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Longitudinal evidence of the impact of normal thyroid stimulating hormone variations on cognitive functioning in very old age

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Abstract

The purpose of this study was to examine longitudinal associations among thyroid stimulating hormone (TSH) levels and cognitive performance. Data collected at the first three assessment times, approximately 3 years apart, are reported for the survivors (n = 45) from a previously published cross-sectional study. Participants were aged 75-93 years at baseline, and data reported were collected in the Kungsholmen Project, a longitudinal project investigating aging and dementia. Analyses revealed that although declining verbal fluency and visuospatial abilities were accompanied by simultaneously declining TSH levels, **the pattern of cross-sectional and longitudinal results are interpreted such** that declining TSH levels may have caused episodic memory deficits later on. These results were obtained in the examination of 6-year but not 3-year change, **and after removal of the cognitive variation associated with depressive mood symptoms.**

Keywords: Thyroid function; Cognitive function; TSH; Episodic memory; Old age; Longitudinal

Although the deleterious effects of thyroid disease on cognitive functioning is well documented (e.g., Osterweil et al., 1992), the association between normal variation of thyroid functioning and cognitive performance in old age has been subjected to a limited number of reports. In one of the first published studies (Wahlin et al., 1998) we found that, within normal ranges, Thyroid Stimulating Hormone (TSH) but not thyroxine predicted cognitive performance cross-sectionally among elderly persons between 75 and 96 years. Interestingly, there was a strong positive relationship between levels of TSH and episodic memory performance, but the associations with other cognitive abilities (i.e., verbal fluency, visuospatial ability, short-term memory, and perceptual-motor speed) were less pronounced. Prinz and colleagues (1999), showed in a subsequent cross-sectional study of elderly euthyroid men with a mean age of 72 years that thyroxine but not trijodothyronine or TSH levels were related to various cognitive performance measures including tests of verbal and general cognitive abilities. Volpato et al. (2002), published data on physically impaired women, aged 65 years and older, and with normal thyroid gland function at baseline, showing that low baseline thyroxine but not TSH within normal ranges predicted cognitive decline across three years, as assessed by the Mini-Mental State Examination Scale (MMSE: Folstein et al., 1975). No cross-sectional associations were detected in this study. Interestingly, item analyses revealed that the prospective thyroxine-MMSE association was related to the orientation and memory aspects of the scale, both involving episodic memory components. Finally, van Boxtel et al. (2004), examined a random sample from the Maastricht Aging Study, aged 49-71 years. The test battery included a variety of tasks, among them tests of episodic memory. This study failed to detect any cross-sectional associations involving TSH and cognitive performance.

As is evident, the results from the aforementioned studies are contradictory as to which indicator of thyroid functioning is the most relevant marker of cognitive performance,

and which domain of cognitive performance, if any, is primarily affected by thyroid hormonal variations. The contrasting results might be due to sample differences, where age could potentially constitute an explanatory factor. Thus, the inconsistencies in the work reviewed, may in part be due to the varying age ranges involved. Evidence showing that increasing age results both in growing thyroid and cognitive variability (Marrioti et al., 1995; Bäckman et al., 1999) supports this hypothesis. Thus, increased variability in thyroid and cognitive functioning should be expected among the oldest persons.

Thyroid functioning is commonly assessed by means of TSH obtained in serum. Although TSH is a sensitive method for detecting low values indicative of hyperfunction, diagnosis of hypothyroidism may require additional tests. Importantly, thyroid hormones increase the response of the beta-adrenergic receptor to norepinephrine, which may serve as an adaptive mechanism of neuromodulation (Whybrow and Prange, 1981; Dratman and Gordon, 1996). More specifically, low TSH levels are also associated with elevated steroid hormone levels within the hypothalamus-pituitary-adrenal axis (van Haasteren et al., 1996). Increased levels of cortisol, which is part of this circuitry, may result in hippocampal cell loss and impair episodic memory performance (Lupien et al., 1994). Therefore, although thyroid hormones may be associated with a variety of cognitive abilities, there might be a particularly strong link to episodic memory.

Yet, to the best of our knowledge, no study has been published showing analyses of longitudinal relationships among cognitive and normal thyroid functioning involving longitudinal assessment of both thyroid indicators and cognition. Such analyses would permit safer conclusions about whether (a) there is a causal relationship between normal variations in thyroid functioning and cognitive performance, or (b) cognitive and thyroid functioning are both subject to the influence of a third causative factor or process potentially responsible for

the presence or absence of significant thyroid-cognition associations as documented in the studies published to date.

One such factor, known to be associated deficient thyroid functioning (e.g., Brown, 1980; Denicoff et al., 1990) and to account for TSH-cognition associations (van Boxtel et al., 2004), is mood symptoms. Thus, in the present study, we controlled for depressive mood symptoms before examination of TSH-cognitive performance associations. The mood variable was derived from the Comprehensive Psychopathological Rating Scale (CPRS: Åsberg et al., 1978). In Sweden, this scale is commonly used as a basis for diagnosing major depression according to DSM-IV criteria.

In the present study, we follow a sample for which cross-sectional data have already been reported (Wahlin et al., 1998) across two follow-up assessments separated by approximately three years. The three points of data collection are from now on referred to as T1, T2, and T3. Although both thyroxine and TSH were available at baseline, only TSH was considered necessary for diagnostic purposes at follow-ups within the larger project. Hence, this study will focus exclusively on the relationship between normal TSH variations and cognitive abilities.

We hypothesised, first, that the selective relationship of normal TSH levels with episodic memory functioning should be detectable also with a longitudinal data design. Hence, we expected this selective association both cross-sectionally at T1, T2, and T3 and with respect to longitudinal associations among longitudinal change indicators. Second, we hypothesised that if longitudinal associations were detected, they would not be entirely due to a parallel change in TSH and cognitive functioning. Instead, we expected previous longitudinal change in TSH to cause differences in cognitive performance later on. Thus, in order to arrive at such a conclusion, some clear discrepancies in the pattern of associations among cross-sectional and longitudinal change data were necessary. Finally, in stating these

hypotheses we make the assumption that biological change (i.e., TSH) causes differences in cognitive functioning, and that the reverse causal direction is less likely.

To achieve these goals, we analyzed longitudinal data collected from the surviving participants of the sample reported in our first study from the Kungsholmen Project on cross-sectional associations among TSH and cognitive functioning.

Methods

The Kungsholmen project (KP) involves longitudinal assessment of three independent populations. The present sample was taken from the Kungsholmen parish of Stockholm, Sweden, aged 75 years and older at the first time of assessment (see Fratiglioni et al., 1992, for an overview of the study). Diagnosis of dementia, depression (major depression and dysthymia), and general anxiety disorder were made according to established criteria (i.e., DSM-III-R: American Psychiatric Association, 1987; DSM IV: American Psychiatric Association, 1994) at each phase of data collection. Cross-sectional data for the sample selected for longitudinal analysis (n = 200), was reported in a previous publication (Wahlin et al., 1998). From this sample, data collected from participants who completed the cognitive testing and had normal TSH values also at the first and second follow-up are reported in the present study (n = 45). Retest intervals for this sample were approximately 3 years (T1-T2: M = 2.86 years, SD = .49; T2-T3: M = 3.51 years, SD = .50). All procedures were approved by the ethics committee at Karolinska institutet, and in accordance with the Helsinki Declaration of 1975.

Laboratory Tests

Across all three times of assessment, the same procedure and methods were applied for the collection of laboratory data. Thus, blood samples were collected in the morning on the same day as the cognitive testing. These analyses involved a variety of health indices, of which TSH was selected for the present study. For the analysis of TSH, the immunoradiometric

method was used (Seth et al., 1984). The immunoradiometric assay is an ultrasensitive method that allows detection of very low TSH values, indicative of hyperthyreosis. Inter- and intratest variability of the method within the normal range is 2.5% and 1.5% respectively.

The same cutoff values as in our previous study were applied. These cutoff scores were chosen according to clinical recommendations in order to exclude subjects with potential thyroid-related disease. Thus, the lower limit for TSH was set at 0.4 mU/liter, and the upper limit at 5.0 mU/liter (Griffin and Solomon, 1986). For these reasons, subjects with TSH values outside the normal range at either of the two follow up assessments were excluded. In addition, for the purpose of prospective analyses, thyroxine data collected at T1 were added to the data set. Free thyroxine levels were assessed by means of a radioimmunoassay method (Giles, 1982). The methods used to assess TSH and thyroxine are both highly reliable within normal ranges (Giles, 1982; Seth et al., 1984), **as reflected by the variability. For thyroxine the intra-test variability is almost undetectable (.04%), and the inter-test variability (1%) is similar to that of TSH.**

Next, we computed percentage change in TSH values between the three times of assessment. Among the three possible time frames (T1-T2, T2-T3, and T1-T3), we selected for further analysis the entire time range (T1-T3) and the last three years (T2-T3). This was done in order to compare the impact of 3-year with 6-year TSH change on cognitive performance at the end of the respective time interval. Since the T1-T2 range was already included in the T1-T3 range, it represented redundant information and was therefore considered only in a control analysis to be reported below.

Mood symptoms

Four items were selected from the CPRS (i.e., dysphoria, appetite disturbance, feelings of guilt, and suicidal thoughts). At each of T1-T3, the four mood symptoms were added to form a composite mood score with a possible range of 0-4. In order to avoid dividing by zero in the

computation of mood change scores, 1 was first added to all scores at T1, T2, and T3 respectively.

Participants

At T1 two hundred subjects ranging in age between 75 and 96 years were selected for study on the basis of their euthyroid status (see Wahlin et al., 1998). As expected, a large number of the participants died before the two follow up assessments. At T2, 36 subjects had died, 7 refused to participate, and 2 had moved and could not be located. At T3, another 48 persons had died, 5 refused to participate, and 1 person had moved. From the remaining sample, 10 refused to take part in the blood testing at either T2 or T3, and 46 participants were excluded as they had TSH values outside the normal ranges at either T2 or T3. Due to the small sample remaining after these exclusions, we decided not to remove incident dementia cases at either T2 ($n = 6$) or T3 ($n = 9$). None of the participants were diagnosed with depression, dysthymia or general anxiety disorder at any time point, and no participants were treated with thyroid hormones. The remaining 45 participants were subjected to the analyses of longitudinal data reported in this article. Table 1 provides descriptive information for demographic, thyroxine, TSH, and mood symptom data. In addition, the table provides descriptive information for the persons excluded due to their TSH values being outside the normal range.

Insert Table 1 About Here

Cognitive Tests

The same cognitive tests as reported in our 1998 publication were selected for further examination. However, for the digit span tests, the rank-order stability of change was relatively constant across individuals, resulting in reduced variance and attenuated

associations. These problems resulted in non-interpretable findings. Thus, we therefore excluded the digit span tests from the analyses.

In order to control for practice effects, the tasks were administered in two orders and, for the tests of episodic memory, five versions. These combinations were counterbalanced across age and time of testing. Thus, no participant received identical tests at any of the three test occasions.

Episodic memory. Four episodic memory tests (requiring the participant to remember also that the to-be-remembered materials were presented to him/her during study, that is, the personal, temporal and spatial source information) comprising free recall of 12 semantically unrelated words presented at either rapid (2 sec/word) or slow (5 sec/word) pace, free recall of organizable words, and category cued recall of organizable words where presentation for the organizable words were 5 sec/word. In all four tasks, nouns were used as study items.

Verbal fluency. Three fluency tasks were administered. In two letter (initial N and S) fluency tasks, participants were given 60 seconds to produce as many words as possible. In a third category fluency task, participants were asked to produce, within 60 seconds, as many exemplars of food as possible.

Visuospatial ability. To assess this domain, we used the block design test from the Wechsler Adult Intelligence Scale - Revised (Wechsler, 1981). Standard procedures for administration and scoring were applied.

Perceptual-motor speed. Shortened versions of the Trail Making A and B (TMT: Reitan and Davidson, 1974) were administered, and time scores were used as the outcome measure. The TMT was modified such that part A had a maximum score of 12 and part B had a maximum score of 11. This modification was done to make sure that severely impaired subjects could also be assessed. Both tasks were administered according to standard procedures and the time scores indicated the time to complete the task.

Results

In order to reduce the number of dependent variables and to increase reliability, composite cognitive scores were created. Thus, we created a composite score for episodic recall of random words, where the correlations across T1-T3 were .60, .42, and .47 respectively ($p_s < .01$), a composite recall of organizable words, where the T1-T3 correlations were .89, .86, and .92 ($p_s < .01$), a composite letter fluency score (r_s .83, .69, .67, $p_s < .01$), and a composite TMT score (r_s .31, .40, .29, $p_s < .05$). In all cases, the composite score constituted the mean of the summed scores. Missing data (< 5% in all cases) were inputed using the EM algorithm in SPSS.

Finally, and similar to the TSH data, we computed for each dependent measure, percentage change from T2 - T3, and T1 - T3, respectively. Table 2 provides summary statistics for the cognitive variables across T1, T2, and T3, and the time intervals of primary interest.

Insert Table 2 About Here

Although the demographic and dementia information were not correlated with any of the TSH cross-sectional or change scores (demographic $p_s > .05$; dementia $p_s > .10$), they were significantly correlated with several of the cognitive performance composite scores. Thus, even if the demographic and incident dementia data may not be confounded with the TSH effects, we considered it to be informative to generalize the results across the mean level of these parameters. Importantly, running the analyses reported below without these control variables resulted in very similar findings. Hence, in all analyses that followed, age at baseline, years of education, gender, and incident dementia diagnosis at either of T2 or T3, and the relevant mood score were used as control variables. Data were analyzed by means of

hierarchical regressions, where age, education, gender, the two dummy-coded incident dementia diagnose variables, and the relevant mood score were entered in the first step. In the second step, the relevant TSH predictor variable was entered. The analyses were structured into four sections. First, we examined at T1, T2, and T3 the cross-sectional associations between TSH level and cognitive performance. As a control, we examined also whether thyroxine at T1 predicted T1 performance. Second, T2-T3 and T1-T3 percentage cognitive change was predicted from baseline TSH and thyroxine values. Third, T2-T3 and T1-T3 percentage cognitive change was predicted from percentage TSH change in the corresponding time intervals. Fourth, and finally, we predicted in two separate sets of analyses cognitive performance at T3 with T2-T3 percentage TSH change, or T1-T3 percentage TSH change as predictors. Here, we added as a control analysis the prediction of cognitive performance at T2 from percentage TSH change within the T1-T2 time frame. The results of the analyses are presented next.

Cross-sectional associations. The cross-sectional associations of TSH with cognitive performance were examined at each of the three points of assessment. The two **incident** dementia variables were as expected the strongest predictors among the control variables, accounting for significant portions of variations in several of the tasks across the three times of assessment. Age, gender, and education predicted performance on the fluency tasks, but only at T1 and T2. Number of mood symptoms were not significantly associated with performance at any of T1, T2, or T3 (all p_s >.10), but most of the ß-weights indicated associations in the expected directions (i.e., more symptoms were associated with worse performance). Although all TSH-performance associations were in the expected direction (i.e., higher level of TSH indicated better performance), it approached significance for recall of random words only. This association was marginally significant at both T1 (β = .265, incr. R^2 = .065, p = .05), and T3 (β = .273, incr. R^2 = .064, p = .06), although the association at T2

was not reliable (β = .206, incr. R^2 = .039, p = .16). Thyroxine level did not predict performance in any of the cognitive tasks at T1 (all p_s > .45).

Baseline TSH and thyroxine relative to cognitive change. In two sets of separate analyses we examined the extent to which baseline TSH or thyroxine would predict cognitive change scores between T1-T3 and T2-T3, respectively, after accounting for the block of control variables. Results showed that both baseline TSH and thyroxine levels were unrelated to all cognitive change scores (all p_s > .30). The impact of the control variables are reported in the next set of analyses.

TSH change relative to cognitive change. In the third set of analyses we sought to determine whether changing TSH values would predict changing cognitive performance. As indicated above, the time intervals examined were T1-T3, and T2-T3. Results are shown in Table 3. Note that the time intervals are combined in the table, so that the T2-T3 TSH-cognitive change associations are shown in the upper part, and the T1-T3 associations in the lower part of the table.

Insert Table 3 About Here

As can be seen in the lower section of Table 3, TSH T1-T3 change significantly predicted change on the two fluency tests and on the test of visuospatial ability. In all cases, positive change in TSH level was associated with less decline on these tasks. No significant TSH-cognitive performance associations were found in the T2-T3 time interval. Among the control variables, longer education predicted decline in TMT performance across the T2-T3 time interval. Apart from a single positive association between T1-T3 mood and visuospatial change scores, mood symptoms were unrelated to all performance scores. Unexpectedly,

incident dementia at T2 was positively related to cognitive change in both time intervals. The beta-weights for incident dementia at T3 were however in the expected directions.

TSH change relative to cognitive performance at T3 and T2. In the final set of analyses, we examined the extent to which changing TSH values would predict cognitive performance. Here, we selected cognitive performance at T3 as the endpoint, and regressed, first, the respective cognitive variable on three year TSH change (T2-T3), and second, the same dependent measures on six year TSH change (T1-T3). Finally, as a control analysis, we regressed the T2 cognitive performance scores on three year (T1-T2) TSH change. Table 4 shows a summary of the results obtained.

Insert Table 4 About Here

As can be seen in the upper section of Table 4 where T3 cognitive data constitute the outcome, short-term (T2-T3) TSH change (2a) did not account for a significant portion of the variation in any of the tasks. This general outcome was replicated using T2 cognitive data as the dependent measures (lower part of Table 4) and again short-term (T1-T2) TSH change as predictor. Turning to long-term (T1-T3) TSH change, a different picture emerged. Looking at the upper section of Table 4, where long-term TSH change was entered into the regressions in the second step (2b), TSH T1-T3 change accounts for 7.2% of the variation in episodic recall of random words and 8.8% of the variation in episodic recall of organizable words. Note also that all beta-weights were positive, indicating that decline of TSH values was associated with worse cognitive performance, the exception being TMT where the negative beta-weight indicate that worse time performance was associated with decline of TSH. As for the control variables, across analyses, all significant associations were in the expected directions. Higher age, and incidence of dementia were related to lower levels

of performance while longer education and being a woman were related to higher levels of performance. Changing mood symptoms did not predict any of the cognitive performance scores.

Age by TSH interactions. In order to test the hypothesis that the chronological age range under scrutiny may be a factor explaining why TSH-cognition associations are not always detected, we computed Age X TSH and Age X TSH change cross-product interaction terms and repeated all analyses with the relevant interaction term entered in the third step. No interaction term approached significance in any of the analyses (all $p_s > .05$).

Examination of outliers. Inspection of the TMT scores (see Table 2) revealed that one subject exhibited extreme time scores at T3. To check whether this accounted for the lack of effects in this particular task, this value was truncated at the next level considered to be a high but not extreme time score (i.e., 209 sec), and the analyses involving TMT repeated. Results revealed that TMT performance was still unrelated to TSH.

Examination of impending death. Proximity to death is known to be associated with decline of cognitive functioning (e.g., Small & Bäckman, 1996), a phenomenon sometimes referred to as 'terminal drop'. Five of the participants in the study had died within one year after T3, and three of those were incident dementia cases during this study. Correlations showed that impending death was significantly associated with more and slightly increasing mood symptoms (all $p_S <.05$), and slightly associated with most cognitive performance and change scores ($p_S >.05$). No reliable association with the TSH indicators was found (all $p_S >.10$), although the direction of the correlations were negative in all cases (i.e., impending death was associated with lower and declining TSH values. As a final control, we examined whether impending death accounted for the detected TSH-cognition associations by repeating all main analyses including death within one year after T3 as a dummy-coded

control variable. Results revealed that although impending death was weakly ($\underline{p}_S$ >.10) associated with declining cognitive abilities, the main findings remained unchanged.

Discussion

The chief objective of the present study was to further examine the previously documented cross-sectional positive associations between normal variation in levels of thyroid stimulating hormone and cognitive and episodic memory performance by means of longitudinal data. For this purpose, we used data from the Kungsholmen Project collected during the first three times of assessment (T1, T2, T3) between 1987 and 1996. The study is unique in two respects. First, associations among longitudinal thyroid and cognitive data have, to the best of our knowledge, not previously been reported. Second, the age range examined (75-93 years at baseline) is rare in this type of study. Due to high death rates and presence of TSH values indicative of thyroid dysfunction across T2 and T3, the original sample reported in the previous study (Wahlin et al., 1998) was reduced to 45 participants. We therefore decided to include both non-demented persons and cases of incident dementia at either of T2 or T3.

Data were analyzed cross-sectionally, prospectively, and longitudinally, where percentage difference scores were employed to indicate change over time. The main findings were, first, that six year change in TSH levels were found to selectively predict episodic memory performance at the final assessment. This association was however not detected using three-year TSH change, irrespective of whether T2 or T3 cognitive data constituted the outcomes. Second, at the cross-sectional level of analysis, the selective association of TSH with episodic memory performance was detected at T1 and T3, but only for episodic recall of random words. In the analyses of T1-T3 and T2-T3 cognitive change predicted from baseline TSH and thyroxine levels, no significant association was detected. Third, turning to associations among change scores, a different pattern of results emerged, showing that six

year change in TSH was significantly associated with six year change in the two indicators of verbal fluency and the visuospatial ability indicator. In these analyses, the relationships to the two indicators of episodic memory were less pronounced and did not reach conventional levels of statistical significance. No reliable associations were detected in any of the analyses involving three year change scores, and age did not interact with TSH or thyroxine to influence any of the foregoing.

The finding that the reliable TSH-cognitive performance associations were all positive, both cross-sectionally and longitudinally, may seem at odds with previous studies showing that hypothyroidism (in which TSH values are high) constitute a risk factor for developing dementia at a later stage (e.g., Breteler et al., 1991; Ganguli et al., 1996). It is however not uncommon that the predictive power (both in terms of strength and direction) changes outside normal ranges (e.g., Wahlin et al., 1996) or that the predictive directions are best described as an inverted U-shaped form. Importantly, in this study we took great care in excluding persons with TSH values outside normal range at any of the three occasions of data collection.

Although the present data do not permit definite conclusions about causality, the outcome of the main analyses present an interesting pattern suggesting the existence of some direct TSH change-cognition effects, and some effects indicating that TSH levels and cognitive performance change in parallel, possibly due the existence of a third variable. The main comparison to be made is that of the results from the TSH change relative to cognitive change, and TSH change relative to cross-sectional cognitive differences, respectively. As shown in Table 3, changing TSH values were accompanied by changing letter and category fluency scores, and changing visuospatial ability scores. In these analyses, the TSH-episodic memory association failed to reach conventional levels of significance. Table 4 presents the opposite result, where six year change in TSH levels predicted performance on the two

episodic memory tests at T3, but no other cognitive ability. Thus, the results suggest that declining TSH levels are accompanied by parallel decline in fluency and visuospatial performance, while the very same TSH decline results in episodic memory deficits only at the end of six years change. However, it is still possible that TSH change might cause deficits in fluency and visuospatial performance, but that the time needed for such deficits to occur is longer than six years.

As noted, the four previously published studies present quite disparate findings. Prinz et al. (1999) found cross-sectional associations between thyroxine but not TSH and verbal and global cognitive functioning. Wahlin et al. (1998) found cross-sectional associations between TSH but not thyroxine and episodic memory. Volpato et al. (2002) and van Boxtel et al. (2004) failed to find any cross-sectional associations involving thyroxine and TSH, respectively, but the Volpato et al. study found that baseline thyroxine levels predicted future cognitive decline, particularly on tasks involving episodic memory components. Van Boxtel and colleagues (2004) argued that one explanation for the lack of TSH-related effects in their study, was that their sample was younger than that examined by Wahlin et al. (1998). In order to test this hypothesis, Age x TSH level cross-product interaction effects were tested, but similar to the present study they were found to be non-significant. However, the problem associated with detecting significant interaction effects are well documented (McClelland and Judd, 1993). Therefore, the age of the studied sample may still be a valid concern. Also, a study involving an age range covering both that of van Boxtel et al. (49-71 years) and our study (75-93 years) might still present a different outcome showing significant age by TSH interaction effects. However, common to all previous studies was that no information was available regarding longitudinal change of the thyroid indicators. In light of the present findings, it may be that both T4 and TSH require long-term change in order to correlate with cognitive performance, where TSH actually exerts an impact on episodic memory

functioning, while the longitudinal associations with other types of cognitive abilities are merely an expression of shared variation possibly caused by a third factor. Note in this context that we controlled for a likely third variable, that is, depressive mood symptoms. Van Boxtel and colleagues (2004) found mood symptoms to account for much of the TSH-episodic memory associations in their study, **while number of mood symptoms or change scores had little impact on the outcome variables in the current study.** Whether this is a result of the strict selection procedure in combination with the age range studied, remains to be determined by future research.

It is noteworthy that six-year change was required to detect significant longitudinal associations among TSH and cognitive variations. This finding does however not necessarily indicate that varying TSH levels exert long-term but not short-term change effects on cognitive functioning. Inspection of Table 2 shows, first, that cognitive decline was larger across six years than three years and, second, that the variation increased proportionally to the means. This is in accordance with previous research showing that in order to detect reliable cognitive decline, six years is the minimal test interval required (e.g., Zelinski and Burnight, 1997). Interestingly, TSH levels did not present this pattern (see Table 1). Thus it may be premature to draw any firm conclusions as to the time aspect of the TSH-cognition association.

The prospective analyses of baseline TSH and thyroxine regressed on cognitive change were included in order to replicate the study by Volpato et al. (2002). Similar to that study, we found that baseline TSH did not predict future decline of cognitive performance. However, we failed to replicate their findings that thyroxine levels at baseline predicted future memory decline. It is yet to be established whether this is a reliable difference, since the Volpato et al. study reported longitudinal data on thyroid status for only a subset of their participants, while we defined our sample by their normal thyroid levels at both follow-ups.

In a series of control analyses, we examined, first, whether the lack of TSH-related effects on TMT performance was due to the existence of extreme scores. Second, proximity to death was covaried in order to check whether the results were accounted for by the terminal drop phenomenon. Note in this context that the terminal drop phenomenon itself is likely to be accounted for by various biological indicators (e.g., Berg, 1996). In brief, our analyses showed that although impending death was marginally associated with declining cognitive performance and reliably associated with increasing mood symptoms, the main findings were unchanged by statistical control for death within one year after the third assessment. Although no firm conclusion is possible here, it seems that the terminal decline phenomenon is not confounded with the association between individual differences in cognitive performance and normal TSH status.

Performance on the Trail Making Test was not significantly related to TSH in any of the analyses. We believe that this may be due to the characteristics of the task. Trailmaking is an omnibus test that requires multiple cognitive skills, whereas the remaining cognitive tasks involved in the study draw on more specific skills. Provided the relatively complex outcome of the analyses showing dissociations in the results depending on the ability being examined, the failure to find any associations with the Trail Making test may be expected.

Although it is customary to separate dementia from non-dementia in cognitive aging studies, we decided to include participants who were diagnosed with incident dementia either at the first or the second follow-up. Concerns about statistical power formed the basis of our decision to do so, and to instead control for dementia by means of statistical procedures. We did however repeat all analyses without the incident dementia subjects (data not shown). The pattern of results were not changed by this, but as expected few results approached significance. This outcome together with the absence of significant TSH -

dementia correlations justifies in our view the inclusion of the incident dementia cases. Also, the anomaly in Table 3, where incident dementia at the first follow-up was positively related to some of the cognitive change scores were due to a few extreme individual change scores in this small group ($n = 6$) caused by very low initial cognitive scores in two individuals.

In support of the results in our first cross-sectional study (Wahlin et al., 1998), the present data suggest a particularly strong association among individual variations in normal TSH levels and episodic memory performance. Saying that, one should note that the cognitive change scores display a mixed pattern of decline and improvement over time. This is commonly found in most studies (see Hultsch et al., 1998). However, the trends were most consistent for the episodic memory variables. Thus, the proposed selective association of normal TSH with episodic memory should be interpreted with caution, since this discrepancy across the cognitive performance measures may have contributed to this finding. **In addition, Table 1 reveals that the sign of the TSH change scores were also somewhat inconsistent. Importantly, the correlations among the cross-sectional TSH variables were all positive and significant ($r_s = .54 - .69$; $p_s < .001$), and the correlations among the change scores of primary interest (i.e., TSH T2-T3 vs T1-T3 change; TSH T1-T2 vs TSH T1-T3 change) were both positive and highly significant ($r_s = .58$ and $.54$, $p_s < .001$)**

Finally, the number of exclusions due to TSH values outside normal range may seem large, but was motivated by our wish to take a conservative approach in order to avoid spurious associations. It is known that preturbations of thyroid hormones and TSH concentrations in the absence of thyroid dysfunction are commonly observed in a number of nonthyroidal illnesses that may also exert an impact on cognitive performance (McIver and Gorman, 1997). Thus, although we cannot definitely confirm the excluded participants had thyroid illnesses, the potential impact on cognitive functioning of their borderline TSH values may have inflated the results obtained in this study had they been included.

Hence, as a separate control, we repeated all analyses including the subjects with out of range TSH values. In order to minimize effects of outliers, low and high TSH values were truncated at the lower (i.e., 0.4 mU/liter) or upper (i.e., 5.0 mU/liter) end of the normal distribution. Although the increased sample size provided more power to the analyses, most of the TSH-cognition associations disappeared (data not shown). This was however to be expected, since the clinical symptomatology of hyper- or hypothyroid persons may vary from hyperactivity to lethargy, causing quite disparate effects on cognitive performance. Descriptives of the group with out of range TSH values are shown in Table 1.

In sum, we found that, within normal ranges, declining TSH levels were associated with declining verbal fluency and visuospatial abilities, but not with deficits in those abilities at the end of three- or six year change time windows. With respect to episodic memory the longitudinal TSH change relative to cognitive change associations were also present, although they did not approach conventional levels of statistical significance. By contrast, six year changes in TSH levels were positively and significantly related to differences in episodic memory performance at the end of the follow-up interval. The results suggest that although most of the association between TSH and cognitive abilities may be due to shared change variation, TSH may exert a direct impact on episodic memory. It is suggested that the mechanism for such effects are increased cortisol levels, known to affect episodic memory functioning in particular (Lupien et al., 1994; van Haasteren et al., 1996). In order to further clarify this topic, it is necessary to expand the age range under scrutiny to cover both younger and older participants, and to add indicators of both relevant thyroid indexes (TSH and thyroxine), and steroid hormone levels.

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Table 1

Summary Statistics for Demographic and Laboratory Data For Study Sample, and Persons Excluded Due to Out of Range TSH Levels

	Study sample (n = 45)				Out of range TSH (n = 46)			
	Min	Max	M	SD	Min	Max	M	SD
Age at T1	75.00	92.00	84.87	3.62	75.00	93.00	78.95	3.64
Gender (% females)	87				65			
Education (years)	7.00	18.00	9.15	3.11	7.00	18.00	9.75	3.51
T4 at T1 [a]	12.00	23.00	14.76	2.32	12.00	21.00	15.61	2.43
TSH at T1 [b]	.60	4.90	1.84	1.06	.50	4.90	2.07	1.08
TSH at T2 [b]	.60	3.80	1.54	.81	.10	6.20	1.79	1.28
TSH at T3 [b]	.42	5.00	1.60	1.11	.03	8.10	.69	1.65
TSH % change T1-T2	-70.45	100.00	-6.68	35.73	-97.96	175.00	-10.86	50.99
TSH % change T2-T3	-58.46	233.33	7.02	56.19	-95.91	1400.00	-32.71	227.82
TSH % change T1-T3	-66.54	117.39	-5.48	50.12	-98.16	350.00	-67.54	74.39
Mood symptoms at T1	0	1.5	.06	.24	0	1.5	.13	.34
Mood symptoms at T2	0	1	.38	.49	0	3.5	.31	.69
Mood symptoms at T3	0	3.5	.48	.87	0	3.5	.45	.91
Mood % change T1-T2	-60	100	34	51	-50	350	21	68
Mood % change T2-T3	-50	350	19	82	-78	250	21	70
Mood % change T1-T3	-60	350	45	89	-50	250	21	55

[a] pmol/liter.

[b] mU/liter.

Table 2

Descriptive Statistics for Percentage Change in the Dependent Cognitive Variables

Dependent Variables	Min	Max	M	SD
EM random T1	1.00	9.00	5.11	1.78
T2	1.00	9.50	5.04	1.56
T3	.50	8.00	3.44	1.77
% change T2-T3	-75.00	57.00	-25.22	25.75
% change T1-T3	-75.00	104.09	-23.77	34.43
EM organized T1	2.50	11.00	7.18	2.43
T2	.00	11.50	6.62	1.97
T3	.00	12.00	5.66	2.69
% change T2-T3	-86.78	832.16	7.00	132.85
% change T1-T3	-89.47	166.33	-12.32	46.63
Letter fluency T1	.50	33.50	11.45	6.96
T2	3.00	19.50	10.39	3.54
T3	.00	28.50	13.00	6.20
% change T2-T3	-93.55	211.11	30.34	60.33
% change T1-T3	-93.93	940.30	58.62	162.35
Category fluency T1	3.00	33.00	19.00	7.25
T2	8.00	28.00	17.35	4.45
T3	.00	36.00	20.57	9.14
% change T2-T3	-145.45	79.42	-13.07	44.09
% change T1-T3	-95.65	624.47	25.98	106.15
Block design T1	2.00	21.00	12.61	5.02
T2	2.00	21.00	12.83	4.59
T3	1.00	19.00	9.09	4.62
% change T2-T3	-150.00	75.85	-5.50	43.95
% change T1-T3	-84.61	315.66	-15.13	63.85
TMT T1	26.00	360.00	114.08	67.77
T2	20.00	205.00	87.21	43.56
T3	25.00	477.00	113.36	68.74
% change T2-T3	-47.34	119.19	63.79	185.27
% change T1-T3	-80.81	167.04	52.83	256.95

Table 3

Hierarchical Regression Examining TSH Change Scores as Predictors of Cognitive Change Scores in the T1-T3 and T2-T3 Time Intervals

Table 4

Hierarchical Regression Examining TSH Change Scores as Predictors of Cognitive Performance Scores at T2 and T3