Published in final edited form as:

Biol Psychiatry. 2001 July 1; 50(1): 35–43.

Cognitive Disturbance in Outpatient Depressed Younger Adults: Evidence of Modest Impairment

Merida M. Grant, Michael E. Thase, and John A. Sweeney

Department of Psychology, University of Nebraska, Lincoln (MMG) and the Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (MET, JAS).

Abstract

Background—Investigations of cognitive disturbances among patients with mood disorders have yielded inconsistent results. Although marked neuropsychologic deficits have been reported in elderly patients and in midlife patients with severe depression, the severity of cognitive impairments in medically healthy younger ambulatory adults with depression has not been well characterized.

Methods—A comprehensive battery of standard neuropsychologic tests and experimental computerized measures of cognitive functioning were administered to unmedicated ambulatory younger adults with mild to moderate nonbipolar depression and to a group of age- and gender-equated healthy subjects.

Results—Patients demonstrated a notable absence of widespread cognitive impairment. Deficits in executive functions were observed on the Wisconsin Card Sort Test but not on several other tests. Despite the absence of significant impairment on tests of attention, memory, and motor performance in the total sample, symptom severity and age of illness onset were correlated with poorer performance on some tests of cognitive functioning even after correction for age.

Conclusions—These findings, derived from a large sample of unmedicated depressed outpatients, indicate that major depressive disorder in healthy younger ambulatory adults does not cause appreciable impairments in cognitive functioning in the absence of clinical and course-of-illness features.

Keywords

Cognition; depression; young adults; memory; executive functioning; CANTAB

Introduction

Depression-related disturbances of cognitive function have been demonstrated in a range of domains, including attention (Cornblatt et al 1989; Nelson et al 1998), memory (Austin et al 1992; Wolfe et al 1987), executive functioning (Merriam et al 1999; Silberman et al 1983; Sweeney et al 1998), and psychomotor functioning (for a review, see Sobin and Sackeim 1997). These abnormalities appear particularly pronounced in elderly patients and among midlife patients with melancholic or psychotic features (Austin et al 1992; Beats et al 1996;

Nelson et al 1998; Palmer et al 1996) but have not been well characterized in younger ambulatory patients with mild to moderate depression.

Structural abnormalities associated with aging, such as white matter lesions and subcortical volumetric changes, may explain some of the cognitive disturbances reported in elderly depressed patients (Alexopoulos et al 1997; Krishnan et al 1993). Moreover, altered glucocorticoid activity (i.e., hypercortisolemia), a correlate of more severe depression, has also been associated with atrophy and neurotoxicity in human and animal models of stress and aging (Lupien et al 1998; McIntosh et al 1998) and with cognitive disturbances primarily involving memory (Bemelmans et al 1996; Silberman et al 1983).

Although the precise mechanism is not clear, neuropsychological findings to date argue for a possible cumulative pathologic effect of recurrent episodes of depression or protracted duration of illness on frontostriatal and mesio-temporal brain regions in relation to depression. Animal models, for example, suggest repeated exposure to stress-induced secretion of corticosteroids may alter functioning of specific neural circuits, particularly those involving the hippocampus (McIntosh et al 1998). As well, hippocampal volume loss among depressed patients has been associated with the extent of past history of depression, plausibly mediated by glucocorticoid-induced neurotoxicity (Bremner et al 2000; Sheline et al 1999). Together, these studies suggest a possible mechanism for why more profound disturbances of cognitive function have been observed in elderly rather than younger adult depressed patients.

Remarkably few investigations of cognitive functioning have focused on younger depressed adult patients, and those that have been completed have reported inconsistent and contradictory findings. For instance, Austin et al (1992, 1999), in comparisons of endogenous and nonendogenous midlife medicated inpatients, found nonendogenous patients to be largely intact in most areas of functioning except memory (i.e., verbal learning and recall). This is similar to our recent findings (Sweeney et al 2000) in which nonbipolar depressed inpatients demonstrated deficits only on tests of episodic memory. In contrast, a recent study of young medicated inpatients (Fossati et al 1999) found no evidence of memory impairment but reported disturbances in several areas of executive functioning in relation to concept formation, cognitive flexibility, and response initiation. Similarly, Purcell et al (1997) reported only mild disturbances of executive functioning on a small number of attentional set shifting tasks and found no evidence of memory impairment. Discrepant outcomes across these few existing studies of younger depressed patients likely reflect the complex effects of psychotropic medications, small sample sizes, and the small number of tests often utilized to evaluate cognitive status.

Clarifying the extent of cognitive deficits in younger adults with depression is critical to the development of models of pathophysiology of the disorder. Specifically, it is important to determine whether cognitive deficits are the result of progressive effects over the course of illness and whether these deficits are present in younger as well as elderly adults. Determining the neuropsychological status of ambulatory depressed younger adults also may have important implications for clinical management. Such cognitive deficits could have a significant impact on social and occupational role functioning and may affect suitability of specific psychotherapeutic strategies and subsequent illness course (e.g., Thase et al 1996, 1997).

The aim of our study was to comprehensively assess a large cohort of unmedicated outpatients with major depression in the age range of young adulthood to midlife. We utilized both a battery of standardized neuropsychological tests of attention, memory, abstract problem solving, and motor skills and a computerized battery of cognitive tests, the

Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray et al 1996), to further target cognitive functions subserved primarily by the frontal and temporal lobes.

Methods and Materials

Patients

One hundred twenty-three outpatients with DSM-IV–defined nonbipolar, nonchronic (i.e., index episode less than 24 months) major depressive disorder without psychotic features were included in the current study. Diagnoses were established using the Structured Clinical Interview for DSM-IV Diagnoses (First et al 1997). In addition, a symptom severity score of ≥ 15 on the first 17 items of the Hamilton Rating Scale for Depression (HRSD; Hamilton 1960) was required for inclusion. Medical histories were taken, and where indicated, patients underwent physical examinations and laboratory screenings to verify the absence of medical conditions likely to cause depression or cognitive deficits. Other psychiatric illnesses reported among patients included current anxiety disorders ($n = 20$), a past history of alcohol/substance abuse and dependence ($n = 10$), past anxiety ($n = 1$), eating disorder ($n = 1$), and past history of dysthymia ($n = 2$). An age- and gender-equivalent healthy comparison group ($n = 36$) was recruited from the community by newspaper advertisement. Healthy individuals had never met criteria for an affective or psychotic illness, and no subject (neither patients nor healthy subjects) had a history significant for neurologic disease or substance abuse disorder within the past 6 months. Among the healthy subjects, a small number reported a past history of social phobia ($n = 2$), anorexia ($n = 1$), and substance abuse ($n = 1$).

Assessment of current clinical status was obtained with measures of clinician-rated symptomatology (i.e., 17-item HRSD), self-report (Beck 1967), and clinician-rated level of global functioning (Global Assessment Functioning, DSM-IV). Demographic and clinical characteristics of the samples are summarized in Table 1. Cognitive testing was performed following a 28-day medication-free period, during which subjects received supportive clinical management and single-blind placebos to ensure the presence of persistent depressive symptoms at the time of testing (Thase et al 2000). The neuropsychologic battery was administered to all patients admitted to the study, and CANTAB was administered to the last 48 patients recruited and to all healthy comparison subjects.

Neuropsychological Assessment

Participants completed a battery of neuropsychological tests designed to evaluate four domains of cognitive functioning: attention, motor speed, memory and learning, and executive processes. The entire evaluation took approximately 3.5 hours to complete, including about 90 min for CANTAB.

ATTENTION/MOTOR—Attention and motor speed were assessed with three measures, the Halstead–Reitan Trail Making Test (Part A) of psychomotor speed, the Digit Span test of verbal attention, and the Continuous Performance Test (CPT; Cornblatt et al 1989) of sustained attention. Performance scores on visual and verbal components of the CPT were expressed by d' , a measure of actual discriminative ability. A measure of conservative response bias (β) was also obtained to reflect the degree of certainty required before subjects identified stimuli as actual targets.

MEMORY/LEARNING—Both verbal and visuospatial memory and learning were evaluated. The Hopkins Verbal Learning Test (Brandt 1991) was administered to assess immediate and delayed verbal memory. The test requires subjects to recall a list of 12 words after each of three presentations. Measures of free recall and recognition memory were

obtained after a 30-min delay. The Weschler Memory Scale–Revised, Visual Reproduction (Weschler 1987) was used as a measure of immediate and delayed visual memory.

EXECUTIVE FUNCTIONS—Executive functioning was assessed with several measures: 1) the Halstead–Reitan Categories Test of concept formation; 2) the Controlled Oral Word Fluency test of verbal fluency (form FAS); 3) the Wisconsin Card Sort Test (WCST), which assesses concept formation and the ability to maintain and shift mental sets; and 4) the Trail Making Test (Part B), which assesses the ability to flexibly shift response sets.

Computerized Cognitive Testing

CANTAB (Fray et al 1996), a set of computerized tests of memory, attention, and executive processes, was presented on a high-resolution touch-screen monitor. This battery included control tasks such as Big Circle/Little Circle, Five Stage Reaction Time, and Match to Sample tests to assess psychomotor speed, spatial perceptual ability, and general ability to follow instructions, which may influence performance on higher cognitive tasks. The Big Circle/Little Circle task tested reaction time and the ability to follow and then reverse rule-based responses. The Match to Sample visual search task was used to evaluate both simple reaction time and movement time. Subjects were shown a pattern presented inside a red square; similar patterns then appeared in a circle of boxes around the edge of the screen. Subjects held down a press pad and released it to identify the matching pattern by touch.

TESTS SENSITIVE TO FRONTOSTRIATAL DYSFUNCTION

Planning Task: The Stockings of Cambridge task is a measure of planning ability based on the Tower of London task (Shallice 1982). Subjects are required to rearrange colored balls in vertical columns to replicate the pattern presented and are instructed to plan the sequence of moves before initiation of movement. Performance is assessed on the basis of the time necessary to complete the pattern and the total number of moves required to correctly arrange the colored balls.

Spatial Working Memory Task: The Spatial Working Memory task is a self-ordered search task assessing both mnemonic and strategic aspects of working memory. Subjects are asked to search through boxes on the screen to discover hidden tokens. They are instructed that once a token is discovered on a trial, that box will no longer hide tokens on subsequent trials. Both between-search errors (searching a box in which a token was found on a previous trial) and within-search errors (searching the same box twice in a trial) are tabulated. The subject's ability to adopt a consistent search strategy is also evaluated. Task difficulty is manipulated by increasing the number of boxes presented in a block of trials (i.e., hiding targets behind 4, 6, or 8 boxes).

Intradimensional/Extradimensional (ID/ED) Attentional Set Shifting Task: This test was designed to examine processes similar to those evaluated by the WCST (Berg 1948). It assesses the ability to maintain attention to different examples within a stimulus dimension (intradimensional stages) and the ability to shift attention to a previously irrelevant stimulus dimension. Performance is assessed on the basis of the number of stages/categories completed and the number of errors before and during the extradimensional shift.

Spatial Recognition Memory Task

This task assesses visuospatial recognition ability. Five squares are presented sequentially at different locations on the screen, followed by a paired series of novel and previously shown items. Subjects must identify the location at which a square was previously presented.

TESTS SENSITIVE TO TEMPORAL AND PARIETAL LOBE DYSFUNCTION

Simultaneous and Delayed Match to Sample: This task assesses the ability to recognize complex visual designs over different delay intervals (0, 4, 12 sec). Subjects are shown a target at screen center, and after the delay interval, four surrounding stimuli are presented. Subjects are told to identify the design identical to the one initially presented. Performance is based on the ability to identify the previously presented stimulus from an array following a delay interval.

Pattern Recognition Memory Task: This task assesses the ability to recognize previously presented stimuli in the form of abstract patterns. After a series of patterns are displayed, subjects are presented pairs of patterns, one novel and one previously shown. Subjects are asked to identify the pattern previously presented.

Paired Associates Learning: This task is a measure of the ability to learn visuospatial associations. Designs are presented in boxes on the screen at varying locations. The designs are then presented sequentially in the center of the screen and subjects are instructed to indicate the box in which each design was initially presented. Subjects are asked to indicate the box in which each design was presented.

Spatial Span Test: This task is a test of spatial short-term memory that examines the ability to remember the location of sequentially presented stimuli, similar to the Corsi block test (Milner 1971). Nine white squares are presented on the monitor and the squares change color one by one. Subjects are then to indicate the order in which the squares change color. Trials progress from sequences of 2–9 squares. If a subject fails to correctly remember the order of color change in all three trials, the test is terminated. Performance is assessed according to the number of items remembered in sequence.

Statistical Analysis

The primary statistical analyses were *t* tests and χ^2 tests contrasting the performance of patients and healthy individuals. Repeated-measures analyses of variance (ANOVAs) were performed on tasks with experimentally manipulated levels of difficulty. Log transformations (base 10) were performed on several measures to normalize skewed distributions, including measures from the Wechsler Memory Scale, WCST, ID/ED shift, Recognition Memory (Spatial and Pattern), and Stockings of Cambridge. The means and SDs presented in the tables represent the raw data. The unequal variance *t* statistic, degrees of freedom, and *p* values were used when variances were not equal across groups. Age-corrected exploratory correlational analyses between clinical measures and cognitive performance also were performed.

Analyses were also conducted to address whether there were significant differences in cognitive functioning between patients whose depressive symptoms improved over 28 days in the absence of treatment and those with more persistent symptoms. Separation of patients with persistent depressive symptoms from those who improved was made according to two criteria: 1) an improvement dimension indicating a greater than 20% decrease on the HRSD total score between the baseline evaluation and the time of neuropsychological testing and 2) a symptom severity dimension using the HRSD score at the time of neuropsychological evaluation to stratify patients into two groups (above/below 20).

Results

Neuropsychological Battery

ATTENTION/MOTOR—Performance of both subject groups on each cognitive task and univariate group comparisons are presented in Table 2. No performance differences were found between patients and healthy subjects on any measure of attention or psychomotor functioning.

MEMORY—No deficit in memory functioning was observed in the depressed patients. In fact, patients actually performed better than healthy subjects on measures of immediate and delayed visual memory assessed by the Wechsler Memory Scale–Revised, verbal learning trials 2–3, and delayed recall on the Hopkins Verbal Learning Test. No differences were found for either trial 1 or recognition memory testing on the Hopkins Verbal Learning Test.

EXECUTIVE—Patients showed impaired performance on the WCST on several parameters, including the number of categories completed, perseverative responses, perseverative errors, and failures to maintain set. However, deficits were not seen in any of the other tests of executive functioning, including Trails B, Categories, and Verbal Fluency.

CANTAB (See Table 3)

No significant group differences were noted for measures of executive functioning (Table 3), including the strategy score on the Spatial Working Memory, Spatial Recognition Memory, the Stockings of Cambridge, and the ID/ED shift tests (t values between 0.20 and 1.09, *ns*). Similarly, no significant differences between depressed patients and healthy individuals were noted for measures of memory and learning, including the Simultaneous and Delayed Match to Sample, Pattern Recognition Memory, Paired Associates Learning, and Spatial Span tasks.

Correlations of Clinical Status with Cognitive Performance

ACUTE ILLNESS SEVERITY—Age-corrected exploratory analyses of correlations between clinical measures of depression and neuropsychologic functioning did not reveal significant relationships between either self-reported or clinician-rated severity of depression and measures of executive functioning, memory, attention, or psychomotor performance on the standardized neuropsychologic battery. However, modest relationships between clinician-rated level of depression severity and performance on some tasks from CANTAB were found on measures of executive functioning, including the number of stages completed and the total number of errors on the ID/ED shift task ($r = -.39$ and $.38$, respectively; $p < .01$). Motor skill and reaction times as assessed by the Five Stage Reaction Time task were also related to clinician-rated illness severity, such that increased severity was associated with slower reaction times ($r = .32$, $p < .05$). No significant correlations were found between illness severity and other CANTAB measures.

PERSISTENCE OF DEPRESSIVE SYMPTOMS—No performance differences were found between patients whose HRSD scores improved at least 20% between the presenting level of severity and the completion of the 28-day lead-in on any measure of attention, memory and learning, executive functioning, or psychomotor functioning on the standard neuropsychologic battery. Differences were noted, however, on the CANTAB Delayed Match to Sample task (total correct, all delays and the probability of an error given the correct response on the preceding trial, $t = 3.21$ and $t = 3.33$, $p < .05$).

Consistent with our findings on executive functioning in patients and healthy subjects, patients whose HRSD scores remained above 20 after the 28-day lead-in performed more

poorly on the WCST than those whose HRSD scores improved (categories completed, $t = 2.01$; number of errors, $t = 2.62$; perseverative errors, $t = 2.61$, $p < .05$), but not on the other measures of executive functioning. No significant differences were found for measures of attention, memory and learning, or psychomotor performance. Findings from CANTAB also revealed more impaired executive functioning on the ID/ED task in those patients whose HRSD scores were above 20 at the time of testing (stages completed and total number of errors, $t = 2.54$, $p < .05$; $t = 2.73$, $p < .01$).

COURSE OF ILLNESS—Age-corrected correlations between neuropsychologic tasks and illness characteristics such as age of onset and duration of illness revealed somewhat more robust relationships than were found for acute illness severity. Significant age-corrected correlations were found between age of onset of first episode and measures of attention (visual discrimination on the CPT, $r = -.42$, $p < .01$), psychomotor speed (Digit Symbol, $r = -.35$, $p < .05$), and executive functioning (WCST: number of categories completed, $r = -.33$, $p < .05$; number of errors, $r = .35$, $p < .05$; failure to maintain set, $r = .29$, $p < .05$). These findings consistently indicated poorer performance associated with later age of onset, even after controlling for current age. The only significant neuropsychologic correlate of duration of the index episode was failure to maintain set on the WCST, such that longer depressive episodes were associated with poorer performance ($r = .35$, $p < .05$). Exploratory ANOVAs did not reveal significant relationships between the number of prior episodes (0, 1–2, and 3 or more episodes) and neuropsychologic functioning on either the standard battery of tests or CANTAB.

Discussion

The most striking finding from the current study was the absence of significant cognitive impairment on the majority of both standardized neuropsychologic tests and experimental computerized cognitive measures in younger ambulatory adults with major depression. Intact attentional, memory, and motor functioning were noted across batteries, with some suggestion of impaired executive functioning provided by the WCST. These findings from a large sample of younger (average age 39.0 years), unmedicated depressed patients using a comprehensive neurocognitive assessment indicate that major depressive disorder per se in young ambulatory adults is associated with only minimal cognitive deficits. These findings are consistent with those of several other recent studies of smaller samples of younger medicated depressed patients (Fossati et al 1999; Purcell et al 1997) but are notably different from the more consistent findings of cognitive impairments reported among older depressed patients (Beats et al 1996; Elliott et al 1996; Harvey et al 1997; Palmer et al 1996).

Executive Processes

Although overall cognitive performance was largely unimpaired, there was some suggestion of disturbance in executive functioning among the depressed group on the WCST. Depressed patients completed fewer categories and showed increased perseveration and poor maintenance of set, suggesting some disturbance in the ability to generate and subsequently maintain problem-solving strategies in working memory, as well as in set-shifting ability. Across tasks, however, there was no consistent evidence of disturbances of executive functioning. Similarly, findings from CANTAB on tasks of spatial working memory, dimensional set shifting, and recognition memory did not reveal impaired performance among depressed patients.

These findings are in contrast to those from several prior studies that have reported disturbances in frontal lobe functions in nonbipolar depressed patients (Elliott et al 1996; Franke et al 1993; Merriam et al 1999; Savard et al 1980; Sweeney et al 1998). However,

subjects in those studies were often inpatients and were typically more severely ill. For comparison purposes, it should be noted that disturbances reported in prior studies of younger depressed patients were not as severe as those demonstrated by patients with schizophrenia (Goldberg et al 1993; Merriam et al 1999).

Attention and Motor Skills

No impairment of attention or motor performance was noted among depressed patients when compared with healthy subjects. Again, this was true across tasks from both the standardized neuropsychologic battery and CANTAB, suggesting no significant disturbance of attentional or motor system functioning among younger ambulatory depressed patients.

Memory and Learning

We observed no impairment on memory and learning tests, with depressed patients performing either as well as or better than healthy individuals. These findings were somewhat surprising, given findings from prior studies suggesting disturbances of memory that have been associated with mesial temporal lobe abnormalities in nonbipolar depression (Bemelmans et al 1996; Isley et al 1995; Sheline et al 1999; Wolfe et al 1987). Prior studies have suggested a link between impaired memory in depression and elevated cortisol levels. Again, previous studies demonstrating memory and temporal lobe abnormalities have primarily focused on older or more severely ill patients. These deficits may be explained by structural or functional changes associated with illness severity, aging effects, or a possible cumulative pathologic effect of depression on brain structure and function across recurrent episodes of illness (Alexopoulos et al 1997; Krishnan et al 1993).

Clinical Correlates of Performance

Higher symptom severity scores were not associated with impaired functioning on measures of attention, memory, executive functioning, or psychomotor functioning after correcting for age effects on the standardized neuropsychologic battery. On CANTAB, modest relationships between illness severity and performance deficits were observed for attentional shifting and psychomotor speed. Further analysis of persistent severity among patients did reveal a modest relationship with impaired executive functioning. Although the existing literature, including our previous reports, indicates cognitive deficits among more severely ill young hospitalized adults with depression, our current findings indicate that cognitive impairments are modest and not pervasive, even among the more severely depressed of our patients.

There was a notable absence of a relationship between the number of prior episodes of depression and cognitive impairment in younger ambulatory depressed adults, an observation that may have important clinical implications. For example, after controlling for age differences, Thase et al (1995) found that ambulatory young patients with recurrent depression were more likely to manifest disturbances of sleep neurophysiology and were subsequently less likely to remain well after treatment with cognitive behavior therapy (Thase et al 1996). Similar relationships have been observed in studies using various measures of hypercortisolism (e.g., Meador-Woodruff et al 1987; Thase et al 1996). Together, these findings suggest recurrent depression might result in persistent neurobiological and neurocognitive changes. However, findings from our study did not support this relationship and instead suggest only modest impairment of some executive functions. These contrasting findings regarding sleep neurophysiology and neuroendocrine functioning in comparison to cognitive functioning among younger ambulatory depressed patients indicate perhaps either divergent pathophysiology underlying these dysfunctions or possible differences in susceptibility to dysregulation between functions.

Despite the absence of widespread impairment among this younger sample, there were some indications that course of illness measures were associated with impaired functioning, such that a relatively later age of onset was associated with poorer performance, even after controlling for age. It should be noted that, though a robust relationship between symptom severity and cognitive functioning was not found, the range of severity was truncated by the nature of the study sample (i.e., outpatients), which may have limited the ability to discern between-group differences. Also, our study design was unique in that there was a 28-day lead-in before neuropsychologic evaluation. No active medications were allowed during this time. This was done to ensure that we were assessing persistent depression rather than more transient dysphoric states. Although symptoms persisted, mean severity on the clinician-rated scale (17-item HRSD) at testing was in the mild to moderate range (mean = 16.7, SD = 5.4).

It is possible that cognitive deficits may have been more evident when patients first presented for treatment. However, our analyses revealed only modest relationships between persistent illness severity and some impairment on executive tasks. These findings indicate that major depressive disorder in ambulatory younger adults does not typically cause appreciable changes in neurocognitive functioning, although deficits may exist among those with later age of onset or perhaps marked acute illness severity. Interpretation of the associations between clinical status and cognitive function needs to be tempered by our use of unprotected exploratory analyses that were included primarily for the purpose of providing a complete presentation of our data and generating hypotheses for future investigations. Of course, further prospective investigations of illness factors are needed to extend these findings to more severely ill young adults with depression and to compare cognitive functioning in depressed individuals over the life span, utilizing methods that prospectively assess duration of illness.

Acknowledgments

This work was supported in part by Grants Nos. MH41884, MH01433, MH42969, and MH30915 (Mental Health Clinical Research Center for the Study of Affective Disorders) and by the John D. and Catherine T. MacArthur Foundation Research Network on Psychopathology and Development.

The authors acknowledge Amy Fasiczka, M.A., Julie Kmiec, B.A., and Jill Brown for their technical assistance with data collection and management in the completion of this research.

References

- Alexopoulos GS, Meyer B, Young R, Kakuma R, Silbersweig D, Charlson D. Clinically defined vascular depression. *Am J Psychi* 1997;154:305–312.
- Austin M, Mitchell P, Wilhelm K, Parker G, Hickie I, Brodaty H, et al. Cognitive function in depression: A distinct pattern of frontal impairment in melancholia. *Psychol Med* 1999;29:73–85. [PubMed: 10077295]
- Austin M, Ross M, Murray C, O'Carroll R, Ebmeier K, Goodwin G. Cognitive function in major depression. *J Affect Disord* 1992;25:21–30. [PubMed: 1624644]
- Beats BC, Sahakian BJ, Levy R. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol Med* 1996;26:591–604. [PubMed: 8733217]
- Beck, AT. *Depression: Clinical, Experimental and Theoretical Aspects*. Harper & Row; New York: 1967.
- Bemelmans K, Goekoop J, van Kempen G. Recall performance in acutely depressed patients and plasma cortisol. *Biol Psychiatry* 1996;39:750–752. [PubMed: 8731465]
- Berg EA. A simple objective treatment for measuring flexibility in thinking. *Journal of General Psychology* 1948;39:15–22. [PubMed: 18889466]

- Brandt J. The Hopkins Verbal Learning Test: Development of a new verbal memory test with six equivalent forms. *Clin Neuropsychol* 1991;5:125–142.
- Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. *Am J Psychiatry* 2000;157:115–117. [PubMed: 10618023]
- Cornblatt B, Lenzenweger M, Erlenmeyer-Kimling L. The continuous performance test, identical pairs version: II. Contrasting attentional profiles in schizophrenic and depressed patients. *Psychiatry Res* 1989;29:65–85. [PubMed: 2772099]
- Elliott R, Sahakian BJ, McKay AP, Herrod JJ. Neuropsychological impairments in unipolar depression: The influence of perceived failure on subsequent performance. *Psychol Med* 1996;26:975–989. [PubMed: 8878330]
- First, MB.; Spitzer, R.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), Clinician Version. American Psychiatric Press; Washington, DC: 1997.
- Fossati P, Amar G, Raoux N, Ergis A, Allilaire JF. Executive functioning and verbal memory in young patients with unipolar depression and schizophrenia. *Psychiatry Res* 1999;89:171–187. [PubMed: 10708264]
- Franke P, Maier W, Hardt J, Frieboes R, Lichtermann D, Hain C. Assessment of frontal lobe functioning in schizophrenia and unipolar major depression. *Psychopathology* 1993;26:76–84. [PubMed: 8321896]
- Fray PJ, Robbins TW, Sahakian BJ. Neuropsychiatric applications of CANTAB. *Int J Geriatr Psychiatry* 1996;11:329–336.
- Goldberg T, Gold J, Greenberg R, Griffin S, Schulz C, Pickar D, et al. Contrasts between patients with affective disorders and patients with schizophrenia on a neuropsychological test battery. *Am J Psychiatry* 1993;150:1355–1362. [PubMed: 8352346]
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62. [PubMed: 14399272]
- Harvey PD, Powchek P, Parella M, White L, Davidson M. Symptom severity and cognitive impairment in chronically hospitalized geriatric patients with affective disorders. *Br J Psychiatry* 1997;170:369–374. [PubMed: 9246257]
- Isley J, Moffoot AP, O'Carroll RE. An analysis of memory dysfunction in major depression. *J Affect Disord* 1995;35:1–9. [PubMed: 8557882]
- Krishnan KR, McDonald W, Doraiswamy P, Na C, Jusain M, Figiel G, et al. Neuroanatomical substrates of depression in the elderly. *Eur Arch Psychiatry Clin Neurosci* 1993;243:41–46. [PubMed: 8399409]
- Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci* 1998;1:3–4. [PubMed: 10195096]
- McIntosh LJ, Hong KE, Sapolsky RM. Glucocorticoids may alter antioxidant enzyme capacity in the brain: Baseline studies. *Brain Res* 1998;791:209–214. [PubMed: 9593898]
- Meador-Woodruff JH, Gurguis G, Grunhaus L, Haskett R, Greden JF. Multiple depressive episodes and plasma postdexamethasone cortisol levels. *Biol Psychiatry* 1987;22:583–592. [PubMed: 3580433]
- Merriam E, Thase M, Haas G, Keshavan M, Sweeney JA. Prefrontal cortical dysfunction in depression determined by Wisconsin card sorting test performance. *Am J Psychiatry* 1999;156:780–782. [PubMed: 10327916]
- Milner B. Interhemispheric differences in localization of psychological processes in man. *Br Med Bull* 1971;27:272–277. [PubMed: 4937273]
- Nelson EB, Sax KW, Strakowski SM. Attentional performance in patients with psychotic and nonpsychotic major depression and schizophrenia. *Am J Psychiatry* 1998;155:137–139. [PubMed: 9433355]
- Palmer P, Boone K, Lesser I, Wohl M, Berman N, Miller B. Neuropsychological deficits among older depressed patients with predominantly psychological or vegetative symptoms. *J Affect Disord* 1996;41:17–24. [PubMed: 8938201]
- Purcell R, Maruff P, Kyrios M, Pantelis C. Neuropsychological function in young patients with unipolar major depression. *Psychol Med* 1997;27:1277–1285. [PubMed: 9403899]

- Savard R, Rey A, Post RM. Halstead-Reitan category test in bipolar and unipolar affective disorders: Relationship to age and phase of illness. *J Nerv Ment Dis* 1980;168:297–304. [PubMed: 7365494]
- Shallice T. Specific impairments of planning. *Philos Trans R Soc Lond B Biol Sci* 1982;298:199–209. [PubMed: 6125971]
- Sheline Y, Sanghavi M, Mintun M, Gado M. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 1999;19:5034–5043. [PubMed: 10366636]
- Silberman E, Weingartner H, Post RM. Thinking disorder in depression. *Arch Gen Psychiatry* 1983;40:775–780. [PubMed: 6860078]
- Sobin C, Sackeim HA. Psychomotor symptoms of depression. *Am J Psychiatry* 1997;154:4–17. [PubMed: 8988952]
- Sweeney JA, Kmiec J, Kupfer D. Neuropsychological impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biol Psychiatry* 2000;48:674–684. [PubMed: 11032979]
- Sweeney JA, Strojwas M, Mann JJ, Thase ME. Prefrontal and cerebellar abnormalities in major depression: Evidence from oculomotor studies. *Biol Psychiatry* 1998;43:584–594. [PubMed: 9564443]
- Thase ME, Dubé S, Bowler K, Howland RH, Myers JE, Friedman E, Jarrett DB. Hypothalamic-pituitary-adrenocortical activity and response to cognitive behavior therapy in unmedicated, hospitalized depressed patients. *Am J Psychiatry* 1996;153:886–891. [PubMed: 8659610]
- Thase ME, Friedman ES, Berman SR, Fasiczka AL, Lis JA, Howland RH, Simons AD. Is cognitive behavior therapy just a “nonspecific” intervention for depression? A retrospective comparison of consecutive cohorts treated with cognitive behavior therapy or supportive counseling and pill placebo. *J Affect Disord* 2000;57:63–71. [PubMed: 10708817]
- Thase ME, Greenhouse JB, Frank E, Reynolds CF, Pilkonis PA, Hurley K, et al. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Arch Gen Psychiatry* 1997;54:1009–15. [PubMed: 9366657]
- Thase ME, Kupfer DJ, Buysee DJ, Frank E, Simons AD, McEarchran AB, et al. Electroencephalographic sleep profiles in single-episode and recurrent unipolar forms of major depression: I. Comparison during acute depressive states. *Biol Psychiatry* 1995;38:506–515. [PubMed: 8562662]
- Wechsler, D. Wechsler Memory Scale-Revised Manual. Psychological Corp.; San Antonio: 1987.
- Wolfe J, Granholm E, Butters N, Saunders E, Janowski D. Verbal memory deficits associated with major affective disorders: A comparison of unipolar and bipolar patients. *J Affect Disord* 1987;13:83–92. [PubMed: 2959704]

Table 1

Demographic Characteristics of Patients and Matched Healthy Comparison Subjects

	Patients (<i>N</i> = 123) Mean (SD)	Healthy subjects (<i>N</i> = 36) Mean (SD)	Test statistic	<i>p</i>
Variables				
Age	39.0 (10.4)	40.2 (9.7)	<i>t</i> = 0.58	.55
Education	15.1 (2.4)	14.9 (2.6)	<i>t</i> = 0.36	.72
IQ (Verbal)	107.9 (11.4)	107.1 (14.1)	<i>t</i> = 0.31	.75
Gender	48:75	13:23	χ^2 = .10	.75
HRSD-17	16.7 (5.4)	1.4 (1.5)	<i>t</i> = 28.2	.001
BDI	17.3 (9.1)	1.5 (1.6)	<i>t</i> = 18.4	.001
GAF	60.6 (9.4)	85.6 (3.6)	<i>t</i> = 24.2	.001
Number of episodes	2.5 (3.0)			
Single episode	42 patients			
1–2 episodes	38 patients			
3+ episodes	43 patients			
Duration (weeks) ^a	25.9 (20.9)			
Age of onset (years) ^b	27.9 (12.5)			

IQ (Verbal), Ammons Verbal IQ score; HRSD-17, 17-item Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; GAF, Global Assessment of Functioning.

^aOf the index episode.

^bAt first episode of depression.

Table 2

Comparisons of Patients and Healthy Comparison Subjects on the Standard Neuropsychologic Battery

Measure	Patients (N = 123) Mean (SD)	Healthy subjects (N = 36) Mean (SD)	t value
Attention/motor			
Trail Making Test (A)			
Response time (sec)	27.6 (8.3)	28.3 (8.6)	$t = 0.48$, ns
Digit Span			
Numbers recalled	11.0 (2.6)	10.8 (2.8)	$t = 0.28$, ns
Continuous Performance Test			
d' verbal	1.9 (0.9)	2.0 (0.8)	$t = 0.85$, ns
d' visual	1.6 (0.7)	1.6 (0.8)	$t = 0.43$, ns
Digit Symbol			
Number of symbols	60.2 (10.3)	62.2 (9.7)	$t = 1.05$, ns
Memory/learning ^a			
Wechsler Memory Scale, Visual Reproduction			
Immediate recall ^b	35.7 (3.2)	34.3 (3.2)	$t = 2.25$, $p = .03$
Delayed recall ^b	34.8 (3.6)	31.7 (5.5)	$t = 3.11$, $p = .03$
Hopkins Verbal Learning Test			
Trial 1	6.5 (0.9)	6.1 (2.02)	$t = 0.96$, ns
Trial 2	9.2 (1.6)	8.4 (2.0)	$t = 2.33$, $p = .02$
Trial 3	10.2 (1.4)	9.4 (1.8)	$t = 2.35$, $p = .03$
Delayed recall	9.3 (2.0)	7.2 (3.5)	$t = 3.07$, $p = .004$
Discrimination index	10.8 (1.1)	10.0 (2.1)	$t = 1.73$, ns
Executive			
Trial Making Test (B)			
Response time (sec)	58.02 (16.9)	60.01 (16.7)	$t = 0.61$, ns
Halstead-Reitan Categories Test	43.2 (26.9)	45.5 (23.2)	$t = 0.44$, ns
Verbal fluency			
Words generated	40.5 (10.7)	43.3 (9.7)	$t = 1.36$, ns
Wisconsin Card Sort Test			
Categories ^b	5.1 (1.4)	5.6 (0.9)	$t = 2.24$, $p = .03$
Errors	29.5 (18.0)	24.0 (16.2)	$t = 1.61$, ns
Perseverative responses ^b	16.2 (11.5)	11.5 (7.9)	$t = 2.39$, $p = .02$
Perseverative errors ^b	13.2 (6.5)	10.6 (4.7)	$t = 2.23$, $p = .03$
Failure to maintain set ^b	1.0 (1.2)	0.5 (0.7)	$t = 2.01$, $p = .05$
Learning to learn ^b	-0.5 (3.2)	0.2 (2.2)	$t = 2.59$, $p = .02$

^aHigher scores indicate better performance. Depressed subjects reported no deficits and actually performed better than healthy subjects.^bLog transformation (base 10) of data performed before analysis.

Table 3

Comparison of Patients and Healthy Comparison Subjects on CANTAB

	Patients (N = 48) Mean (SD)	Healthy Subjects (N = 31) Mean (SD)	t value
Big Circle/Little Circle			
Mean correct latency	760 (148)	812 (175)	$t = 1.42$, ns
Delayed Match to Sample			
Latency, simultaneous	2962 (842)	2879 (586)	$t = 0.48$, ns
Latency, all delays	3661 (1,088)	3489 (834)	$t = 0.75$, ns
ID/ED shift			
Pre-ED errors	6.4 (4.6)	6.4 (2.8)	$t = 0.03$, ns
EDS errors, adjusted ^a	10.8 (3.1)	11.1 (3.9)	$t = 0.50$, ns
Stages completed	8.8 (0.7)	8.87 (0.5)	$t = 0.37$, ns
Match to Sample			
Percent correct	94.9 (4.4)	96.5 (3.1)	$t = 1.79$, ns
Mean correct latency	1239 (639)	1843 (573)	$t = 4.21$, $p = .001$
Paired Associates Learning			
Total errors, adjusted	9.56 (8.5)	11.9 (17.8)	$t = 0.73$, ns
Reaction time			
5-choice reaction time	332 (48)	373 (70)	$t = 3.04$, $p = .003$
5-choice movement time	561 (108)	624 (112)	$t = 2.44$, $p = .02$
Spatial/pattern Recognition Memory			
% correct, Spatial ^a	83.4 (10.4)	80.7 (11.7)	$t = 1.09$, ns
% correct, Pattern ^a	87.6 (11.0)	88.6 (8.7)	$t = 0.43$, ns
Spatial Span			
Span length	6.8 (1.4)	6.2 (1.3)	$t = 1.94$, ns
Spatial Working Memory			
Strategy	33.3 (5.5)	35.1 (2.9)	$t = 1.65$, ns
Spatial Working Memory, between-search errors			
8 boxes	18.9 (11.9)	22.37 (12.7)	$t = 1.21$, ns
6 boxes	7.7 (7.4)	7.8 (6.3)	$t = 0.06$, ns
4 boxes	0.6 (1.4)	0.8 (1.4)	$t = 0.73$, ns
Stockings of Cambridge			
Problems solved in minimum moves	8.2 (1.6)	7.6 (1.5)	$t = 1.25$, ns
Initial thinking time, 5 moves ^a	7,638 (4,747)	7,206 (4,720)	$t = 0.57$, ns
Initial thinking time, 4 moves ^a	6,791 (4,058)	4,497 (1,506)	$t = 2.30$, $p = .02$
Initial thinking time, 3 moves ^a	3,208 (4,356)	3,150 (2,675)	$t = 0.57$, ns
Initial thinking time, 2 moves ^a	1,684 (968)	1,337 (598)	$t = 0.88$, ns

All response times/latencies are reported in milliseconds. CANTAB, Cambridge Neuropsychological Test Automated Battery; ID/ED, Intradimensional/Extradimensional. EDS, Extradimensional shift.

^aLog transformation (base 10) of data performed before analysis.