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**What is This?**
Methodology and Preliminary Results From the Neurocognitive Outcomes of Depression in the Elderly Study

David C. Steffens, MD, MHS, Kathleen A. Welsh-Bohmer, PhD, James R. Burke, MD, PhD, Brenda L. Plassman, PhD, John L. Beyer, MD, Kenneth R. Gersing, MD, and Guy G. Potter, PhD

ABSTRACT

A methodology is presented for following a cohort of older depressed patients to examine neurocognitive outcomes of depression. A total of 265 depressed individuals and 138 healthy, nondepressed controls age 60 and older who completed at least 1 year of follow-up data underwent periodic clinical evaluation by a geriatric psychiatrist. A subset of 141 patients and 137 controls had neuropsychological testing. A consensus panel of experts reviewed 63 depressed subjects with suspected cognitive impairment. Twenty-seven individuals in the depressed group were assigned diagnoses of dementia, including 11 with Alzheimer’s disease, 8 with vascular dementia, and 8 with dementia of undetermined etiology. In addition, 25 individuals had other forms of cognitive impairment, and 11 were considered cognitively normal. Among elderly controls, 2 developed substantial cognitive impairment with clinical diagnoses of dementia. Among the depressed group, the incidence rates for dementia for this age are much higher than would be expected. These results are consistent with prior evidence linking depression and later dementia. Future studies are needed to examine neuroimaging and genetic, clinical, and social predictors of neurocognitive decline in depression. (J Geriatr Psychiatry Neurol 2004;17:202-211)

Keywords: depression; elderly; cognition; dementia; outcomes

Although the majority of longitudinal research on geriatric depression has focused on the course of depressive symptomatology, it is increasingly recognized that other long-term outcomes of late-life depression are also important to consider. Similar to other serious diseases that afflict older adults, depression has consequences for physical health, cognition, functional status, and mortality. Among these outcomes, recent epidemiological studies have identified cognitive decline and dementia, particularly Alzheimer’s disease, as potential sequelae of geriatric depression; however, biological factors linking depression and dementia in the elderly are poorly understood. Because more evidence exists supporting the underlying biological substrates of dementia, it will be important to investigate the physiological correlates of depression. For example, the relationship between hippocampal changes and cognitive impairment is well established, and there is also substantive evidence indicating that cognitive impairment may result from cerebrovascular disease as well. Another possible biological substrate is the ε4 allele of the apolipoprotein E gene (APOE 4), a genetic locus that has been shown to be a risk factor for development of Alzheimer’s disease.

Clinical studies of geriatric depression will be strengthened if they are able to prospectively examine the relationship between key biological markers and subsequent cognitive decline. To achieve a goal of characterizing various cognitive outcomes in late-life depression, there must first be a methodology that is valid and reliable for this purpose. With this aim in mind, we obtained support from
the National Institute of Mental Health (NIMH) to follow a group of nondemented elderly depressed patients enrolled in a mental health clinical research center. We sought to determine the neurocognitive outcomes of elderly depressed individuals and nondemented controls who were not demented at baseline. To emphasize the new focus on cognition and development of dementia, the study is now designated the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study. In this article, we report the methods of clinical and neuropsychological assessment and initial findings of the NCODE study.

METHOD

Development of the NCODE Cohort
Beginning in November 1994, investigators at Duke University Medical Center began enrolling depressed patients aged 60 years and older in the NIMH-sponsored Mental Health Clinical Research Center for the study of Depression in Later Life (MHCRC) and into its longitudinal sister study. The latter study sought to examine neuroimaging factors related to depression outcomes. A neuropsychological evaluation was added in 1997. In conjunction with the newly established Conte Center for the Neuroscience of Depression in the Elderly, the longitudinal study (NCODE) was renewed in 2001 with a focus on both depressive outcomes and neurocognitive outcomes of depression.

Subjects
Depressed subjects who meet criteria for a current episode of unipolar major depression and are age 60 and older are enrolled in the study. Subjects are referred to the study from the Duke inpatient and outpatient psychiatry services and from the Duke General Internal Medicine Clinic. Exclusion criteria include presence of another major psychiatric illness such as schizophrenia, schizoaffective disorder, bipolar disorder, lifetime alcohol or substance dependence, and dementia. Patients with psychotic depression are included, as are those with comorbid anxiety disorders, as long as major depression is deemed by the study psychiatrist to be the primary psychiatric disorder. Aside from dementia, other neurological illnesses that could affect structural brain magnetic resonance imaging (MRI) scans are excluded, such as Parkinson’s disease, multiple sclerosis, and seizure disorder. Subjects with contraindications to brain MRI are also excluded. Subjects who subsequently developed alcoholism are not dropped from the study. After complete description of the study to the subjects, written informed consent was obtained.

Controls for the study are recruited from the Center for Aging Subject Registry at Duke University, which includes more than 1900 community-dwelling elders in the Durham, Chapel Hill, and Raleigh (North Carolina) area who have expressed willingness to participate in the Duke Center for Aging Research. Eligible controls must have a nonfocal neurological examination, no self-report of neurologic or depressive illness, and no evidence of a lifetime depression diagnosis based on the Diagnostic Interview Schedule portion of the Duke Depression Evaluation Schedule (DDES).

Structured Interview and Depression Assessment
At baseline, a geriatric psychiatrist interviews each depressed subject and completes standardized clinical assessments, including the 17-item Hamilton Rating Scale for Depression,12 the Montgomery Asberg Depression Rating Scale (MADRS),13 and the Clinical Global Impression scale. A trained interviewer administers the DDES,14 which assesses depression using the NIMH Diagnostic Interview Schedule15 as well as cognitive status, physical health, and the four measures that compose the Duke Social Support Index: instrumental social support, social interactions, subjective social support, and nonfamily social network.16 Clinical assessments are repeated when clinically indicated but at least every 3 months. For the present study, the MADRS is the main depression outcome measure. All raters are trained on completion of the MADRS, and high interrater reliability (κ > 0.9) is established.

Baseline Cognitive Screen
Subjects are excluded if they have dementia or suspected dementia at baseline based on information available to the assigned MHCRC geriatric psychiatrist, who examines the subject, reviews medical records, and confers with referring physicians for all patients. While most (n = 227 of 260, 87.3%) depressed subjects enrolled to date had Mini-Mental State Examination (MMSE)17 scores greater than 24 at baseline assessment, with 200 (76.9%) scoring 27 or higher, 33 (12.7%) severely depressed subjects had scores less than 25, MHCRC protocol is to follow such patients through an acute (8-week) phase of treatment to determine if cognition improves. Subjects whose MMSE scores at baseline. All controls had MMSE scores of 24 or higher, with 2 missing baseline MMSEs. Among controls, 124 of 136 (91.1%) had MMSE scores of 27 and higher. Regarding those depressed subjects with initial MMSE scores less than 25, MHCRC protocol is to follow such patients through an acute (8-week) phase of treatment to determine if cognition improves. Subjects whose MMSE scores remain less than 25 are not followed longitudinally in the MHCRC. Thus, in the clinical judgment of the study geriatric psychiatrist and by established MHCRC protocol, dementia is effectively excluded at or close to baseline in all elderly depressed MHCRC subjects.

Clinical Follow-up of Depressed Subjects
The MHCRC operates in a naturalistic treatment milieu using treatment guidelines established by the Duke Affective Disorders Program.18 Treatment modalities available include antidepressant medications, electroconvulsive therapy, and individual and group cognitive-behavioral psychotherapy. Treatment is monitored to ensure that
clinical guidelines are followed appropriately. As indicated above, patients are evaluated when clinically indicated and at least every 3 months while they are in the study. The protocol recommends that patients receive continuation treatment for at least 1 to 2 years (some indefinitely) once they achieve remission. Each patient is thus ensured to receive the most appropriate care we are able to provide.

Referral of Subjects With Cognitive Impairment
When subjects present with cognitive complaints, if family members bring concerns to the study geriatric psychiatrist, or if the psychiatrist has a clinical suspicion of cognitive impairment or dementia, he or she has the option to refer the patient to the Memory Disorders Clinic at Duke University Medical Center. When this happens, the study obtains copies of those medical records.

Biological Variables: APOE Genotype and Neuroimaging Variables
Both APOE genotype and neuroimaging data are collected as part of the NCODE study. Since this article will not include analyses using this information, we will only briefly describe the collection methods of each of these types of data.

Determination of APOE Genotype
All subjects are asked to donate a blood sample for APOE genotyping. White blood cells are processed using a method previously described.19

MRI Protocol
All subjects are screened for the presence of cardiac pacemakers, neurostimulators, metallic implants, metal in the orbit, aneurysm clips, or any other condition in which MRI is contraindicated. Subjects are imaged with a 1.5-T whole-body MRI system (Signa, GE Medical Systems, Milwaukee, Wis) using the standard head (volumetric) radiofrequency coil. Our MRI acquisition protocol has been described previously.19,20

Neuropsychological Battery
In July 1997, formal neuropsychological testing was added to the MHCRC, which until that time included only serial MMSE assessments at 6-month intervals. The test battery is administered to depressed subjects at baseline while still symptomatic and then annually regardless of depression status. Subjects enrolled between November 1994 and July 1997 who became cognitively impaired were usually referred to the Duke Memory Disorders Clinic; these cases were also reviewed at the consensus conference (see below).

The neuropsychological assessment consists of a brief screening battery for dementia supplemented by additional measures to enhance sensitivity and specificity of the detection of early-stage dementia. This battery was designed for efficient neurocognitive evaluation of geriatric patients and now has been successfully employed in a number of clinical and epidemiological settings.21 It is comprised of the Consortium to Establish a Registry in Alzheimer’s Disease (CERAD) neuropsychological battery,22 a collection of neuropsychological measures with normative standards for the elderly and established utility in longitudinal studies of cognitive impairment.23 The CERAD measures include (1) the MMSE; (2) language tasks consisting of category fluency (animal naming) and object naming24; (3) constructional praxis and visual memory, requiring copy of 4 geometric designs, with delayed recall and delayed recognition procedures; and (4) verbal learning and memory, consisting of immediate recall of 3 learning trials of a 10-item word list, delayed recall of the list, and recognition/discrimination of target words from non-target foils. The CERAD battery is supplemented by other common neuropsychological measures used in clinical practice for assessing (1) immediate and delayed verbal memory (Logical Memory subtest of the Wechsler Memory Scale—Revised25), (2) visual immediate memory (Benton Visual Retention Test26), (3) verbal initiation/lexical fluency (Controlled Oral Word Association Test from the Multilingual Aphasia Examination27), (4) attentional/executive functions (Trail Making Test,28 Symbol Digit Modalities Test,29 Digit Span subtest of the Wechsler Adult Intelligence Scale—Revised30 and a separate ascending Digit Span task modeled after the Digit Ordering Test31), and (5) premorbid verbal ability (Shipley Vocabulary Test32). In addition, at the time of testing, a knowledgeable informant completed the Dementia Severity Rating Scale,33 a measure of cognitive and functional status.

This neuropsychological assessment battery has proven useful in our previous work in depressed cohorts, allows accurate case ascertainment of dementia in large-scale epidemiological studies,21,34-36 and is effective in tracking the longitudinal changes of AD.34,37 It also meets 6 important criteria we were striving to achieve: (1) it is well tolerated by the elderly, (2) it includes measures sensitive to early changes of AD,38-40 (3) it is reasonably comprehensive, (4) it captures a range of cognitive abilities (minimizes floor and ceiling effects), (5) it is sufficiently “mainstream” that results can be easily interpreted by most researchers in dementia, and (6) it is sufficiently simple to allow reliable administration by trained technicians. The neuropsychological assessment requires approximately 60 minutes to administer and has been well tolerated by the vast majority of subjects. To minimize possible fatigue effects, subjects receive a 5-minute rest period after 20 minutes of testing. For patients who are to have electroconvulsive therapy and are enrolling in the study, testing occurs prior to the electroconvulsive therapy course.

Initial Review by a Neuropsychologist
All neuropsychological data are reviewed first by a licensed clinical neuropsychologist, and provisional diagnoses are determined using the accepted conventions of clinical practice.41 These include consideration of pertinent demo-
graphic factors, performance relative to normative values, and consistency in patterns of performance with respect to those commonly seen among depressed, cognitively impaired, and normally aging elders. The purpose of the review is 2-fold: first, to alert treatment providers to conditions that may require further evaluation and, second, to identify individuals for inclusion in the consensus conference (see below) based on the criterion of suspected cognitive impairment.

Consensus Diagnostic Conference
Subjects are assigned to be reviewed by the consensus panel if they meet one of the following criteria: (1) the study geriatric psychiatrist suspects dementia or clinically significant cognitive decline, (2) the subject is given a neuropsychological diagnosis consistent with dementia or cognitive impairment (except for isolated cognitive syndromes), or (3) a neurological consultation results in a diagnosis of dementia or cognitive impairment. Therefore, the only subjects who thus far have not come to the consensus diagnostic conference are those whose study geriatric psychiatrist has not identified a cognitive problem and, for those with neuropsychological testing, have provisional neuropsychological diagnoses of being broadly normal.

We have convened 2 consensus diagnostic conferences at this point in the study. Using a model developed in our epidemiological studies of dementia, we convened a panel of experts to review each case. The panel consisted of a core group of experts, including 3 geriatric psychiatrists (J.L.B., K.R.G., D.C.S.), a cognitive neuroscientist (B.L.P.), 1 or 2 neuropsychologists specializing in memory disorders (K.A.W.-B.; G.G.P. also participated in the second consensus conference), and a neurologist specializing in memory disorders (J.R.B.). Each panel member reviewed a binder that contained the following information for each patient presented: the initial and most recent clinical depression study notes, neuropsychological testing profiles and provisional diagnoses for all subjects who underwent cognitive testing, and neurological consultations when available. The treating study psychiatrist (J.L.B., K.R.G., or D.C.S.) briefly presented the case, and a neuropsychologist (K.A.W.-B.) reviewed the neuropsychological findings. Discussion among panel members would then ensue, and a consensus cognitive diagnosis was assigned.

Panel members chose among several clinical diagnoses (see Table 1). We used published criteria for diagnoses of probable and possible Alzheimer’s disease and probable and possible vascular dementia. For any diagnoses of incident Parkinson’s dementia, Lewy body dementia, or alcoholic dementia, we decided to rely on clinical judgment. The category of dementia of undetermined etiology was used when a subject met Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria for dementia, but no clear diagnosis could be assigned based on the subject’s history and presentation. Thus, a diagnosis of dementia of undetermined etiology would not necessarily exclude Alzheimer’s disease or vascular dementia.

We also included several categories of nondementia diagnoses selected a priori based on our previous studies (see Table 1). Subsyndromal Alzheimer’s disease was defined as early or prodromal stages of Alzheimer’s disease. This term is broader than mild cognitive impairment, in that it may include mild impairment in function or in 1 or more cognitive domains (ie, not just memory impairment), which is clinically suggestive of the early stages of Alzheimer’s disease. Subsyndromal vascular dementia was defined as cognitive decline consistent with progression of cerebrovascular disease but not meeting dementia criteria. A diagnosis of cognitive impairment, no dementia was assigned to subjects with cognitive impairment by report or on neuropsychological testing accompanied by mild or no functional impairment (as evidenced by clinician report or report of knowledgeable informant on the Dementia Severity Rating Scale) and who did not present with syndromes consistent with subsyndromal Alzheimer’s disease or subsyndromal vascular dementia. We adopted this definition from criteria described previously. The final diagnostic category was normal/noncase.

Table 1. List of Clinical Diagnoses That Could Be Assigned at Consensus Diagnostic Conference

<table>
<thead>
<tr>
<th>Dementia Diagnoses</th>
<th>Nondementia Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable Alzheimer’s disease</td>
<td>Subsyndromal Alzheimer’s disease</td>
</tr>
<tr>
<td>Possible Alzheimer’s disease</td>
<td>Subsyndromal vascular dementia</td>
</tr>
<tr>
<td>Probable vascular dementia</td>
<td>Cognitive disorder, not demented</td>
</tr>
<tr>
<td>Possible vascular dementia</td>
<td>Poststroke cognitive syndrome</td>
</tr>
<tr>
<td>Dementia of Parkinson’s disease</td>
<td>Depression</td>
</tr>
<tr>
<td>Alcoholic dementia</td>
<td>Other neuropsychiatric disorder</td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>Current alcoholism</td>
</tr>
<tr>
<td>Huntington’s dementia</td>
<td>Other neurological disorder (specify)</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Other medical disorder (specify)</td>
</tr>
<tr>
<td>Frontal lobe dementia</td>
<td>Toxic exposure</td>
</tr>
<tr>
<td>Severe head trauma with residual dementia</td>
<td>Mild head injury</td>
</tr>
<tr>
<td>Hypoperfusion dementia</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>Postencephalitic dementia</td>
<td>Normal pressure hydrocephalus (specify)</td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>Normal/hydrocephalus</td>
</tr>
<tr>
<td>Dementia of undetermined etiology</td>
<td>Normal/hydrocephalus</td>
</tr>
</tbody>
</table>

Statistical Analyses
We compared controls and patients on a variety of demographic and clinical variables, using χ² analyses for dichotomous measures and t tests for continuous measures. For neuropsychological tests, we developed a series of linear models controlling for age, gender, and education. Each model included a covariate for case/control; we report the
significance level of that coefficient. These data were heterogeneous regarding distribution. Accordingly, some models were estimated using ordinary least squares and the remainder by generalized linear models using either \( \gamma \) or binomial (logistic) distributions as appropriate.

Age-specific incidence of dementia was calculated using the person-years approach by dividing the number of cases by the number of person-years at risk given as 5-year age intervals starting at age 60 years (these are multiplied by 1000 to get rates per 1000 person-years). The number of person-years contributed by each subject who had no dementia is calculated by taking the time between their baseline examination and their last follow-up examination. For subjects with dementia, the number of person-years is calculated by the time from baseline to the age at which dementia was assigned by the consensus diagnostic review. The date of the last follow-up examination is also used as the end point for subjects who die or drop out since dementia status is unknown at the time of death or dropout.

RESULTS

There have been 328 depressed subjects enrolled between 1995 and 2003. Thirty-one have died, and 121 have withdrawn from the study. During this time, 159 nondepressed controls have been enrolled, and of these, 4 have died and 46 have withdrawn. For depressed and nondepressed subjects no longer in the study, we used their last available clinical and neuropsychological data.

The current sample for this study consisted of 265 depressed individuals and 138 controls who had been followed for at least 1 year as of September 2003 (see Figure 1). The depressed sample was 64.91% female, while 71.74% of controls were female. Mean age at baseline was 69.69 (±7.48) years for patients and 70.49 (±6.25) years for controls. The racial distribution for patients was 85.7% Caucasian, 10.6% African American, and 3.7% other race. The 10 subjects in the latter category were composed of 4 mixed race, 2 Native Americans, 2 Middle Eastern, 1 Asian, and 1 Indian. Among controls, 82.6% were Caucasian, 15.2% were African American, and 2.12% identified themselves as mixed race. There were no differences between patients and controls on age, gender, or race. The mean educational level was 13.57 (±3.06) years for patients (1 patient was missing education data) and 15.36 (±1.81) years for controls \( (t = 7.35, df = 393, P < .0001) \). Among patients, baseline MADRS score was 27.15 (±7.89). The mean time of follow-up in the study was 4.23 (±2.33) years for depressives and 3.43 (±1.25) years for controls \( (t = -4.46, df = 401, P < .0001) \). The mean MMSE score from baseline neuropsychological testing was 27.58 (±3.07) for depressed patients and 28.85 (±1.43) for controls \( (t = -5.62, df = 390, P < .0001) \).

Neuropsychological data were available on 141 patients and 137 controls. Demographic characteristics for this subsample are shown in Table 2 along with age-, sex-, and education-adjusted analyses on the neuropsychological tests. In addition, the mean MADRS score among depressives was 17.70 (±10.10), indicating, on average, a moderate level of depression at time of testing. As might be predicted, nondepressed controls consistently performed better than did the depressed patients on all neuropsychological variables on the baseline examination (Table 2).

Thus far, 63 depressed subjects have been reviewed at one or both consensus diagnostic conferences. Cognitive outcomes of the subjects are shown in Table 3. For primary diagnoses, 11 were assigned a consensus diagnosis of Alzheimer’s disease, 8 had a diagnosis of vascular dementia, and 8 were given a diagnosis of dementia of undetermined etiology. Thus, the total number of demented subjects identified was 27. The time to dementia starting from age at enrollment to age of dementia onset was 5.70 ± 1.84 years (range, 2-8 years). In addition, 25 individuals were placed in one of the cognitively impaired categories. Eleven were considered cognitively normal based on consensus panel assignment. When combined with the 201 individuals deemed cognitively normal by their treating geriatric psychiatrists or with broadly normal neuropsychological test-
ing, the total number of noncases in the sample of 265 is 212 (80.0%).

Thus, for the depressives, the crude incident rate is 27 of 265, or 10.2%. When accounting for years of follow-up, the incidence rate is 24.10 per 1000 person-years. When we examined rates for 5-year age spans, we found an increase in incidence with increasing age group (see Table 4).

Two control subjects have developed substantial cognitive impairment, and their local physicians have diagnosed both with dementia; their cases will be reviewed at a future consensus diagnostic conference.

CONCLUSIONS

In preliminary results from the NCODE study, we found that among 265 depressed subjects with at least 1 year of longitudinal data, 27 have become demented over an average of 4 years of follow-up. The diagnostic assignments were fairly evenly divided among Alzheimer’s disease, vascular dementia, and dementia of undetermined etiology. In addition, there were 25 individuals with clinically significant cognitive impairment, most of whom were placed in the category of cognitively impaired, no dementia. Our results are striking given the relatively short length of follow-up for the sample. For this age group, the incidence rate of dementia of 10.2% (or 24.1 per 1000 person-years) in this depressed sample exceeds incidence rates in community samples reported in other studies.46,47 Our findings are consistent with previous literature demonstrating that a prior history of depression is associated with increased risk of dementia, particularly Alzheimer’s disease.48-53 The relatively large proportion of vascular dementia cases is consistent with literature linking geriatric depression and cerebrovascular disease.54,55

Among 138 controls, 2 have developed cognitive decline with clinical diagnoses of dementia, which is similar to rates previously reported in this age group.47 As expected, controls performed better than did depressed patients on

Table 2. Comparisons of Depressed Subjects and Controls on Demographic Characteristics and Baseline Neuropsychological Measures Using Linear Regression Controlling for Age, Sex, and Education

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Controls (n = 137)</th>
<th>Patients (n = 141)</th>
<th>Control Versus Patient (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean SE</td>
<td>Mean SE</td>
<td></td>
</tr>
<tr>
<td>Female*</td>
<td>70.54 0.50</td>
<td>68.89 0.56</td>
<td>.3947</td>
</tr>
<tr>
<td>Caucasian race*</td>
<td>102 (74.45)</td>
<td>85 (60.28)</td>
<td>.0118</td>
</tr>
<tr>
<td>Education</td>
<td>18 (90.13)</td>
<td>127 (90.07)</td>
<td>.3100</td>
</tr>
<tr>
<td>Age</td>
<td>15.88 0.21</td>
<td>14.48 0.27</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Global cognitive tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>28.80 0.12</td>
<td>27.73 0.22</td>
<td>.0071</td>
</tr>
<tr>
<td>Shipley Vocabulary Test†</td>
<td>34.62 0.39</td>
<td>31.13 0.55</td>
<td>.0049</td>
</tr>
<tr>
<td>Tests of memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benton Visual Retention Test‡</td>
<td>6.54 0.15</td>
<td>5.31 0.19</td>
<td>.0001</td>
</tr>
<tr>
<td>Word List Memory, first trial</td>
<td>5.34 0.14</td>
<td>4.42 0.15</td>
<td>.0004</td>
</tr>
<tr>
<td>Word List Memory, second trial</td>
<td>7.57 0.13</td>
<td>6.35 0.15</td>
<td>.0001</td>
</tr>
<tr>
<td>Word List Memory, third trial</td>
<td>8.45 0.12</td>
<td>7.26 0.16</td>
<td>.0001</td>
</tr>
<tr>
<td>Word List Memory, recall task</td>
<td>7.37 0.15</td>
<td>5.95 0.19</td>
<td>.0001</td>
</tr>
<tr>
<td>Logical Memory I</td>
<td>28.55 0.63</td>
<td>22.54 0.73</td>
<td>.0001</td>
</tr>
<tr>
<td>Logical Memory II</td>
<td>24.81 0.70</td>
<td>18.42 0.82</td>
<td>.0001</td>
</tr>
<tr>
<td>Tests of working memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digits, forward§</td>
<td>8.85 0.23</td>
<td>8.20 0.21</td>
<td>.0369</td>
</tr>
<tr>
<td>Digits, backward§</td>
<td>7.62 0.23</td>
<td>6.75 0.22</td>
<td>.0173</td>
</tr>
<tr>
<td>Digits, ascending§</td>
<td>9.59 0.19</td>
<td>8.08 0.25</td>
<td>.0001</td>
</tr>
<tr>
<td>Tests of language</td>
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<td></td>
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<tr>
<td>Boston Naming Test</td>
<td>14.49 0.07</td>
<td>13.89 0.13</td>
<td>.0013</td>
</tr>
<tr>
<td>Controlled Oral Word Association</td>
<td>45.80 0.99</td>
<td>39.02 0.99</td>
<td>.0004</td>
</tr>
<tr>
<td>Verbal fluency (animals)</td>
<td>19.72 0.45</td>
<td>15.70 0.45</td>
<td>.0001</td>
</tr>
<tr>
<td>Tests of executive function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trails A, seconds‖</td>
<td>36.08 1.09</td>
<td>54.89 3.82</td>
<td>.0001</td>
</tr>
<tr>
<td>Trails B, seconds‖</td>
<td>87.04 3.36</td>
<td>140.91 6.85</td>
<td>.0001</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test‖</td>
<td>44.72 0.80</td>
<td>35.59 1.03</td>
<td>.0001</td>
</tr>
<tr>
<td>Tests of constructional praxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constructional Praxis, total†</td>
<td>10.59 0.07</td>
<td>9.98 0.12</td>
<td>.0024</td>
</tr>
<tr>
<td>Constructional Praxis, delay†</td>
<td>9.29 0.16</td>
<td>7.96 0.24</td>
<td>.0012</td>
</tr>
</tbody>
</table>

*Values are expressed as n (%).
†Sample size for the Shipley, the Constructional Praxis tests, and Trails A for patients = 140.
‡Sample size on the Benton Visual Retention Test (number correct) for controls = 136 and for patients = 139.
§Sample size on the 3 digits tests for controls = 116 and for patients = 119.
‖Sample size on Trails-B and Symbol Digit Modalities Test for patients = 137.
baseline neuropsychological measures. Superior general neuropsychological performance for controls compared with depressed subjects has been reported previously, and the difference may be mediated to a substantial degree by decreased working memory and speed of processing characteristic of late-life depression.

The NCODE study rests on the notion that the structural changes detected on MRI that are most closely related to cognitive outcomes of geriatric depression are derived from 2 etiologies: vascular and neurodegenerative. Figure 2 shows a model of biological factors in geriatric depression. It emphasizes the important role of progression of vascular lesions in the fronto-striatal region (subcortical gray and frontal deep white matter hyperintensities) in increasing the risk of late-life depression. In turn, depression leads to cognitive impairment, possibly mediated through decreased hippocampal volume. APOE genotype may be an independent risk factor for cognitive decline in elderly depressives. The scientific importance of this paradigm is obvious: if vascular lesions and hippocampal changes of the brains of older people lead to secondary depression with clinical characteristics similar to primary depressions, then these structural changes may provide important clues to the brain sites involved in depression in general. The model does not include the social factors (decreased social support and negative life events), medical conditions, and functional impairment that may also contribute to adverse outcomes in late-life depression.

Evidence that individuals with late-life depression and comorbid cognitive impairment frequently develop dementia within a few years after the presentation of their depression suggests that late-life depression may be a prodrome of dementia in certain individuals. This notion is also supported by epidemiological studies. The longitudinal nature of the NCODE study will allow us to examine more closely the question of depression as a prodrome of dementia in the elderly. In addition, since we are currently following a cohort of nondepressed controls, we will be able to compare incidence rates among depressed and nondepressed subjects.

A large number of depressed individuals were assigned a diagnosis of dementia of undetermined etiology. This may be an artifact of our methodology. We tend to be conservative in assigning definitive diagnoses. For example, for a diagnosis of Alzheimer’s disease, we require both an insidious onset and a typical course of progressive cogni-
tive decline. With our consensus conference approach, we detect dementia in early stages; without benefit of further longitudinal information, we tend to place such subjects in the dementia of undetermined etiology category. Our intention is to continue to follow individuals with a diagnosis of dementia of undetermined etiology longitudinally to see if we can better characterize the cognitive decline over time and place them in a more definitive category.

This study also demonstrates the need to follow cognitively impaired depressed patients longitudinally for possible improvement of cognition. Initially, at least 12% of our sample had very low MMSE scores. Yet after initial treatment, their scores improved, and they were not classified as demented. Of note, the patient with the lowest MMSE score of 9 at study entry has scored 30 on the MMSE after treatment and has maintained that score for several years. Thus, a substantial number of treated older depressive patients appear to experience a positive cognitive outcome, in contrast with those whose cognition deteriorates as part of a neurodegenerative process or one of progressive cerebrovascular disease. On the other hand, in future studies, we will also be able to determine whether some degree of baseline cognitive impairment or weakness (eg, measured globally on the MMSE or on specific neuropsychological tests) predicts later dementia.

There are some limitations of our method that are worth mentioning. The presence of the study geriatric psychiatrist at the consensus conference may bias the panel in the direction of the psychiatrist’s judgment. We considered not having the psychiatrist present, but in our experience, having a clinician present who has seen the subject is invaluable, as the panel may ask questions and provide feedback to the psychiatrist in terms of diagnosis or need for further evaluation. Another limitation is that treatments provided through NCODE are essentially naturalistic, that is, a decision made between psychiatrist and patient. To limit variability in treatment approach, we have instituted a somatic depression treatment algorithm to provide some consistency in treatment. We have not instituted guidelines for treatment of cognitive disorders. Demented patients may be prescribed medications for dementia as clinically appropriate. Although taking a medication to treat symptoms of dementia should not alter the consensus diagnosis, it may affect the course of both depression and cognitive decline.

Another limitation with our study, as with other studies of cognitive outcomes, is identifying an appropriate gold standard diagnosis. Some may argue that neuropathological studies are needed to provide definitive diagnoses of dementia; however, these studies are few with regard to depression. The current methodology has been shown in previous studies to be reasonably sensitive compared with neuropathological findings. We plan to obtain eventually neuropathological data by enrolling individuals in our depression cohort in an autopsy program established as a collaboration between the Conte Neuroscience Center for the Study of Depression in the Elderly and the Bryan Alzheimer’s Disease Research Center, both at Duke University Medical Center.

The number of demented individuals in the present sample is relatively small, particularly among the non-depressed sample. This limitation may make it difficult to generalize to other older populations. However, if our cohort is followed for many years, as we plan to do, the number of person-years in the denominator of an incidence rate could be large, making our findings comparable to other studies.

Our method of identifying individuals for inclusion in the consensus conference review based on neuropsychological test performance or clinician suspicion of cognitive impairment may lead to an underestimate of cognitively impaired individuals in our sample, including those with dementia. For instance, not everyone has neuropsychological testing, and clinicians may not always detect cognitive difficulties in patients. A risk of high false negatives is doubtful, however, given that experienced geriatric psychiatrists would be unlikely to overlook dementia. We also do not have current cognitive status on patients who withdrew from the study. To address these limitations, our plan is to bring information from all cases deemed cognitively normal by testing and/or clinician evaluation to subsequent consensus conferences for review over the next 2 years. Indeed, we will be in a position to better examine longitudinally the likely heterogeneity of neuropsychological test performance among “clinically normal” subjects. Included among them could be individuals who score in the impaired range on one isolated test (eg, a memory test) or show suppression in a particular cognitive domain (eg, executive function). Examination of all “normal subjects” at the consensus conference will allow us to determine our false-negative rate.

There may also be a potential for bias between depressed and control groups based on a degree of asymmetric data collection between groups. We generally have contact with nondepressed controls and their informants on an annual basis, while we evaluate depressed patients quarterly. We formally seek input from informants in both groups annually at the time of neuropsychological testing; however, informants may provide more informal feedback to study coordinators and study geriatric psychiatrists at the quarterly visits. Thus, there may be an increased risk of bias toward higher rates of recognition of cognitive impairment in the depressed group.

The clinical importance of our focus on cognitive outcomes of geriatric depression has both direct and indirect implications. For instance, prevention of late-onset depressions and cognitive decline may be exerted through control of cerebrovascular risk factors and of risk factors for Alzheimer's diseases. Treatment of late-life depression for some individuals may need to include both adequate treatment of risk factors and appropriate anticoagulation or cholinesterase inhibition. Consequences of worsening of
cerebrovascular disease or hippocampal atrophy among depressives may include a chronic course of depression, as well as an increased risk of stroke and dementia. Before costly or controversial prevention or treatment trials can be undertaken, research must establish the consequences of neuroimaging changes and other biological markers.

The aim of the NCODE study is to examine and establish the psychiatric and neurocognitive outcomes of structural changes identified on MRI brain scans and the role of APOE genotype and cognitive decline in elderly depressives. Particularly interesting to those who study dementia will be outcomes of those with different types of cognitive impairment. In time, we expect that all subjects will come to expert consensus review. We will then be able to capitalize on the unique features of this study and combine clinical, neuroimaging, and genetic data. Thus, this study will be well positioned to characterize the course of cognitively impaired as well as cognitively normal depressed individuals and to identify key predictors of cognitive outcomes.

References


