Evidence for a Specific Defect in Hippocampal Memory in Overt and Subclinical Hypothyroidism

Neuman Correia,* Sinead Mullally,* Gillian Cooke, Tommy Kyaw Tun, Niamh Phelan, Joanne Feeney, Maria Fitzgibbon, Gerard Boran, Shane O'Mara, and James Gibney

Departments of Endocrinology (N.C., T.K.T., N.P., J.G.) and Chemical Pathology (G.B.), Adelaide and Meath Hospital, incorporating the National Children's Hospital, Tallaght, Dublin 24, Ireland; and Trinity College Institute of Neuroscience (S.M., G.C., J.F., M.F., S.O.), Dublin 2, Ireland

Context: Declarative memory largely depends upon normal functioning temporal lobes (hippocampal complex) and prefrontal cortex. Animal studies suggest abnormal hippocampal function in hypothyroidism.

Objective: The aim of the study was to assess declarative memory in overt and subclinical (SCH) hypothyroid patients before and after L-T_4 (LT4) replacement and in matched normal subjects.

Design and Setting: A prospective, open-labeled interventional study was conducted at a teaching hospital.

Participants and Intervention: Hypothyroid (n = 21) and SCH (n = 17) patients underwent neuropsychological tests at baseline and 3 and 6 months after LT4 replacement. Normal subjects were studied at the same time-points.

Main Outcome: Tests of spatial, verbal, associative, and working memory; attention; and response inhibition and the Hospital Anxiety and Depression Scale were administered.

Results: Baseline deficits in spatial, associative, and verbal memory, which rely upon the integrity of the hippocampal and frontal areas, were identified in patients with overt hypothyroidism. Spatial and verbal memory were impaired in SCH patients ($P < 0.05$). TSH levels correlated negatively ($P < 0.05$) with these deficits. After LT4 replacement, verbal memory normalized. Spatial memory normalized in the SCH group but remained impaired in the hypothyroid group. Associative memory deficits persisted in the overt hypothyroid group. Hospital Anxiety and Depression Scale scores did not correlate with cognitive function. Measures of attention and response inhibition did not differ from control subjects.

Conclusion: Cognitive impairment occurs in SCH and more markedly in overt hypothyroidism. These impairments appear predominantly mnemonic in nature, suggesting that the etiology is not indicative of general cognitive slowing. We propose that these deficits may reflect an underlying disruption of normal hippocampal function and/or connectivity. **(*J Clin Endocrinol Metab* 94: 3789–3797, 2009)**

Although impairment of cognitive function in overt hypothyroidism has been recognized for more than a century, the nature and severity of this impairment and the degree of recovery after treatment remain unclear (1). Some studies have reported general cognitive slowing (2, 3), whereas others suggest a more specific mnemonic deficit (4, 5). Deficits in hippocampal-dependent memory tasks (6) that are reversible with thyroid hormone replace-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2008-2702 Received December 11, 2008. Accepted July 1, 2009.
First Published Online July 7, 2009
* N.C. and S.M. contributed equally to this work.

Abbreviations: FT4, Free T_4; LT4, L-T_4; ROCF, Rey-Osterrieth Complex Figure (task); SCH, subclinical hypothyroidism.

ment (7–9) are apparent in animal models of hypothyroidism, whereas studies in hypothyroid rats have demonstrated impaired hippocampal neurogenesis, providing a potential mechanistic explanation for these mnemonic deficits (10). It is not known whether similar mnemonic deficits occur in humans.

It is also not known whether the neurocognitive deficits associated with overt hypothyroidism occur in patients with subclinical hypothyroidism (SCH), which is defined as persistently raised serum TSH level in the presence of normal free T_4 (FT4) and which occurs in 4–10% of the adult population (11). Although some studies suggest impairment of cognitive function in SCH, there remain inconsistencies in the range and degree of these deficits. One study reported an attenuation of logical memory (12), whereas other investigations point to specific deficits in working memory (13, 14) or verbal fluency (15). These apparently conflicting findings potentially reflect differences in the age of the populations studied, differing degrees of severity of SCH, and a lack of uniformity in administered cognitive tests.

We hypothesized that specific impairments in hippocampal and possibly frontally driven memory processes could be demonstrated in subjects with overt hypothyroidism and to a lesser degree in SCH, and these deficits would improve after L-T_4 (LT4) replacement. To address this, we conducted a battery of cognitive tests shown previously to be sensitive to deficits in hippocampal- and frontally driven cognitive processes. We tested patients with overt and subclinical hypothyroidism before and after LT4 replacement and normal control subjects matched for age and educational status. Control subjects were retested at 3 and 6 months to control for learning effects. We assessed anxiety and depression, which are more marked in hypothyroid (2, 16) patients and could potentially confound assessment of cognitive function.

Patients and Methods

Participants

Twenty-one patients with hypothyroidism (FT4 $<$ 11 pmol/liter; elevated TSH), and 17 patients with SCH (TSH $>$ 4 mU/liter; normal FT4), ages 18–65 yr, participated in this study. The majority of patients were recruited from General Practitioner referrals to Endocrinology outpatient service, the remainder being direct referrals to the Endocrinology department from other specialist teams within the hospital. Nineteen healthy control subjects of similar age and education were recruited. All participants were native English speakers. Exclusion criteria included a previous history of ischemic heart disease, stroke, diabetes, head injury, epilepsy, psychiatric illness, significant visual impairment, or pregnancy. Care was taken to avoid testing during periods of significant stress (*e.g.* death of relative). All study subjects gave their written signed consent to the study, which was approved by the Research Ethics Committee of the Adelaide and Meath Hospital and St. James's Hospital (Dublin, Ireland).

Experimental design

At diagnosis, a neurocognitive battery of memory and executive function tasks was performed (session 1), lasting approximately 1 h (including a 5-min break midway through the session). SCH and hypothyroid subjects were commenced on LT4 replacement after initial neurocognitive assessment; they had an additional thyroid hormone level checked 6 wk after commencing LT4. LT4 was prescribed as an initial dose of 50 μg/d and subsequently titrated depending on TSH levels. Cognitive functioning and thyroid hormone levels were reassessed at approximately 3-month (session 2) and 6-month (session 3) intervals. When possible, alternative versions of cognitive tests were administered at each session to minimize practice effects.

Neurocognitive battery

We selected tasks that focused specifically on general intelligence, anxiety and depression levels, learning, memory, and executive functioning. The tests were administered in the same order to all participants by a single tester who was not blinded to the subject group. An estimate of premorbid intelligence was obtained using the National Adult Reading Test (17), and self-reported mood and well-being were obtained using the Hospital Anxiety and Depression Scale (18).

Tests for declarative memory were: visual memory, the Rey-Osterrieth Complex Figure; verbal memory, the Rivermead Behavioral Memory Test: Story Recall Subset; and associative memory, Face-Name Learning and Recall. Tests for executive function were: focused attention; working memory, n-Back Task; and response inhibition, the Stroop Task.

Declarative memory tests

Visual memory: the Rey-Osterrieth Complex Figure (ROCF). The ROCF was designed to measure visuospatial ability and nonverbal memory (19, 20) and is sensitive to medial temporal lobe damage (21, 22). It consists of a two-dimensional line drawing that participants are required to copy as accurately as possible (Copy Trial, maximum score = 36). Twenty minutes later, they redraw the figure from memory (Delayed Recall Trial), and a memory accuracy score is calculated (Delayed Recall/Copy Trial*100). The Modified Taylor Complex Figure (23), a comparable version of the ROCF, was used at session 2 to minimize practice effects across sessions. Note: the ROCF was readministered at session 3.

Verbal memory: the Rivermead Behavioral Memory Test: Story Recall Subset. The Rivermead Behavioral Memory Test (24) is used to assess gross memory impairments and has been shown to correlate with everyday memory complaints (25). This verbal subset consists of a paragraph of four sentences (21 units) that are read out to the subject. Subjects are then required to recall the story in as much detail as possible at the immediate and delayed (30 min after learning) levels.

Associative memory: Face-Name Learning and Recall. This task represents an ecologically valid measure of associative learning. Clinical and neuroimaging data suggest that this ability depends principally on the hippocampal formation (26). Subjects were required to encode (memorize) and subsequently recall eight novel face-name pairs that were presented on a computer screen. They performed four successive learning and recall trials (Face-Name Encoding), followed by a Delayed Recall Trial (Face-Name Recall; 15 min after learning).

Executive function tests

Focused attention. Each of the four encoding and recall trials in the face-name task was separated by a 30-sec visual attention task. Participants were required to respond to a rapid and repetitive visual stimulus. This sought to prevent subvocal rehearsal of the pairs and offered a brief measure of focused attention.

Working memory: the n-Back Task (0-Back, 1-Back, and 2-Back Levels). The n-Back Working Memory Task was performed at three levels of difficulty (0-, 1-, and 2-Back). The 0-Back level represents a sensorimotor control, whereas the 1- and 2-Back levels place incrementally increasing working-memory loads (27). Successful performance on this task is believed to depend upon the integrity of the dorsolateral prefrontal cortex (28–30).

Response inhibition: the Stroop Task—Naming Colored Words version. This task assessed the subject's ability to make an appropriate response when presented with two conflicting stimuli (31). Subjects were presented with one of four words (red, yellow, green, blue) on a computer screen in red, yellow, green, or blue font. Subjects were instructed to respond to the font color of the word displayed on screen (using a color-coded response pad). Therefore, a behavioral conflict occurred when there was a mismatch between the meaning of the written word and the font color (*e.g.* "RED"). Resolution of this conflict (which requires the exertion of control mechanisms) is believed to require the successful engagement of areas such as the anterior cingulate cortex and dorsolateral prefrontal cortex (32).

Analytic measurement

Using the DPC Immulite 2000 analyzer (Diagnostic Products Corp., Los Angeles, CA), serum TSH concentrations were measured using a third-generation chemiluminescent immunometric assay and FT4 was measured using a competitive analog immunoassay (coefficient of variation <5% for all).

Statistical analysis

Analyses were carried out using SPSS (version 14) for PC (SPSS Inc., Chicago, IL). All data were expressed as means ± SE, unless specified otherwise. ANOVA was the primary statistical tool used. When performance on a specific task was repeated across multiple trials and/or testing sessions "mixed between-within subject ANOVAs" (33) were used to compare performance across the repeated levels and between the groups. Where significant ($P < 0.05$), main effects and interactions were observed and, if appropriate, *post hoc* analyses were conducted. Subsequent one-way ANOVAs compared the dependent variable at each level (trial and/or session) between the groups. In the presence of significance between-group differences, *a priori* planned comparisons were used to test specific differences between the SCH and control groups (comparison 1) and the hypothyroid and control groups (comparison 2). A Bonferroni adjustment to the α level (α/no. of comparisons; $0.05/2 = 0.025$) was applied to these comparisons to maintain a reasonable α level across all tests. Note: group differences are reported for the SCH and hypothyroid groups relative to control group only. The relationship between TSH levels and all dependent variables was investigated using Pearson correlations. Due to a lack of normality in the TSH data, the data were transformed using a Log_{10} transformation.

Results

No differences in age, gender, or education level were observed between the control, SCH, and hypothyroid groups (Table 1). Significant differences in TSH and FT4 levels between SCH and hypothyroid compared with controls are also shown in Table 1.

Results of predicted IQ scores and levels of anxiety and depression are displayed in Fig. 1. Predicted full-scale IQ was significantly lower in the hypothyroid group, but not in the SCH patients compared with controls. Predicted IQ did not change in any of the groups after treatment. A significant positive correlation was found between IQ and performance at the Rivermead Behavioral Memory Task and the Face-Name Learning and Recall task. Before treatment, scores of anxiety and depression were significantly elevated in SCH and hypothyroid patients compared with controls. Although there was improvement observed in both groups after LT4 replacement, scores remained elevated compared with control subjects by the end of the study. However, no correlations were observed between reported anxiety or depression levels and any of the administered cognitive tasks [with the exception of depression levels and verbal recall (Rivermead short stories, immediate level; $r = -0.352$; $P < 0.05$)], suggesting that depression or anxiety levels did not significantly influence measured cognitive abilities.

Pretreatment cognitive profiles

Results of tests of visual, verbal, and working memory are displayed in Fig. 2.

Visual memory: the ROCF Task

A significant deficit was also noted in hypothyroid patients at the copy level, indicating an impairment of visuospatial constructional ability. Due to this deficit, the memory accuracy score (delayed recall/copy*100) was used to assess mnemonic performance at the delayed recall level. An overall group difference was observed here, suggesting that thyroid dysfunction impaired visual memory ($P < 0.001$). *Post hoc* analysis revealed significant deficits in the

TABLE 1. Comparison of control, SCH, and hypothyroid groups

	Control	SCH	Hypothyroid
n	19	17	21
Age (yr)	46.1 ± 9.3	50.0 ± 9.2	44.0 ± 10.9
Females:males	19:0	16:1	20:1
Education (yr)	13.3 ± 2.8	12.8 ± 2.2	12.5 ± 3.1
TSH (mU/liter)	1.3 (0.4–2.1)	6.1 (4.4–13.6)	38.9 (10.8–>75.0)
FT4 (pmol/liter)	16.3 (13.6–19.2)	12.8 (10.7–16.3)	7.6 (<3.5–10.0)

Age and education level are presented as mean ± SD. TSH and FT4 levels are expressed as median (minimum-maximum) due to a high level of kurtosis in the data.

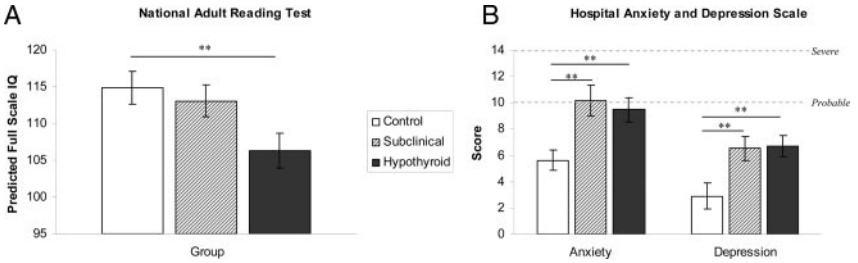

FIG. 1. Pretreatment patient profiles. A, Predicted full scale IQ, derived using the National Adult Reading Test. B, Scores obtained on the Hospital Anxiety and Depression scale; the *dotted lines* indicate the point at which the anxiety/depression score is considered to reflect probable/severe levels of anxiety/depression.

hypothyroid group, and in the SCH group compared with control subjects.

Verbal memory: the Rivermead Behavioral Memory Test: Short-Stories Subset

Significant verbal memory deficits were found in both the immediate ($P < 0.001$) and delayed recall ($P < 0.001$) of the short story. Compared with normal subjects, both hypothyroid and SCH groups recalled significantly fewer units immediately after story exposure (Immediate Recall) and 30 min after learning (Delayed Recall), indicating impairment in verbal memory.

Working memory and attention: the n-Back Task (0-Back, 1-Back, and 2-Back levels)

No significant group differences were observed at any of the three levels of the n-Back Task. A trend toward significance was, however, noted at the 1-Back level ($P = 0.072$). This trend was not evident at the 2-Back level ($P = 0.169$), although these results should be interpreted with caution because fewer patients were actually able to attempt the task [16% of control participants, 47% of SCH patients, and 33% of hypothyroid patients withdrew at the 2-Back level].

Associative memory: Face-Name Learning and Recall

Results of tests of associative memory are displayed in Fig. 3. The total face-name pairs successfully encoded (blocks 1–4) differed significantly between groups ($P < 0.05$). Although this difference was statistically significant only between the hypothyroid and control groups, a strong trend toward significance was observed in patients with SCH ($P = 0.039$; $\alpha = 0.05/2$; Bonferroni corrected). There was also a strong trend ($P = 0.05$) toward a significant difference between hypothyroid and control subjects in the Delayed Recall Trial.

Focused attention task

No significant group differences were observed.

Response inhibition: the Stroop Task

Mean performance accuracy (percentage) and reaction times (milliseconds) were compared across the two trials (congruent and incongruent) and between groups. Although an overall significant difference in performance accuracy was found across the two trial types ($P < 0.001$), indicating that incongruent trials were more difficult than congruent trials, no trial by group interactions or overall group differences were observed. No difference between the groups was observed when the congruent and incongruent trials were compared.

TSH correlations

Table 2 summarizes performance of SCH and hypothyroid groups on the cognitive tasks compared with controls, correlations with pretreatment TSH and performance improvement after treatment. Pretreatment TSH levels correlated negatively and significantly with predicted IQ, visuospatial construction ability, and visuospatial, verbal, associative, and working memory. No significant correlations were observed between TSH levels and measures of attention or response inhibition.

Effects of treatment on cognitive functioning

The effect of LT4 replacement on tests of visual, verbal, and working memory are displayed in Fig. 2.

Visual memory: the ROCF task

Changes in performance between the three groups, across the three testing sessions [session 1 (baseline) *vs.* session 2 (3 months) *vs.* session 3 (6 months)], were assessed. Despite strong main effects of Session ($P < 0.001$) and Group ($P < 0.01$), no significant Group × Session interaction was observed. However, the observed baseline impairment in SCH patients' performance no longer differed from that of the control group at the 3-month time-point, whereas the hypothyroid group remained impaired throughout. Deficits in visuospatial constructional ability (copy trial) in the hypothyroid group observed at baseline were no longer evident at the 3-month time-point.

Verbal memory: the Rivermead Behavioral Memory Test: Short-Stories Subset

Changes in performance between the three groups and across the three testing sessions and two task levels (immediate and delayed recall) were assessed. A significant interaction between Group and Session ($P < 0.01$) was

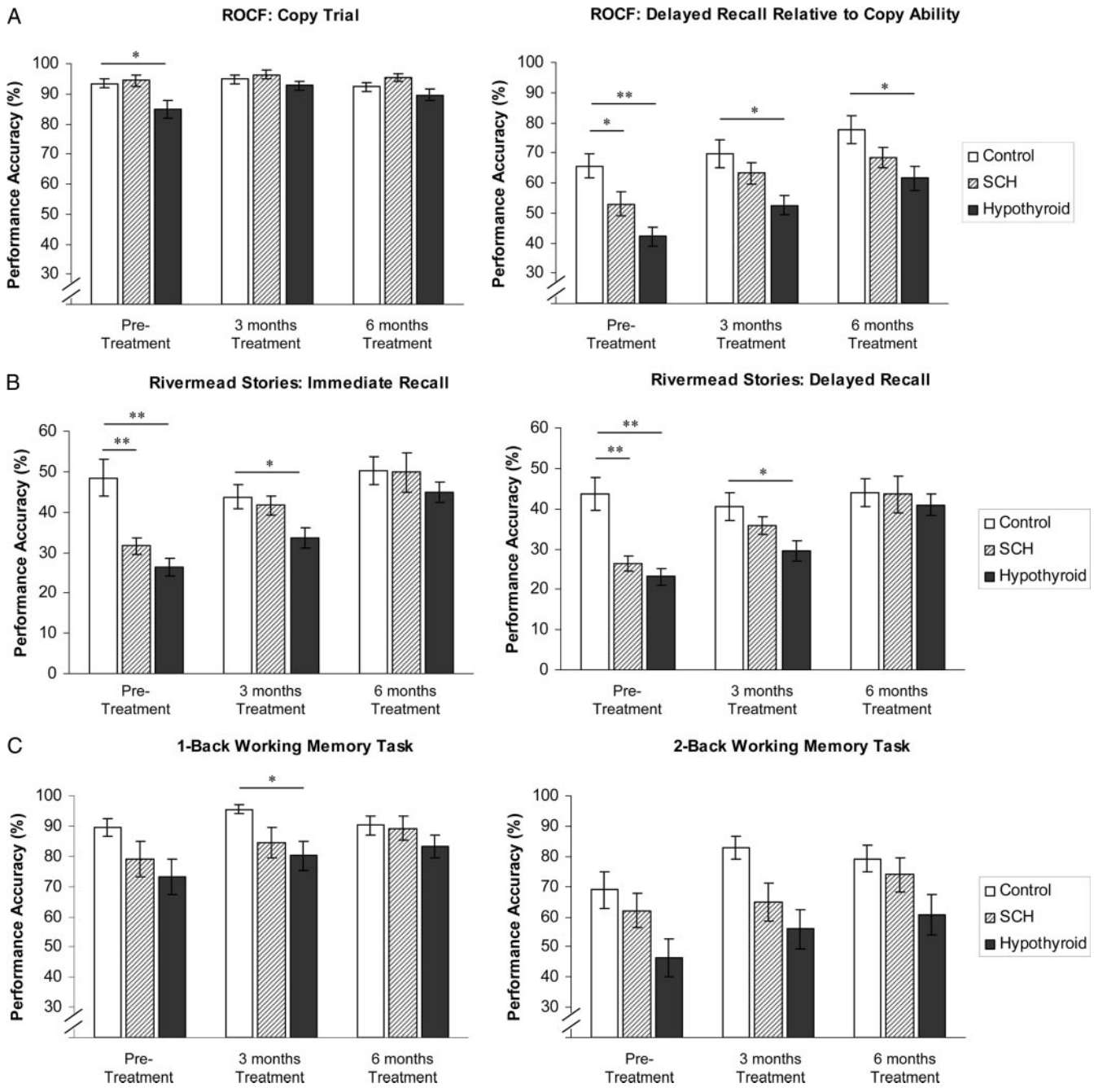

FIG. 2. A, The ROCF Task. Mean (± SEM) units accurately drawn at copy and 30 min later from memory in the control, subclinical hypothyroid and hypothyroid groups across the three testing sessions (pretreatment, 3 and 6 months of LT4 treatment). B, The Rivermead Short Stories Task. Mean (± SEM) units recalled immediately and 30 min later. C, n-Back Working Memory Task. Mean (± SEM) performance accuracy, across the three testing sessions, at the 1-Back and 2-Back levels.

observed. A substantial main effect for Session ($P < 0.001$) reflected the improved performance of both patient groups after LT4 replacement. A significant main effect of Group ($P < 0.01$) was also evident and was further explored using one-way ANOVAs. At the 3-month time-point, significant differences in immediate and delayed recall remained between hypothyroid and control groups, but were no longer apparent between SCH and control groups. At the 6-month time-point, no between-group differences could be demonstrated.

Working memory: the n-Back Task (0-Back, 1-Back, and 2-Back levels)

Performance accuracy at the 0-Back level was assessed between groups and across sessions. No Session × Group interaction or main effects of Session or Group were observed. These analyses were repeated for the 1-Back and 2-Back performance accuracy scores, and again, no Group × Session interactions were observed. A significant main effect of group was, however, found at the 1-Back level ($P < 0.05$); with the hypothyroid group performing

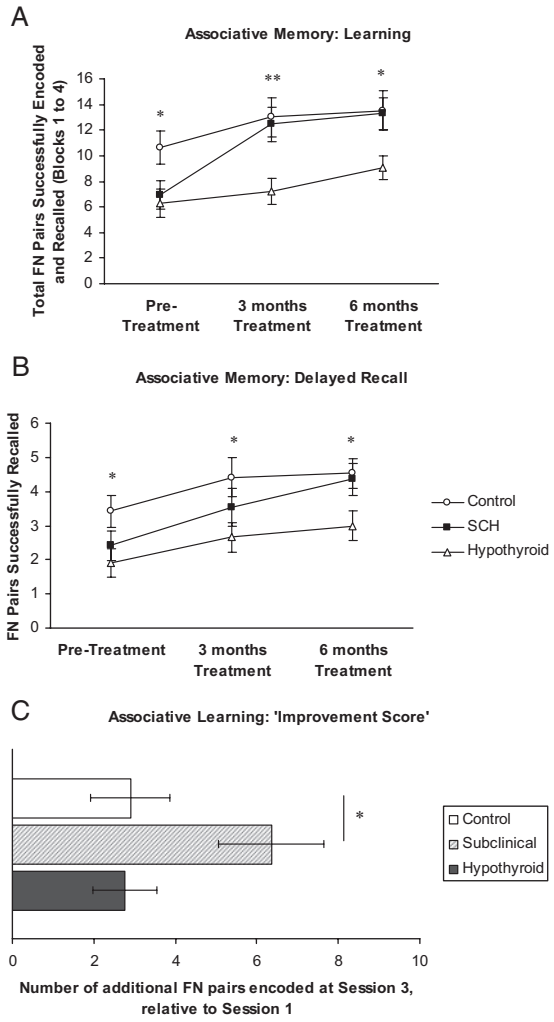

FIG. 3. A, Mean (± SEM) face-name pairs successfully recalled across the four learning and recall blocks (*i.e.* total learning). B, Mean (± SEM) pairs recalled 30 min after learning (*i.e.* delayed recall). C, Total number of face-name pairs successfully encoded across the four learning trials at session 1 (pretreatment total Face-Name Learning Score, Version 1) subtracted from the total Face-Name score at session 3 (after 6 months of treatment; Total Face-Name Learning Score, Version 3), rendering an associative learning "Improvement Score" for each of the three groups (expressed as mean ± SEM). FN, Face-name.

less accurately than controls ($P < 0.05$). One-way ANOVAs confirmed this difference at the 3-month, but not the 6-month, time-point.

To further elucidate this change in working memory ability across the 6 months of follow-up, paired-sample *t*-tests were conducted (exploring the change in performance accuracy between baseline and the 3-month time-point). No change in 1-Back performance was observed in the control group, whereas both the SCH ($P = 0.056$) and the hypothyroid ($P = 0.061$) tended to improve at the 6-month time-point compared with baseline. Compliance issues confounded interpretation of the 2-Back data, but similar trends were observed at this level.

Associative memory: Face-Name Learning and Recall (Fig. 3)

Changes in performance between the three groups, across the three testing sessions, were explored. A significant Group × Session interaction ($P < 0.05$) was observed, indicating a differential change in the groups' associative memory abilities across the testing sessions. An overall significant main effect of Group ($P < 0.01$) was consistent with the observed impairment of associative memory in hypothyroid subjects observed in the baseline studies. Hypothyroid patients ($P < 0.01$) remained significantly different relative to controls at the 3- and 6-month time-points.

Despite the nonsignificant baseline deficit observed on this measure (see *Pretreatment cognitive profiles*), SCH patients showed the greatest level of improved performance between sessions (see Fig. 3, *Improvement Score*). This performance change reflects the difference in performance between session 3 relative to session 1, while controlling for the corresponding change in the control group. The significantly enhanced performance observed in the SCH group relative to the control group ($P < 0.025$) demonstrates that the SCH group improved significantly beyond "practice effects" after 6 months of treatment. As indicated above, a corresponding effect of treatment was not evident in the hypothyroid group ($P = 0.92$).

Focused attention

Mean performance accuracy across the four blocks was compared across the three sessions, revealing no Session × Group interaction or main effects of either Session or Group.

Response inhibition: the Stroop Task

Changes in performance accuracy between the three groups and across the three testing Sessions and two Trial Types (congruent and incongruent trials) revealed no Session × Group, or Session × Group × Trial-Type interactions. Overall performance accuracy was not compromised in this population, and analyses revealed no overall group difference at any of the three testing points for either congruent or incongruent trials. No group differences were observed when reaction time data were considered.

Discussion

This cross-sectional and interventional study provides preliminary evidence that a specific deficit in memory rather than a general cognitive slowing is present in overtly hypothyroid patients, and to a lesser extent in SCH patients. We observed deficits in visuospatial, verbal, and associative memory before LT4 treatment. After 6 months

TABLE 2. Performance of SCH and hypothyroid groups on the cognitive tasks compared with controls, correlations with pretreatment TSH, and performance improvement after treatment

	Impaired (pretreatment)[a]		TSH correlations[b]	Normalized (T_4 treatment)[c]	
	SCH	H		SCH	H
Cognitive domain					
General intelligence, NART	$P = 0.59$	$P < 0.01$	−0.33*		No
Visual-spatial construction, ROCF copy level	$P = 0.76$	$P < 0.025$	−0.27*		Yes (3 months)
Visual-spatial memory, ROCF memory accuracy score	$P < 0.025$	$P < 0.001$	−0.47***	Yes (3 months)	No
Verbal memory					
Immediate story recall	$P < 0.001$	$P < 0.001$	−0.52***	Yes (3 months)	Yes (6 months)
Delayed story recall	$P < 0.001$	$P < 0.001$	−0.55***	Yes (3 months)	Yes (6 months)
Associative memory					
Face-Name encoding	$P = 0.039$^	$P < 0.025$	−0.31*	+ (3 months)	No
Face-Name delayed recall	$P = 0.124$	$P < 0.025$	−0.31*		No
Working memory, 1-Back Task	$P = 0.072$^	$P = 0.072$^	−0.30*		
Focused attention, Circle Task	$P = 0.072$^	$P = 0.072$^	N.S.		
Response inhibition, Stroop Task: incongruent trials	$P = 0.529$	$P = 0.529$	N.S.		
Affective domain					
Anxiety rating (HADS)	$P < 0.01$	$P < 0.01$	0.31*	No, + (3 months)	No, + (3 months)
Depression rating (HADS)	$P < 0.01$	$P < 0.01$	0.32*	No, + (3 months)	No, + (3 months)

NART, National Adult Reading Test; HADS, Hospital Anxiety and Depression Scale; N.S., not significant.

[a] Pretreatment cognitive and affective profiles: A summary of cognitive abilities in both SCH and hypothyroid patient groups, relative to the control group, reported either in terms of the results of the overall between-group comparisons (nonsignificant findings) or in terms of *a priori* planned comparisons performed after a significant group difference. In these latter cases, the α level is set at 0.025 to control for multiple comparisons (0.05/2 comparisons). All analyses reported were performed on the performance accuracy scores obtained on each task.

[b] Relationship between measured cognitive abilities (plus anxiety/depression ratings) and pretreatment TSH levels.

[c] Change in task performance after 3 and 6 months of LT4 treatment, relative to pretreatment ability. *Symbols* indicate significant between-group differences at the corresponding α level: *, $P < 0.05$; ***, $P < 0.001$. ^, Incidences where P was observed to be approaching significance; +, a significant improvement relative to the within-group baseline level.

of LT4 replacement, patients with SCH no longer differed from normal control subjects, but many deficits persisted in the hypothyroid group.

SCH patients demonstrated significant improvements after 3 months of LT4 replacement on measures of visual-spatial and verbal memory. In contrast, hypothyroid patients remained impaired relative to control subjects on the memory component of the visual-spatial task and the associative memory task despite LT4 replacement. Performance improved at the copy trial of the visual memory task (becoming comparable to control subjects at 3 months) and on the verbal memory task by 6 months. There are a number of possible interpretations of this differential response. Firstly, the cognitive deficits observed in overt hypothyroidism might not be reversible, suggesting a critical time-window during which these cognitive deficits may be alleviated. Notably, in patients with congenital hypothyroidism, amelioration of spatial learning and memory deficits after LT4 replacement treatment is only observed when treatment is initiated within a critical stage of neural development (34). An alternative explanation is that the deficits resolve over a longer period of time. Finally, we cannot rule out the possibility of an enhanced practice effect in SCH compared with overtly hypothyroid patients, although the lack of any improvement in the control group across the three sessions makes this less likely.

Although impairments in working memory have been reported (2), our study revealed no significant group differences at baseline. However, abnormalities in working memory have been observed in cross-sectional studies of hypothyroid patients on stable LT4 replacement, suggesting that this memory domain does not completely respond to restoration of euthyroid status (35). In the current study, no significant difference in working memory was observed between SCH and control subjects, consistent with those of Jorde *et al.* (36). In contrast, deficits in working memory were described in subjects with experimentally induced SCH (13), but TSH levels were more elevated in this group, implying a more marked degree of hypothyroidism.

Not all of our findings were consistent with those reported by Jorde *et al.* (36). Most notably, we demonstrated deficits in the visual and verbal memory in SCH patients. These results should be interpreted with caution because our patients largely presented to their general practitioners with symptoms that prompted measurement of thyroid

hormones, a potential selection bias. Importantly, no differences were observed on attention or response inhibition tasks in hypothyroid or SCH subjects, potentially indicating that cognitive deficits are not generalized but are possibly specific to hippocampal and frontal areas (37). Previous studies in hypothyroid patients have generally (36, 38) but not always reported similar findings (35).

Anxiety and depression scores were higher in both groups compared with control subjects, but there were no correlations with any of our measures of cognitive function. These observations are consistent with previous reports in which improvement of depressive symptoms after LT4 replacement has not been associated with improvement in cognitive function (5, 35, 39).

Further limitations of the study design should be considered. Larger study numbers would have increased the sensitivity to detect abnormal findings. Tests investigating attention and working memory in greater detail would have augmented our findings but would significantly lengthen the test battery.

In summary, we observed an apparent selective mnemonic deficit in hypothyroid and SCH patients. Evidence from animal models suggests that thyroid hormones play a role in the regulation of neuron formation. Thyroid hormone receptors are known to be in abundance in the hippocampal area, and the hormone does play a role in neurogenesis in the adult brain. Thyroid hormone deficiency results in a delay in neuronal differentiation, resulting in a reduction in size and number of granule cells in the hippocampus (40). The mnemonic measures on which we observed the impaired performances are believed to depend upon the integrity of the hippocampus and frontal cortex (41). In addition, the face-name encoding task found to be significantly impaired in overt hypothyroidism is closely linked to underlying hippocampal activity (26). We conclude that neurocognitive impairments specific to memory-related cortical areas are demonstrable in patients with overt and subclinical hypothyroidism. Moreover, in light of the apparent sparing of attention and response inhibition processes in both SCH and hypothyroid groups, together with animal data, we propose that these memory deficits may be more indicative of an underlying hippocampal deficit, rather than a frontal lobe problem, although the exact underlying neuronal deficits will require further elucidation.

Acknowledgments

Address all correspondence and requests for reprints to: James Gibney, Department of Endocrinology and Diabetes, Adelaide and Meath Hospital, Tallaght, Dublin 24, Ireland. E-mail: james.gibney@amnch.ie.

Disclosure Summary: N.C., S.M., G.C., T.K.T., N.P., J.F., M.F., S.O., G.B., and J.G. have nothing to declare.

References

1. **Dugbartey AT** 1998 Neurocognitive aspects of hypothyroidism. Arch Intern Med 158:1413–1418
2. **Constant EL, Adam S, Seron X, Bruyer R, Seghers A, Daumerie C** 2005 Anxiety and depression, attention, and executive functions in hypothyroidism. J Int Neuropsychol Soc 11:535–544
3. **Wekking EM, Appelhof BC, Fliers E, Schene AH, Huyser J, Tijssen JG, Wiersinga WM** 2005 Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. Eur J Endocrinol 153:747–753
4. **Burmeister LA, Ganguli M, Dodge HH, Toczek T, DeKosky ST, Nebes RD** 2001 Hypothyroidism and cognition: preliminary evidence for a specific defect in memory. Thyroid 11:1177–1185
5. **Miller KJ, Parsons TD, Whybrow PC, van Herle K, Rasgon N, van Herle A, Martinez D, Silverman DH, Bauer M** 2006 Memory improvement with treatment of hypothyroidism. Int J Neurosci 116: 895–906
6. **Gerges NZ, Alzoubi KH, Park CR, Diamond DM, Alkadhi KA** 2004 Adverse effect of the combination of hypothyroidism and chronic psychosocial stress on hippocampus-dependent memory in rats. Behav Brain Res 155:77–84
7. **Alzoubi KH, Gerges NZ, Aleisa AM, Alkadhi KA** 2009 Levothyroxin restores hypothyroidism-induced impairment of hippocampus-dependent learning and memory: behavioral, electrophysiological, and molecular studies. Hippocampus 19:66–78
8. **Alzoubi KH, Gerges NZ, Alkadhi KA** 2005 Levothyroxin restores hypothyroidism-induced impairment of LTP of hippocampal CA1: electrophysiological and molecular studies. Exp Neurol 195:330–341
9. **Montero-Pedrazuela A, Venero C, Lavado-Autric R, Fernández-Lamo I, García-Verdugo JM, Bernal J, Guadaño-Ferraz A** 2006 Modulation of adult hippocampal neurogenesis by thyroid hormones: implications in depressive-like behavior. Mol Psychiatry 11: 361–371
10. **Desouza LA, Ladiwala U, Daniel SM, Agashe S, Vaidya RA, Vaidya VA** 2005 Thyroid hormone regulates hippocampal neurogenesis in the adult rat brain. Mol Cell Neurosci 29:414–426
11. **Biondi B, Cooper DS** 2008 The clinical significance of subclinical thyroid dysfunction. Endocr Rev 29:76–131
12. **Baldini IM, Vita A, Mauri MC, Amodei V, Carrisi M, Bravin S, Cantalamessa L** 1997 Psychopathological and cognitive features in subclinical hypothyroidism. Prog Neuropsychopharmacol Biol Psychiatry 21:925–935
13. **Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS** 2007 Health status, mood, and cognition in experimentally induced subclinical hypothyroidism. J Clin Endocrinol Metab 92:2545–2551
14. **Zhu DF, Wang ZX, Zhang DR, Pan ZL, He S, Hu XP, Chen XC, Zhou JN** 2006 fMRI revealed neural substrate for reversible working memory dysfunction in subclinical hypothyroidism. Brain 129: 2923–2930
15. **Bono G, Fancellu R, Blandini F, Santoro G, Mauri M** 2004 Cognitive and affective status in mild hypothyroidism and interactions with L-thyroxine treatment. Acta Neurol Scand 110:59–66
16. **Larisch R, Kley K, Nikolaus S, Sitte W, Franz M, Hautzel H, Tress W, Müller HW** 2004 Depression and anxiety in different thyroid function states. Horm Metab Res 36:650–653
17. **Nelson H** 1982 National adult reading test (NART): For the assessment of premorbid intelligence in patients with dementia. Glasgow, UK: NFER-NELSON Publishing Company, Limited
18. **Zigmond AS, Snaith RP** 1983 The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–370
19. **Rey A** 1941 L'examen psychologique dans les cas d'encéphalopathie traumatique. Archives de Psychologie 28:215–285

20. **Shin MS, Park SY, Park SR, Seol SH, Kwon JS** 2006 Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. Nat Protoc 1:892–899
21. **Spreen OSE** 1998 A compendum of neuropsychological tests. 2nd ed. New York: Oxford University Press
22. **Lezak MD** 1995 Neuropsychological assessment. New York: Oxford University Press
23. **Hubley AM, Jassal S** 2006 Comparability of the Rey-Osterrieth and Modified Taylor Complex Figures using total scores, completion times, and construct validation. J Clin Exp Neuropsychol 28:1482–1497
24. **Wilson BA, Baddeley AD, Cockburn JM** 1989 How do old dogs learn new tricks: teaching a technological skill to brain injured people. Cortex 25:115–119
25. **Parkin AJ, Leng NRC** 1993 Neuropsychology of the amnesic syndrome. Brighton, UK: Psychology Press
26. **Zeineh MM, Engel SA, Thompson PM, Bookheimer SY** 2003 Dynamics of the hippocampus during encoding and retrieval of face-name pairs. Science 299:577–580
27. **Meyer-Lindenberg A, Poline JB, Kohn PD, Holt JL, Egan MF, Weinberger DR, Berman KF** 2001 Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. Am J Psychiatry 158:1809–1817
28. **Goldman-Rakic PS** 1996 The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. Philos Trans R Soc Lond B Biol Sci 351:1445–1453
29. **Jonides J, Smith EE, Lauber EJ, Awh E, Minoshima S, Koeppe RA** 1997 Verbal working memory load affects regional brain activation as measured by PET. J Cogn Neurosci 9:462–475
30. **Smith EE, Jonides J** 1998 Neuroimaging analyses of human working memory. Proc Natl Acad Sci USA 95:12061–12068
31. **Stroop J** 1935 Studies of interference in series verbal reactions. J Exper Psychol 18:643–662
32. **Carter CS, van Veen V** 2007 Anterior cingulate cortex and conflict detection: an update of theory and data. Cogn Affect Behav Neurosci 7:367–379
33. **Tabachnick BG, Fidell L** 2007 Using multivariate statistics. 5th ed. Boston: Pearson Education
34. **Reid RE, Kim EM, Page D, O'Mara SM, O'Hare E** 2007 Thyroxine replacement in an animal model of congenital hypothyroidism. Physiol Behav 91:299–303
35. **Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS** 2007 Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. Thyroid 17:249–258
36. **Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG** 2006 Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J Clin Endocrinol Metab 91:145–153
37. **Bohbot VD, Kalina M, Stepankova K, Spackova N, Petrides M, Nadel L** 1998 Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia 36:1217–1238
38. **Miller KJ, Parsons TD, Whybrow PC, Van Herle K, Rasgon N, Van Herle A, Martinez D, Silverman DH, Bauer M** 2007 Verbal memory retrieval deficits associated with untreated hypothyroidism. J Neuropsychiatry Clin Neurosci 19:132–136
39. **Davis JD, Tremont G** 2007 Neuropsychiatric aspects of hypothyroidism and treatment reversibility. Minerva Endocrinol 32:49–65
40. **Ambrogini P, Cuppini R, Ferri P, Mancini C, Ciaroni S, Voci A, Gerdoni E, Gallo G** 2005 Thyroid hormones affect neurogenesis in the dentate gyrus of adult rat. Neuroendocrinology 81:244–253
41. **Kopelman MD** 2002 Disorders of memory. Brain 125:2152-2190