration of the current depressive episode (d) Specify age of onset of depressive episode</td>
</tr>
<tr>
<td>6. If diurnal variation is present, then provide assessment at opposite time (i.e., if mood worse in the morning, then test later in the day)</td>
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<td>7. Include neurobiological methods such as neuroimaging (i.e., fMRI) or neurochemical (i.e., cortisol) measures</td>
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Note. fMRI = functional MRI.
address these limitations, future investigations (see Table 2) may benefit from better characterizing the sociodemographic and clinical characteristics of the sample to account for potential moderating factors (De Santi et al., 2008; Manly, 2008; Manly & Echennindia, 2007; Marcopulos & McLain, 2003; Salthouse, 2007). Regarding depression severity, this could be enhanced by utilizing both self-report and clinician-rated depressive symptom severity instruments to help clarify the relationship between objective and subjective ratings on cognitive abilities. Also, the use of a standard neuropsychological battery that measures multiple-cognitive functions and includes demographic adjusted data would help to minimize age and education confounds. Given the limitations in prior studies and newer available methods, further research is needed to help clarify the relationship between major depressive disorder and cognitive functioning.

References


Received October 30, 2008
Revision received June 1, 2009
Accepted August 4, 2009