Cognitive Function in Non-Demented Older Adults with Hypothyroidism

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Purpose: (1) to evaluate objectively changes in cognitive function and electrophysiologic characteristics associated with hypothyroidism of varying severity and duration in primarily older persons; (2) to determine whether these changes are reversible when a euthyroid state has been attained after treatment with thyroid hormone.

Subjects and Methods: We enrolled 54 non-demented hypothyroid patients (31–99, mean 68.6 ± 16.4 years) with biochemical evidence of hypothyroidism (38 had overt and 14 had minimal hypothyroidism) and 30 euthyroid controls (31–96, mean 63.7 ± 18.4 years) screened for good general health. We evaluated attention, orientation, memory, learning, visual-spatial abilities, calculation, language, visual scanning, and motor speed using standardized neuropsychological tests. Electrophysiological measures of neurocognitive function included the P300 latency component of the auditory Event-Related Potentials (ERP) and conduction speed from eye to cortex, the P100 latency component of the Patterned Visual-Evoked Potential (PVEP). All patients were studied when hypothyroid. A subset of patients with minimal initial test abnormalities were available to be retested when euthyroid, 5 and 9 months after onset of thyroid replacement therapy.

Results: Hypothyroid patients showed significantly lower scores on the Mini-Mental Status Test (MMS) and on five of 14 neuropsychological tests as compared to controls. The neuropsychological tests affected were copying a cube (visual-spatial function), the Inglis Paired Associates Learning Test-Low and Medium association items (memory and learning), Animal Naming (word fluency/production), and the Trail Making A test (attention, visual scanning and psychomotor function. Hypothyroidism also was associated with longer P100 latencies of PVEPs to 20′ checks, but showed no significant differences in PVEP P100 latency to 50′ checks, nor in the latency of the auditory ERP component P300. There was a statistically significant correlation between a laboratory index of the severity of hypothyroidism (serum T_4) and the Inglis Medium Association items and Animal Naming. There was a statistically significant improvement after 5 months of treatment on three of the timed performance tests that previous studies have shown to be most sensitive to brain dysfunction.

Conclusion: Hypothyroidism in non-demented older adults is associated with impairments in learning, word fluency, visual-spatial abilities, and some aspect of attention, visual scanning, and motor speed. The MMS by itself was sensitive in differentiating hypothyroid patients with cognitive deficits from controls, while electrophysiological measures did not generally differentiate the hypothyroid patients from normal controls. The MMS was not sensitive to treatment effects, but treatment was associated with significant improvements in three of the most sensitive measures of cognitive dysfunction.

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The prevalence of hypothyroidism in a group of adults 60 years and older was 5.9 percent[1] when defined as a thyroid stimulating hormone concentration (TSH) in excess of 10 μU/mL. The total number of older adults at risk for development of hypothyroidism steadily increases with age. It has been estimated that there were almost a quarter million individuals with hypothyroidism resulting from treatment of Grave's disease in the United States alone in 1980, with a considerably larger number at risk.[2]

Hypothyroidism is invariably listed as one of the causes of potentially reversible dementia in older adults,[3] but the frequency, severity, and characteristics of the mental changes induced by hypothyroidism of varying severity are unknown. Hypothyroidism may lead to irreversible mental deficiency in the newborn, and early treatment with thyroid hormone can prevent this outcome.[4,5] Less is known regarding the sensitivity of the mature brain to changes in thyroid function and the potential reversibility of these changes with treatment. Cure or improvement of even a small percentage of cognitive impairment in older adults could be very important for continued independence and quality of life.

An association between thyroid gland function and mental activity in adults has been acknowledged since early descriptions of myxedema.[6–9] Myxedema may cause neurologic and psychiatric abnormalities, including myopathy, ataxia, psychosis, and dementia.[10–25] Asher described confusion, disorientation, and psychosis as "myxedematous madness."[26] Unfortunately, most early studies lacked objective measures of the psychological and cognitive impairment associated with hypothyroidism and failed to adequately describe the effects of treatment with thyroid hormone on outcome.

Several studies using objective behavioral measures reported that cognition is impaired in patients with hypothyroidism and that it improved with thyroid replacement therapy.[23–25] Abnormal electroencephalograms (EEGs) also have been found in hypothyroidism,[27–29] and these changes in the EEG have been

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shown to parallel changes in cerebral metabolism.[30–32] Event-Related Potentials (ERPs) record the electrical manifestations of the brain's reception of, and response to, an external stimulus. ERPs can be effectively utilized to identify changes in brain function and can be useful in evaluating the efficacy of treatment regimes.[33–35] Nishitani and Kooi[36] and Landenson et al[37] found changes in latency and amplitude of visual evoked potentials (VEP) after thyroid hormone replacement therapy in hypothyroidism. Although there are numerous studies reporting the possible utility of other ERP components in evaluating neurocognitive function,[38,39] review of the literature on ERPs reveals no studies measuring such changes in hypothyroid patients.

The objectives of the present study were: (1) to evaluate objectively changes in cognitive function and electrophysiologic characteristics associated with hypothyroidism of varying severity and duration in primarily older persons; (2) to determine whether these changes are reversible when a euthyroid state has been attained by treatment with thyroid hormone.

MATERIALS AND METHODS

Subjects We studied 54 patients, 26 women and 28 men, ranging in age from 31 to 99 years of age (68.6 ± 16.4 years), with biochemical evidence of hypothyroidism (Table 1). Thirty-eight had overt hypothyroidism (TSH = >10 μU/mL, FT_4I or T_4 < 4.2 μg/dL); 14 had minimal hypothyroidism (TSH = >10 μU/mL, T_4 > 4.2 and <11.0 μg/dL or FT_4I = >4.6 and <11.0); serum T_4 was unavailable for two patients, but their TSH was very high. Eight of the overt hypothyroid patients had short-term hypothyroidism (patients after total thyroidectomy for carcinoma, off thyroid replacement for 10 to 20 days). Four had hypothyroidism induced by the iodine-containing drug, amiodarone.

TABLE 1. AGE, GENDER, AND THYROID FUNCTION TESTS OF HYPOTHYROID PATIENTS AND CONTROLS

	Hypothyroid Patients $n = 54$	Euthyroid Controls $n = 30$	*P*-Value
Age (years)			
Range	31–99	30–96	
Mean (standard deviation)	68.6 (16.4)	63.7 (18.4)	NS*
Gender			
Female # cases (%)	25 (46%)	20 (67%)	
Male	29 (54%)	10 (33%)	NS**
Education			
Mean (Standard deviation)	11.2 (3.6)	13.1 (4.1)	NS*
Thyroid function tests			
Serum thyrotropin (TSH)	66.3 (55.4)	1.3 (0.8)	0.0001*
Serum thyroxine (T_4)	2.5 (2.4)	7.7 (2.4)	0.0001*
Serum triiodothyronine (T_3)	68.5 (41.2)	117.0 (24.5)	0.0001*
Free thyroid index (FT_4I)	2.3 (2.2)	8.2 (2.0)	0.0001*

Normal ranges: Thyrotropin 0.3–5.7 μu/mL; Thyroxine 4.2–11.0 μg/dL; triiodothyronine 70–160 ng/dL; Free Thyroid index 4.2–11.0.
NS, Not Statistically Significant, P > 0.05.
* T test for unpaired samples.
** Chi-square.

Thirty euthyroid controls, 20 women and 10 men, aged 31 to 96 years (63.7 ± 18.4 years) were recruited from community sources. They had normal thyroid function tests with a history of good general health and freedom from neurological and significant cardiovascular disorders or any other uncontrolled chronic conditions (Table 1).

Patients were recruited as they were identified by thyroid function tests during routine medical evaluations on endocrine and geriatric services at the VA Medical Centers at West Los Angeles and Sepulveda (n = 27); the Department of Medicine, University of California at Los Angeles (n = 7); the Jewish Homes for the Aging, Reseda, California (n = 17), and other sources (n = 3). The patients had to be alert and in good general health in order to qualify for participation in the behavioral and electrophysiological testing. Exclusion criteria included clinical dementia defined by DSM III-R criteria, thyroid function abnormalities due to non-thyroidal disease, and other major medical and neurological disorders or treatment with medications that could affect cognitive function. All study participants signed a written informed consent approved by the institutional review boards of UCLA, Jewish Homes for the Aging, and the Veterans Administration Medical Center, West Log Angeles.

Serum thyroxine (T_4), triiodothyronine (T_3) and thyrotropin (TSH) concentrations were determined by previously described radioimmunoassay methods.[40] Normal ranges: thyrotropin 0.3–5.7 μU/mL; thyroxine 4.2–11.0 μg/dL; triiodothyronine 70–160 ng/dL; free thyroid index 4.2–11.0.

Procedures Study patients were tested as soon as the diagnosis of hypothyroidism had been made and before the onset of treatment and retested when a euthyroid state had been attained as judged by hormone levels in serum (average inter-test interval 5.3 months ± 3.3). Control subjects were recruited throughout the recruitment period of hypothyroid patients and were retested after 2 months to provide a control for possible practice effects of retesting. To determine whether continuing thyroid hormone replacement has a further positive effect on neuropsychological and electrophysiological tests, 10 hypothyroid patients were tested for a third time, 4 months after the second testing session.

Treatment Patients were placed on standard thyroxine replacement therapy which, in our institution, is initiated whenever TSH is greater than 10 μU/mL. Standard therapy in otherwise healthy, medically stable older adult patients consists of an initial dose of oral Levothyroxine, 25–50 μg daily, and increases by 25–50 μg daily at week intervals until full replacement is achieved (mean final dose 100–150 μg/day). In patients with cardiac disease, therapy is initiated at lower

doses (12.5–25 μg qd) with dose increases of 25 μg daily every 3–4 weeks until full replacement dosage is achieved. It was not ethical to withhold treatment from any hypothyroid patient, so a double-blind, placebo-controlled study was not feasible.

Neuropsychological Tests Nine areas of cognitive function were studied: attention, orientation, learning and memory, visual-spatial abilities, calculation, language, visual scanning, and motor speed. A modified Mini-Mental State exam (MMSE) was utilized to globally evaluate cognitive status. The modified MMSE was developed by Drs. J. Cummings and F. Benson as a modification of the commonly used Folstein Mini-Mental Status[41] that would be more sensitive to screening for Alzheimer disease than the standard MMSE. The items in the standard and modified MMSEs are essentially identical with the exception of two additional language items and an additional drawing item in the modified version. The modified version, like the standard MMSE, has a maximum score of 30, and a score of 23 or less is considered abnormal. Our unpublished comparisons of the two MMSE forms indicate no statistically significant differences in their ability to screen for dementia in the older adult population.

Copying the Cube was scored on a 0–5 scale: 0 = no design produced; 1 = minimal production; 2 = a closed one-dimensional design; 3 = three or four compartments but no three-dimensionality; 4 = reproduction of an imperfect cube, and 5 = a perfect cube. A number of recent studies have suggested that cube copying is a sensitive screening test for dementia in older adults.

The Inglis Paired Associate Learning Test provided a measure of learning and retention.[42] It produces scores for three levels of difficulty: low association, medium association and high association word pairs. Older adult individuals with clinical evidence of memory disorders show significant declines in performance on the medium and low association items of this test,[42] beyond that found in normal older adults when compared to young adults. Scores on the high association items were not expected to be sensitive in detecting mild cognitive change associated with hypothyroidism but did provide a control for possible attention deficits.

Animal Naming is a word production and verbal fluency test.[43] The examinee is asked to name as many types of animals as possible in 1 minute, and the score is the number of animal names. Borod et al reported the accepted norm as ≥12 for individuals >60 years of age,[43] although there is evidence that a correction for educational level must be made. Cummings and Benson reported 10 to 12 as the cutoff for normal performance[44] and found the test to be sensitive in detecting early dementia of the Alzheimer type. Digit Span, a test of attention, was adopted from the Wechsler Adult Intelligence Scale.[45] Digits Forward assesses auditory attention by measuring immediate auditory memory span. Digits Backward measures immediate memory span plus mental control. The Digit Span test produces three scores: Digits Forward, the greatest number of consecutive digits repeated back to the examiner; Digits Backward, the greatest number of digits repeated in reverse order, and the Total Digit Span, the sum of the two scores. In this study only the two separate scores were used. In the older adult four digits forward and three reversed is accepted as normal.[3] Digits Forward is generally not sensitive to the early stages of dementia or diffuse brain damage, while Digits Backward is.[46] Digits Forward provides a control for disorders of attention.

The oral version of the Symbol Digit Modalities Test (SDMT),[47] and Trail Making A and B tests,[48] are timed tests that assess attention, concentration, visual search and scanning abilities, and psychomotor function and are especially sensitive to brain dysfunction of various etiologies and to age-related changes in cognitive function.[46] These timed tests were added to the test battery after the onset of the study in order to increase the sensitivity of the test battery to potential changes in speed of cognitive functions associated with hypothyroidism. The oral version of the SDMT presents the individual with a key consisting of a row of symbols, each paired with a number. The individual is given a page of the symbols and is required to call out the numbers that are paired with each symbol as quickly as possible. The score is the number of symbols correctly named in 90 seconds. In the Trail Making tests, the individual must first draw lines to connect the 25 consecutively numbered circles randomly dispersed on one work sheet (Trail Making A), and then connect the 13 consecutively numbered and 12 consecutively lettered circles ("1, A, 2, B, 3, C . . .") on another work sheet, but must alternate between the two sequences (Trail Making B). The score is the time in seconds to complete each test. Trail Making was shown to be sensitive to the effects of hypothyroidism.[25]

The Language Disorder tests were adapted from the Boston Diagnostic Aphasia Exam (BDAE)[49] and consisted of auditory comprehension, word naming and discrimination, yes-no questions, and sequential commands. In general, performance on these language items is well preserved in early stages of brain dysfunction not specifically involving the language areas of the brain and in non-demented older adults.[50] These tests were included to determine whether the early stages (ie, non-dementia) of possible hypothyroid effects on the brain were similar to those seen in Alzheimer type dementia.

The behavioral tests yielded a total of 15 independent variables (see tests listed in Table 2).

Electrophysiological Tests The P300 Auditory Event-Related Potential (ERP) and the P100 Patterned Visual Evoked Potential (PVEP) tests were administered to evaluate directly brain function related to attention and decision making[39] and to conduction changes in the visual pathways,[34, 36, 37] respectively. In the ERP procedure, standard EEG electrodes are attached to the midline scalp at Fz, Cz, and Pz, all referenced to linked earlobe electrodes. Vertical eye-movements are recorded from electrodes above and below the right eye to monitor and evaluate eye-movement artifacts in the EEG. The target detection procedure used to elicit the ERP has previously been described.[33, 38] Briefly, the patients hear three separate but identical series of 400 tone pips through head-

TABLE 2. NEUROPSYCHOLOGICAL TESTS: EFFECT OF HYPOTHYROIDISM ON PERFORMANCE

	Hypothyroid			Euthyroid Controls			
	n	Mean	(SEM*)	*n*	Mean	(SEM)	*P***
Mini-Mental State Exam	53	26.1	(0.5)	30	28.7	(0.3)	0.0005
Cube (rating 1–5)	47	3.5	(0.2)	28	4.3	(0.2)	0.002
Inglis-low***	46	0.5	(0.04)	28	0.8	(0.05)	0.0001
Inglis-medium***	51	0.81	(0.03)	28	0.95	(0.02)	0.003
Inglis-high***	48	0.93	(0.02)	28	0.98	(0.02)	0.11 NS
Animal Naming (# words/60′)	50	14.7	(0.8)	29	18.4	(1.2)	0.01
Digits Forward (# digits)	51	5.7	(0.2)	29	6.1	(0.2)	0.10 NS
Digits Backwards (# digits)	51	3.6	(0.1)	29	4.1	(0.1)	0.037 NS
Symbol Digit Modality Test (# correct/90′)	25	27.3	(3.0)	27	37.3	(2.7)	0.017 NS
Trail Making A (sec)	26	79.9	(10.5)	27	42.8	(3.4)	0.0013
Trail Making B (sec)	24	127.5	(18.1)	27	113.5	(11.6)	0.5 NS
Oral Reading***	46	0.99	(0.01)	29	0.98	(0.01)	0.65 NS
Word Discrimination***	48	0.92	(0.01)	28	0.96	(0.01)	0.11 NS
Yes/No***	50	0.99	(0.01)	29	0.99	(0.01)	0.88 NS
Sequential commands***	48	0.94	(0.02)	29	0.99	(0.01)	0.06 NS

** SEM = standard error of the mean; ** t test for unpaired samples.*
*NS = Not statistically significant, P > 0.01; *** = proportion correct responses.*

phones. The tone pips are presented at the rate of 1 per 1.5 sec. Each series consists of two different frequencies of tone pips randomly interspersed. The lower 1000 Hz tone pip is presented 85% of the time, while the higher 2000 Hz tone is presented 15% of the time in the series. The patient is asked to maintain a mental count of the occurrence of the 2000 Hz tone pip, designated the target or rare event. Separate evoked potential averages are made to the target and non-target tones for each of the three series. Verbal reports of rare tone counts are obtained after each series to assess attention to the task. The P300 component of the ERP was defined as a positive wave at Pz occurring about 300–700 msec after the tone in the target tone pip evoked potential averages. Latency of the P300 component was defined as the time from stimulus onset to the peak of intersecting tangent lines drawn on the descending and ascending portions of the P300 waveform.[38]

In the PVEP procedure, 180 degree shifts in a black/white checkerboard pattern presented at a rate of 2/sec were used as a visual stimulus to produce the P100 component. Each eye was examined separately. The technical details were similar to those described in previous papers.[34] Two check sizes, 20′ and 50′, were used because previous studies have indicated they are differentially sensitive to mild to moderate changes in visual pathway conduction.[51] Latency of the major positive P100 component was obtained by the "best fit" slope-line intersection method described above. Visual acuity was assessed with a Jaeger chart and subjects were tested with best refraction.

Data Analysis For non-parametric data, chi-square with continuity correction was used. The *t* test was used to compare differences between groups (hypothyroids and controls). Two-way ANOVA was performed to examine the separate and interactive effects on test measures of thyroid status (hypothyroid or euthyroid control) and age (younger, ≤75 years, or older, >75 years). Correlation analyses were also performed between thyroid function measures and performance scores. Correlations are reported as Pearson Product Moment Correlation coefficients (*r*) and the 95% confidence interval (CI) of *r*.

Assessment of treatment effects was somewhat problematic because an adequate untreated patient control group was not available, and the subset of treated patients available for retesting included primarily those with minimal test decrements pre-treatment. Treatment effects were assessed in three ways. First, *t* tests were used to compare the pre-treatment (Exam 1) and post-treatment (Exam 2) scores separately for the hypothyroid group and normal controls. Two-way repeated measures analysis of variance (ANOVA) was performed to examine the separate and interactive effects of thyroid disease (hypothyroid compared to normal controls) and change in test scores over the two examinations. Since only the hypothyroid patients were treated in the interval between the two examinations, a statistically significant interaction effect would support a differential effect of treatment. Finally, for the subset of patients who had two post-treatment exams, repeated measures ANOVA was used to assess changes in scores over all three exams for the hypothyroid patients only. The analyses of treatment effects were conducted only on the subset of tests that had shown statistically significant differences between hypothyroid patients before treatment and the euthyroid controls.

Due to missing data and the introduction of three neuropsychological tests (SDMT, Trail Making A and B) after study onset, the number of cases varies in the different analyses.

A two-tailed *P* value of 0.05 was used to assess statistical significance for analyses of the demographic, thyroid function, and electrophysiological variables. Due to the larger number of statistical tests involved in analyses of cognitive measures, an adjusted *P* value of 0.01 was used to assess statistical significance. It was decided that the more conservative Bonferroni adjust-

TABLE 3. NEUROPSYCHOLOGICAL TESTS: COMPARISON OF CLINICALLY NON-DEMENTED HYPOTHYROID PATIENTS WITH NORMAL AND ABNORMAL MENTAL STATUS SCORES (MMSE)

	Normal MMSE (≥24)			Abnormal MMSE (<24)			
	n	Mean	(SEM*)	*n*	Mean	(SEM)	*P***
MMSE	38	28.0	(0.2)	15	21.4	(0.8)	0.0001
Cube (rating 1–5)	34	3.9	(0.2)	12	2.5	(0.2)	0.0002
Inglis-low***	35	0.61	(0.05)	12	0.28	(0.06)	0.0009
Inglis-medium***	35	0.86	(0.03)	12	0.63	(0.07)	0.002
Inglis-high***	35	0.98	(0.07)	12	0.81	(0.06)	0.0001
Animal Naming (# words/60')	37	16.6	(0.9)	12	9.17	(0.9)	0.0001
Digits Forward (# digits)	37	5.9	(0.2)	13	5.2	(0.3)	0.043 NS
Digits Backwards (# digits)	37	3.8	(0.1)	13	3.1	(0.3)	0.0089
Symbol Digit Modality Test	20	31.3	(3.2)	5	11.2	(1.0)	0.0053
Trail Making A (sec)	20	59.8	(8.8)	6	42.8	(3.4)	0.0013
Trail Making B (sec)	24	127.5	(18.1)	27	147	(37.2)	0.0001
Oral Reading***	35	1.0	(0.0)	10	0.95	(0.04)	0.0093
Word Discrimination***	37	0.96	(0.01)	10	0.80	(0.04)	0.0001
Yes/No***	37	1.0	(0.0)	10	0.96	(0.03)	0.03 NS
Sequential commands***	37	0.95	(0.02)	10	0.90	(0.04)	0.282 NS

** SEM = standard error of the mean; ** t test for unpaired samples.*
*NS = Not statistically significant, P > 0.01; *** = proportion correct responses.*

ment for multiple comparisons would result in an unacceptably high increase in probability of a Type II error and, thus, decreased power.[52] Typically MANOVA would be used to take into account correlations among the multiple variables and to avoid inflation of an overall Type I error rate from the use of multiple uninvariate tests.[53] However, MANOVA was excluded by the presence of random missing values and the late introduction of three key tests, both of which greatly reduced the degrees of freedom in the multivariate procedure.

For treatment effects, a two-tailed *P* value of 0.05 was used to determine statistical significance. However, due to the smaller *n* available in the treatment study, particularly for the three tests introduced after study onset, the power to detect significant changes with treatment was low, typically on the order of 0.35–0.40.[54]

RESULTS

There were no statistically significant differences in age, gender, or educational composition between the study and control groups, although males tended to predominate among the hypothyroids and females among the controls, and there was a trend for patients to have less education than controls (Table 1). The two groups showed the expected statistically significant differences on tests of thyroid function (Table 1).

The Effect of Hypothyroidism and Age on Neuropsychological and Electrophysiological Tests Hypothyroid patients, overt and minimal combined, scored significantly lower than controls on six out of 15 tests at the initial test session: Mini-Mental State Exam, Copying the Cube, Inglis low and medium association pairs, Animal Naming, and Trail Making A (Table 2). Two other tests, Digits Backward and SDMT, did not reach the adjusted *P* value of 0.01, but showed group differences supportive of cognitive dysfunction in hypothyroidism.

On the MMSE 28% of hypothyroid patients were below the threshold for abnormality (<24) versus 3% in the control group (chi square, $P = 0.01$). In order to determine the relative contribution of hypothyroid patients with abnormal MMSE scores to the lower cognitive test scores of the entire hypothyroid group, *t* tests were used to compare scores of patients with abnormal MMSE scores to those with normal MMSE scores (Table 3). The abnormal MMSE hypothyroid subgroup had significantly lower scores than the normal MMSE subgroup on 11 out of the 14 neuropsychological tests (the MMSE scores were significantly different by selection). Only three tests showed no significant difference (Digits Forward, Yes/No and Sequential Commands). The abnormal MMSE hypothyroid subgroup also had significantly higher serum thyroxine (T_4) values (3.5 ± 2.95 μg/dL) than the normal MMSE subgroup (2.02 ± 2.09 μg/dL, $P = 0.042$), but no significant differences for the other thyroid function tests. In addition, the abnormal MMSE subgroup was significantly older than the normal MMSE subgroup (77.7 ± 15.5 yr compared to 64.6 ± 15.4 yr, $P = 0.007$).

A comparison of normal MMSE hypothyroid patients with the normal controls showed no significant differences in 14/15 tests. The normal MMSE hypothyroid patients scored significantly lower than the normal controls on only one test, Inglis Paired Associates, low association items (0.86 ± 0.2 compared to 0.97 ± 0.1, respectively, $P = 0.002$). In contrast, these two groups showed significant differences ($P = 0.0001$) on all thyroid function tests as expected. They did not differ significantly on age (64.6 ± 15.4 for the normal MMSE hypothyroids compared to 63.3 ± 18.6 for the controls, $P = 0.759$).

We performed a two way ANOVA to determine whether age and hypothyroidism (hypothyroid patients compared to controls) were independent factors

related to performance on the tests and, specifically, to test whether the aging brain is affected differently by hypothyroidism than is the younger brain. For this purpose we categorized all subjects into those ≤75 years of age (Younger, $n = 52$) and >75 years of age (Older, $n = 32$) to yield two levels of the age factor because a number of studies have shown that there are significant declines in numerous cognitive and psychomotor performance measures in older adults, particularly in those over 75.[50] We also compared hypothyroids with controls (hypothyroid factor).

In concordance with the data shown in Table 2, a significant difference between hypothyroid patients and controls was found for six of the 15 tests (MMSE, Copying the Cube, Inglis-low, Inglis-medium, Animal Naming, and Trail Making A). A significant difference between older and younger subjects, regardless of whether they were hypothyroid or euthyroid controls, was found for nine of the 15 tests (MMSE, Copy Cube, Inglis-low, Inglis-medium, Animal Naming, SDMT, Trails A, Word Discrimination, Sequential Commands). However, none of the fifteen tests showed a statistically significant interaction between age and hypothyroidism.

We performed a second two way ANOVA to examine thyroid and age effects with three levels of the age factor (Young <50, Old 50–75, Old Old >75 years). Mean ages and number of cases of the three age subgroups for the controls were 37.4 ($n = 8$), 63.4 ($n = 11$), and 81.1 years ($n = 11$), respectively, while mean ages and number of cases for the hypothyroids were 41.0 ($n = 9$), 65.0 ($n = 24$), and 84.3 ($n = 21$), respectively. The results were virtually identical to the analysis with two levels of the age factor. Statistically significant differences between hypothyroid patients and controls were found for five of the fifteen tests (MMSE, Copy Cube, Inglis-low, Inglis-medium, SDMT, and Trail Making A), with two other tests showing $0.01 < P < 0.05$ (Digits Backward and Animal Naming). A significant difference among the three age groups was found for seven of the fifteen tests (MMSE, Copy Cube, Inglis-low, Animal Naming, SDMT, Trail Making A, Word Discrimination). One of the tests, Trail Making A, showed a significant interaction with age and hypothyroidism ($P = 0.008$). For this test, the young hypothyroids had non-significantly better scores than the young controls (26.6 compared to 31.8 sec), while the reverse was true for the two older groups (69.2 and 123.8 for old and old old hypothyroids, respectively, compared to 34.3 and 54.7 sec for the old and old old controls).

To determine whether gender may have affected the neuropsychological tests, we conducted separate two-way ANOVAs on all tests, with thyroid status and gender as the between subject factors. There were no significant main effects for gender nor gender by thyroid status interactions. Main effects for thyroid status were identical to those reported above.

In the PVEP studies there was no significant effect of hypothyroidism on P100 latency using the less sensitive 50-minute check size. However, hypothyroid patients showed significantly longer latencies than controls when the 20-minute check size was used ($P = 0.05$). There was no significant difference in visual acuity between the two groups.

There also was no statistically significant difference in P300 latency between hypothyroid patients and controls. In contrast, older hypothyroid patients (>75) had significantly longer latencies for P100 PVEP and for P300 ERP compared to younger (≤75 years) individuals. There were no significant interactions between age and hypothyroid state for either of the electrophysiological measures. A comparison of abnormal MMSE hypothyroid patients with normal MMSE hypothyroid patients did not show any significant differences in any of the PVEP measures or in P300 latency. The results for a similar analysis with three levels of the age factor showed identical results.

The Effect of Severity of Hypothyroidism on Neuropsychological and Electrophysiological Tests Neuropsychological and electrophysiological test results were statistically no different in minimal hypothyroidism (normal T_4 with TSH ≥ 10 μU/mL) than in the controls, whereas overt hypothyroidism (as well as the combined hypothyroid groups, see above) was associated with significant impairment in many of the neuropsychologic tests. In order to analyze the relationship of severity of hypothyroidism to test results, we used thyrotropin (TSH) and thyroxine (T_4) serum levels as indicators of severity. In the case of TSH, we found no significant differences for any neuropsychological or electrophysiological test when we compared the results in patients above and below cut-off points of 20 μU/mL or 46 μU/mL (the median). Separating patients into a subgroup with TSH > 20 and $T_4 \leq 4.2$ and a subgroup with TSH ≤ 20 and $T_4 > 4.2$ did not reveal significant differences between the subgroups.

Regression analysis showed no correlation between serum TSH and neuropsychological and electrophysiological test measures; however, a small but statistically significant correlation of serum T_4 was found with Inglis medium Association Test items ($r = 0.28$, $P < 0.01$, 95% CI 0.05–0.47) and Animal Naming ($r = 0.3$, $P < 0.001$, 95% CI 0.07–0.49). Regression analysis for serum T_3 did not show significant correlation with any of the neuropsychological or electrophysiological tests, although there were trends for Inglis low Association ($r = 0.25$, $P < 0.05$, 95% CI 0–0.46), Trail Making A ($r = 0.32$, $P < 0.05$, 95% CI 0.02–0.55), SDMT ($r = 0.30$, $P < 0.05$, 95% CI 0–0.55), and Digits Forward ($r = 0.26$, $P < 0.03$, 95% CI 0.02–0.46).

The Effect of Short-Term Hypothyroidism on Neuropsychological and Electrophysiological Test Performance Patients with short-term, but overt hypothyroidism (carcinoma of the thyroid off thyroid hormone replacement) showed no statistical differences in test performance from euthyroid controls.

Thyroid Function Test Results As expected, there was a statistically significant difference in thyrotropin, triiodothyronine, and thyroxine values between hypothyroid patients and normal controls. Within the hypothyroid group, there were significant differences in T_4 levels between the younger (<75) and older (≥75) subgroups; T_4 levels were lower in the younger subgroup. The same trend was observed for T_3, but the

differences did not reach statistical significance. A multiple regression analysis of T_4 level and age as predictors of TSH levels showed that only T_4 was a predictor of TSH ($r = 0.46$). To further evaluate the effect of age on thyroid function, we ran separate one-way ANOVAs of age versus T_4, T_3, and TSH. There were no significant effects of age (younger vs older) on any measure of thyroid function.

The Effect of Treatment on Neuropsychological and Electrophysiological Tests There were no significant differences in age or gender composition between the sub-sample of treated hypothyroid patients and controls with repeat exams, although males tended to predominate among the hypothyroids and females among the controls (Table 4). The retested hypothyroid group showed a significantly lower mean education level than retested controls. The two retested groups showed the expected statistically significant differences on tests of thyroid function pre-treatment (Table 4). The hypothyroid patients showed significant improvements on the tests of thyroid function following treatment, while the controls showed no significant changes (Table 4).

We compared the sub-sample of hypothyroid patients with repeat exams to the entire sample at baseline for neuropsychological testing to determine how representative the sub-sample was of the entire patient sample. In support of the findings for the entire group, significantly lower scores were found for the treated hypothyroid group for MMSE, Copying a Cube, Trail Making A, and Inglis medium and low Association items. In contrast to the entire group analyses there were no statistically significant differences between the two groups for Animal Naming and SDMT.

Table 5 shows the effect of hormone replacement therapy on neuropsychological test performance in the hypothyroid patients. Three tests showed a statistically significant improvement from baseline to 5 months of treatment (SDMT, Trail Making A, Inglis Paired Associates-medium). Three additional tests showed trends in the same direction. Overall, nine out of the 10 tests showed changes indicative of improvement with treatment. Neither the P100 VEP nor the P300 ERP electrophysiological measures improved following treatment.

To take into account potential practice effects, a two-way repeated measures ANOVA (Group factor: Patients vs Controls; Exam factor: 1 and 2) was conducted on each measure and on TSH values. The results for TSH showed there were significant main effects for Group, Exam, and the interaction between Group and Exam. The significant interaction effect indicated that the patients showed the expected decrease in TSH levels from Exam 1 (hypothyroid state) to Exam 2 (euthyroid state after treatment), while the controls showed no change.

Figure 1 shows the results for the Inglis Paired Associates test, medium association items. The main effects for Group and Exam were not significant, but the Group by Exam interaction was statistically significant ($F(1,46) = 5.8$, $P = 0.02$). Separate planned comparison of Exam 1 and Exam 2 differences showed that the hypothyroid group improved (Table 2), while the control group did not change significantly.

Two tests showed trends for significant Group by Exam interactions: Symbol-Digit Modalities Test ($F(1,28) = 3.45$, $P = 0.074$) and Trail Making A ($F(1,28)$

TABLE 4. AGE, GENDER AND THYROID FUNCTION TESTS OF RE-TESTED HYPOTHYROID PATIENTS AND CONTROLS

	Hypothyroid Patients $n = 34$	Euthyroid Controls $n = 20$	P-value
Age (years)			
Range	31 to 99	30 to 87	
Mean (Standard deviation)	65.4 (17.9)	63.4 (17.7)	NS*
Gender			
Female # cases (%)	15 (44%)	14 (70%)	
Male	19 (56%)	6 (30%)	NS**
Education			
Mean (standard deviation)	11.0 (4.0)	13.7 (4.2)	0.043*
Thyroid function tests: Mean (standard deviation)			
Serum thyrotropin (TSH)			
Pre-treatment	66.4 (56.4)	1.4 (0.7)	0.0001*
Post-treatment	4.7 (6.1)***	1.6 (1.0)†	0.0461*
Serum thyroxine (T_4)			
Pre-treatment	2.3 (2.2)	7.8 (2.7)	0.0001*
Post-treatment	8.0 (2.8)***	7.3 (1.9)†	NS
Serum triiodothyronine (T_3)			
Pre-treatment	65.6 (39.4)	111.9 (23.6)	0.0001*
Post-treatment	98.6 (19.7)***	126.5 (28.5)†	0.0002*
Free thyroid index (FT_4I)			
Pre-treatment	2.0 (1.9)	9.6 (2.7)	0.0001*
Post-treatment	6.4 (2.7)***	not done	

NS, Not Statistically Significant, $P > 0.05$.
** t-test for unpaired samples; ** Chi-square.*
**** Comparison of pre- and post-treatment values by paired t test, $P < 0.01$.*
† Comparison of pre- and post-treatment values by paired t test, NS.

TABLE 5. EFFECT OF THYROID REPLACEMENT ON NEUROPSYCHOLOGICAL TEST PERFORMANCE IN HYPOTHYROID SUBJECTS

	Test 1-PreTx Hypothyroid State		Test 2-PostTx Euthyroid State	
	n	Mean (SEM*)	Mean (SEM)	*P***
Modified Mini-Mental State (# items-30 max)	34	26.9 (0.4)	27.2 (0.4)	0.15 NS
Cube (rating 1–5)	31	3.5 (0.2)	3.6 (0.2)	0.65 NS
Inglis-low***	26	0.61 (0.06)	0.70 (0.05)	0.10 NS
Inglis-medium***	29	0.86 (0.04)	0.93 (0.03)	0.006
Animal Naming (# words/60')	31	15.2 (1.1)	16.0 (1.4)	0.31 NS
Digits Forward (# digits)	31	5.8 (0.2)	5.9 (0.2)	0.49 NS
Digits Backward (# digits)	31	3.8 (0.2)	3.8 (0.2)	0.84 NS
Symbot Digit Modalities Test (# correct/90')	11	33.6 (4.5)	37.9 (4.7)	0.016
Trail Making A (sec)	12	67.9 (16.5)	56.4 (15.7)	0.030
Trail Making B (sec)	12	132.8 (19.1)	107.8 (19.0)	0.10 NS

* *SEM = standard error of the mean.*
** *t test for paired samples.*
NS = Not statistically significant, P > 0.05.
*** *Proportion correct responses.*

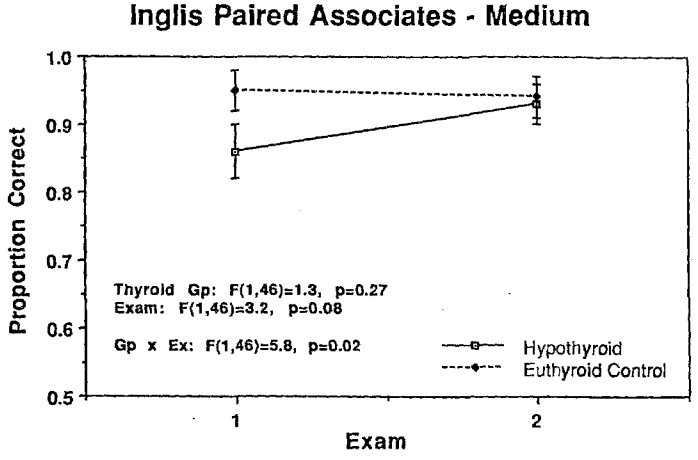

FIGURE 1. Mean values of scores (proportion correct) on the Inglis Paired Associates Test, medium association items, for the hypothyroid and euthyroid controls are plotted at exam 1 (pre-treatment for the hypothyroid group) and exam 2 (approximately 5 months after exam 1 and post-treatment for the hypothyroid group). Results of a two-way repeated measures analysis of variance for Inglis scores are shown on the graph. The group main effect (Thyroid Gp) compares scores for hypothyroid patients and controls across the two exams (ie, it compares the mean of exam 1 and 2 between the two groups). The exam main effect (Exam) compares the scores at exam 1 with those at exam 2 independent of group (ie, it compares the mean of hypothyroid patients and controls between the two exams). The Group by Exam interaction effect (Gp × Ex) compares the difference between exams 1 and 2 for hypothyroid patients compared to euthyroid controls (ie, it compares whether the slopes of the two lines, solid for hypothyroids and dashed for controls, are parallel, indicating no differential treatment effect, or non-parallel, indicating a possible treatment effect).

= 3.98, $P = 0.056$). Neither of these two tests showed significant Group or Exam main effects.

The Inglis Paired Associates Test, low association items showed a significant main effect for Group ($F(1,43) = 11.04$, $P = 0.0018$) and Exam ($F(1,43) = 4.36$, $P = 0.043$), but not for the Group by Exam interaction ($P = 0.43$). None of the other cognitive or electrophysiological tests showed statistically significant main effect for Exam or the Group by Exam interaction.

Further improvement in performance was demonstrated in two of the three neuropsychological tests when patients were studied for a third time 4 months after the second test session. Repeated measures ANOVA showed a statistically significant improvement in two tests over the three exams: SMDT ($F(1,10) = 3.94$, $P = 0.05$) and Trail Making A ($F(1,10) = 4.83$, $P = 0.03$). In both cases the linear contrast was statistically significant ($P < 0.05$). However, statistical comparisons between scores at Test 2 (5 mo) and Test 3 (9 mo) showed no significant improvement on these two tests.

When tested separately, the controls did not show significant changes in performance on any of the tests at the second exam compared with the first exam.

DISCUSSION

We found that hypothyroidism in non-demented older adults is associated with cognitive impairment in six of 15 of the neuropsychological tests administered. Learning, memory, word fluency, visual-spatial skills and mental status were affected. Of clinical interest is the fact that the MMSE, a widely used screening test for cognitive dysfunction indicative of dementia, was sensitive to the effects of hypothyroidism although the mean score was well above the recognized threshold for abnormality (ie, dementia). However, 28% (15/54) of hypothyroid patients and only 3% of euthyroid controls had scores below the threshold for abnormality (<24) although none of the subjects were evaluated as clinically demented.

The hypothyroid patients who had abnormal MMSE scores were significantly impaired on 11 of 14 neuropsychological tests when compared to hypothyroid patients with normal MMSE scores (MMSE was not included as an outcome test in these analyses). The impaired performance of the abnormal MMSE hypothyroid patients is an expected finding since the MMSE contains a broad range of cognitive test items. One important aspect of the differential results for the MMSE subgroups is that hypothyroidism was associated with significantly impaired performance across a

broad range of cognitive functions in only a subset of patients. This finding was not related to age alone since the abnormal MMSE subgroup showed significantly decreased performance in the same set of tests when compared to the subset of controls over 75 years. This finding may reflect differences in the duration of hypothyroidism between the two MMSE subgroups that we were unable to document. It probably doesn't reflect simple differences in severity of hypothyroidism, because T_4 was significantly higher in the low MMSE group, and TSH was not significantly different between the two subgroups.

In contrast to the findings for the abnormal MMSE subgroup, the remaining 72% of hypothyroid patients who had normal MMSE scores did not differ significantly from normal controls on all but one neuropsychological test. For this subgroup, hypothyroidism was associated with minimal test abnormalities.

The language tests were included in the testing battery because Alzheimer patients show a substantial change in language function,[3,44] and it was of interest to see if hypothyroidism similarly affected language function. Language defects were not evident in the full group of hypothyroid patients. However, language defects were evident in the subgroup of hypothyroid patients with abnormal MMSE scores. It is possible that members of this subgroup had a "preclinical" dementia. Whether the low MMSE group would have eventually met the clinical criteria for dementia if left untreated cannot be answered, but we would strongly suspect that this would be the case. Nonetheless, our findings clearly validate the view, long held despite a lack of pertinent data, that patients with mild to moderate cognitive impairment should be screened for hypothyroidism. The data also indicate that the MMSE provided a sensitive measure of cognitive dysfunction associated with hypothyroidism that concorded well with the other neuropsychological results. Only those hypothyroid patients with MMSE less than 24 showed substantial worsening of scores compared to the normal controls.

The analyses of age and thyroid function groups showed that age and hypothyroidism were independent factors in accounting for variance in the neuropsychological test scores. Only one test, Trail Making A, showed an interaction between age and hypothyroidism, with the older hypothyroid group (>75 yr) showing the largest decrements in performance. This test was also shown in previous studies to be sensitive to the effects of hypothyroidism.[48] The significant interaction of age and thyroid status on this one test may be cautiously interpreted to show that hypothyroidism may have a more severe effect on selected cognitive functions in old old adults. Further research is warranted to explore this hypothesis.

Although scores of cognitive function tests did not correlate with TSH levels, there were small, but statistically significant, correlations of T_4 with Inglis Paired Associates—medium association and Animal Naming. However, the low MMSE subgroup had a very high TSH value and its mean T_4, although significantly higher than the normal MMSE subgroup, was still below normal. Both TSH and T_4 can be considered putative measures of severity of hypothyroid disease, and we used them as such. However, duration of hypothyroidism may be an even more significant variable, which we had very little control over. In view of the uncontrolled nature of duration of hypothyroidism, the overall lack of significant correlations between the thyroid function tests and cognitive test performance may not be that surprising.

Furthermore, cognitive function in mild hypothyroidism (ie, moderately elevated TSH and normal T_4) was not different from that in euthyroid persons of comparable age. The same was true of patients with severe hypothyroidism of very short duration. Thus, the data support the view that it requires longer-term and overt hypothyroidism before cognitive dysfunction is detectable in a wide range of tests. The neonatal brain is protected from the effects of low T_3 levels in the circulation by enhanced intraneuronal conversion of T_4 to T_3 and prolonged residence time of T_3 in brain.[55,56] Perhaps these same mechanisms exist in older adults, protecting them from the effects of mild or short-term hypothyroidism. However, it is possible that a more extensive battery of performance tests would have detected changes in mild hypothyroidism.

We confirm a previous report[37] showing significant increase in latencies of the P100 component of visual evoked potentials in hypothyroid patients compared to controls, but only for the smallest check size we used, 20′. This differential sensitivity of small check size to PVEP changes has also been reported in Parkinson's Disease,[51] but the mechanisms may be completely different. In spite of the significant mean decrement in hypothyroid patients, absolute P100 latencies of hypothyroid patients were generally within the normal range for our laboratory. It is possible that there were differences in PVEP procedures or the severity of hypothyroid patients that may explain the apparent difference in magnitude of affect on PVEP latency in our findings compared to a previous report.[37]

As expected from previous reports,[38,39] there was an age-related showing of P300 latency for both euthyroid controls and hypothyroid patients. The age-related difference in P300 latency supports the general sensitivity of the procedure to neurocognitive changes. In contrast, P300 latency does not appear to be sensitive to the effects of hypothyroidism on cerebral function in the absence of clinical dementia. Even the subgroup of hypothyroid patients with abnormal MMSE scores and impaired performance on virtually all neuropsychological tests did not show significant increases in P300 latency. Our finding regarding the lack of sensitivity of P300 in detecting early cognitive abnormalities in hypothyroidism is consistent with findings that P300 does not appear to be sensitive in the earliest stages of dementia.[57–59]

There was evidence for statistically significant improvements associated with hormone replacement therapy in selected areas of cognitive function. SDMT, Trail Making A, and Inglis Paired Associates-medium and low association items all showed evidence of improved functioning following 5 months of thyroid replacement therapy and the return to a euthyroid state. The SDMT and Trail Making A tests have in common

sensitivity to the effects of attention and psychomotor slowing.[46] The Inglis Paired Associates test, particularly for medium and low association items, is most sensitive to changes in learning and memory.[42] However, only the medium items showed a differential treatment effect. Both controls and patients improved on the low association items, the most difficult items in the test, suggesting that a practice effect on this portion of the test overshadowed possible treatment effects.

The lack of significant improvement on the other tests suggests either that some effects of hypothyroidism are permanent or that these tests showed too much intra-individual variability. A more critical factor may be the fact that 12 of the 15 most impaired hypothyroid patients (ie, MMSE scores < 24) before treatment were not available for follow-up. Thus, many of the hypothyroid patients available for retesting may not have been sufficiently impaired on some of the neuropsychological tests to register improvements with thyroid replacement therapy. In addition, the relatively small n available for the treatment study decreased power for detecting changes with treatment.[54] The fact that significant improvement with hormone replacement therapy was noted on some tests in spite of the bias of having only mildly affected patients available for retesting and low power supports our conclusion of a deleterious effect of hypothyroidism on some cognitive functions. It may be suspected that if the hypothyroidism were left untreated, more pronounced cognitive abnormalities would occur.

The cognitive tests that showed significant improvement with treatment also showed the largest hypothyroid effect, with the exception of the MMSE. The improvement in scores on the hypothyroid sensitive tests indicate that the deleterious effect of hypothyroidism is at least partially reversible, particularly for cognitive functions involving speeded motor and cognitive processing. There appeared to be only slight, if any, further improvement in SDMT, and Trail Making A scores after 9 months of replacement as compared to the first 5 months of treatment. That is, once the euthyroid state is reached, the patient will have derived the maximum benefit of treatment and only minor improvements can be expected with continued treatment. Confirmation of this conclusion awaits another treatment study with more severely afflicted patients.

In summary, we have shown a relationship between hypothyroidism and cognitive function in older adults, using relatively simple, commonly used neuropsychological tests. The results justify a more extensive evaluation of neuropsychological changes in hypothyroidism, one that also covers a wider range of severity of hypothyroidism. While our tests indicate that cognitive functions, including memory, learning, word fluency, and visual-spatial skills, as well as visual search scanning, attention, and motor speed are affected, none of the hypothyroid patients were clinically demented. We would expect, however, that the subgroup of hypothyroid patients with abnormal MMSE were very near the threshold for clinical dementia and might have reached this threshold if the hypothyroidism had persisted.

The use of electrophysiological methods (ERP and VEP) to detect hypothyroid-related changes in the absence of clinical dementia yielded rather disappointing results and thus are not recommended at present for routine clinical use to detect or assess effects of hypothyroidism on the central nervous system.

The results also support the need for a larger study of the effects on cognitive function of thyroid replacement therapy in hypothyroidism. We recommend that such a future study focus on individuals over 65 years of age, and particularly those over 75 years of age, who show the most severe hypothyroidism. Such individuals may be more vulnerable to the effects of hypothyroidism on cognitive function.

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