Rzeszów University Press 2025
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2025.1.25

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2025; 23 (1): 155–162

ORIGINAL PAPER

Spatial working memory in hypothyroidism – an observational study on different ranges of thyroid stimulating hormone

Satkarjit Kaur Jhandi [1], Shweta Shenoy [1], A. P. Singh [2], Ajaypal Singh [3]

[1] MYAS- GNDU Department of Sports Sciences and Medicine, Guru Nanak Dev University, Punjab, India
[2] Sri Guru Ram Das University Of Health Sciences, Sri Amritsar, Punjab, India
[3] Fortis Escort Hospital Amritsar, Punjab, India

ABSTRACT

Introduction and aim. Hypothyroidism is associated with cognitive impairments. Clinically, subclinical hypothyroidism (SCH) is very common and patients often experience symptoms such as forgetfulness or memory deficits. Despite achieving normal thyroid stimulating hormone (TSH) levels through levothyroxine (LT-4) treatment, patients still report persistent complaints of lack of memory. Previous imaging studies have shown abnormalities in some cognitive domains, particularly in spatial working memory (SWM), that are characteristic of SCH. Therefore, the current study aimed to investigate SWM function across different ranges of TSH in patients with SCH.

Material and methods. This cross-sectional study included a total of 136 participants. Group 1: 36 controls, group 2: 33 newly diagnosed patients with SCH (TSH levels ≥2.5 mIU/L), group 3: 32 patients with SCH (elevated TSH levels ≥4.0 mIU/L) having L-T4 treatment, group 4: 35 euthyroid (TSH levels <4.0 mIU/L) but ongoing LT-4 treatment. The SWM task was performed for an assessment of SWM function, using a computerized battery (Cambridge Neuropsychological Test Automated Battery-CANTAB).

Results. Our results report a statistically significant difference in the key parameters of SWM task among all groups.

Conclusion. Our findings indicate that patients with SCH show better performance in SWM when their TSH levels decrease with LT-4 treatment, in comparison to patients who were newly diagnosed. The present study suggests a TSH level of 2.5 mIU/L may be the optimal threshold for initiating LT-4 treatment in patients with SCH.

Keywords. hypothyroidism, memory, neuropsychological symptoms, spatial working memory, subclinical hypothyroidism

Introduction

Thyroid hormones play an important role and intervene in the development of the adult brain, exerting multiple effects on various processes such as neurogenesis, dendritic cell proliferation, glial development, synaptogenesis and myelination.[1] As the brain is a major target organ for thyroid hormones, it is known that cognitive impairment occurs along with thyroid dysfunction.[2]

Hypothyroidism cases have shown changes in brain metabolism. These alterations encompass emotional lability, characterized by slowed thought processes, diminished attention, apathy, occasional psychosis, and agitation. Additionally, cognitive functions may experience a decline, including general intelligence, memory, concentration, psychomotor skills, and executive functions.[3]

Subclinical hypothyroidism (SCH), i.e., an elevated TSH level with normal free thyroxine (fT4), is of particular importance due to its high prevalence and its association with cognitive impairment. Several studies have reported subtle impairments in certain cognitive do-

Corresponding author: Satkarjit Kaur Jhandi, e-mail: satkarjitmyas.rsh@gndu.ac.in

Received: 21.06.2024 / Revised: 6.10.2024 / Accepted: 24.10.2024 / Published: 30.03.2025

Jhandi SK, Shenoy S, Singh AP, Singh A. Spatial working memory in hypothyroidism – an observational study on different ranges of thyroid stimulating hormone. *Eur J Clin Exp Med.* 2025;23(1):155–162. doi: 10.15584/ejcem.2025.1.25.

mains; among the domains frequently affected is memory, particularly working memory (WM).[4–7] Working memory, the "sketchbook of rational thought", acts as a platform on which we manipulate and record thoughts.[8] It is capacity limited and denotes a multi-processing that makes task relevant information approachable to some sophisticated cognitive processes such as reasoning, decision making, reading comprehension and learning. Spatial working memory (SWM), i.e. the ability to recall the location of the object or occurrence of an event, is likely to be affected and is generally recognized to require greater attentional resources compared to textual or non-spatial memory.[9-11] Spatial working memory is generally regarded as a fundamental component that supports various higher cognitive functions, including. but not limited to, language learning, language comprehension, reasoning, and decision making. In addition, it shows strong connections with other cognitive behaviors, demonstrating its crucial role in cognitive processing.[12] In addition, imaging studies[13] have shown abnormalities in some cognitive areas, particularly in WM, that are characteristic of SCH. Functional neuroimaging provides a neuroanatomical basis for these reported deficits. Patients with SCH showed poor SWM and abnormal fMRI findings in frontal brain regions.[10]

Clinically, patients with SCH often express complaints, particularly in the cognitive and psychiatric areas; the most common complaints include memory impairment and neuropsychological symptoms (such as insomnia, depressive mood, fatigue, mental fogginess, and apathy).[13]

In addition, patients, in spite of being euthyroid (normal thyroid profile) after treatment, present neuropsychological symptoms. Also, despite achieving normal TSH levels (4 mIU/L), a considerable number of SCH patients undergoing levothyroxine (LT-4) treatment frequently report persistent forgetfulness and mental slowness. Talaie et al. reported that a patient with a TSH ≤4.0mIU/L and no symptoms should be considered to be in the euthyroid state.[14] However, if a patient reports neuropsychological symptoms (such as fatigue, insomnia, depression, and mental fogginess, apathy) a cut off value of TSH 2.5mIU/L should be considered as a guide for initiating LT-4 treatment.

Given the relevance of memory deficits in the SCH population, to the best of our knowledge, no prior study has been conducted at different ranges of TSH for the examination of SWM function.

Aim

The current study was designed to investigate the impairment of SWM function in patients with SCH and euthyroid patients (on LT-4 treatment) compared to newly diagnosed cases (with neuropsychological symptoms) and controls, and also sought to address the gap in the existing literature by investigating the potential direct relationship between TSH levels and depressive symptoms. The findings of this study have important implications for clinical practice, particularly regarding the trajectory of hypothyroidism and the potential long-term cognitive challenges that patients may face.

Material and methods

Study design, participants and clinical evaluation

This cross-sectional study was conducted between May 2022 and July 2023, and included 136 participants, of which 100 were patients with SCH. The patients were recruited from the endocrine outpatient department of multiple health centers in the city as well as through local general medical practices. Written permission was obtained from each consultant physician for the recruitment process. The protocol of this study was approved by the Institutional Ethics committee of Guru Nanak Dev University, Amritsar (302/HG). It is the part of a larger research program which is registered under Clinical Trial Registry of India, CTRI/2022/04/042319. It was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients before study procedure.

Additionally, 36 healthy controls were selected from a cohort of volunteers residing within the local community. These healthy subjects exhibited normal thyroid function results, accompanied by a favorable medical history, indicating good overall health. They also had no reported neurological or significant cardiovascular disorders, or any other unmanaged chronic ailments.

Thirty-three patients were recruited who had complaints of neuropsychological symptoms such as fatigue, forgetfulness, insomnia, and depressive symptoms, and they were directed to undergo thyroid profiling. Upon review of the laboratory findings indicating TSH levels ≥2.5 mIU/L, the consultants established a diagnosis of SCH for these newly identified cases. Thirty-two patients with elevated TSH levels and continued LT-4 who visited due to hypothyroidism symptoms were also enrolled, as were thirty-five euthyroid individuals who were seen for follow-up.

Inclusion criteria: Patients diagnosed with SCH were identified through thyroid function tests and self-reported symptoms. Those who reported neuropsychological symptoms (such as fatigue, forgetfulness, insomnia, and depressive symptoms) and had a TSH 2.5 mIU/L or higher were considered newly diagnosed cases of SCH by the consultants. Patients with symptoms of hypothyroidism (such as fatigue, dry skin, cold intolerance and weight gain) or uncontrolled TSH levels (≥4.0 mIU/L) were included in the study as having elevated TSH levels. Patients with TSH levels below 4.0 mIU/L who were seen for follow-up were classified as euthyroid.

Subjective health and laboratory measures

The patients were interviewed about their subjective complaints, with a focus on any complaints that had developed or worsened since their thyroid pathology. A self-developed assessment form, encompassing all hypothyroidism and neuropsychological symptoms, was administered to the patients. Each subject underwent a clinical and biochemical evaluation of their thyroid function. The serum levels of TSH in mIU/L, free triiodothyronine (fT3) in ng/mL, and free thyroxine (fT4) in µg/dL were measured using the mini VIDAS automated immunoassay system. These assays were performed by a certified medical technologist. Blood samples were collected from patients in a fasted state between 8:00 AM and 10:00 AM.

Any medical comorbidities, personal history of psychiatric disorders, family history of psychiatric disorders, and use of other medications (psychiatric and non-psychiatric drugs) were noted. The patient's medical history included information about their current L-T4 treatment, including specific doses and duration, as well as any previous thyroid replacement therapy and neuropsychological symptoms.

Exclusion criteria: Patients any other neurological disorders or psychiatric disorders; history of antipsychiatry drugs; family history of dementia; any other systemic diseases such as myocardial infarction, hypertension or diabetes mellitus; vitamin B12 deficiency; any drug addiction.

Participants were enlisted on the basis of the biochemical evidence of hypothyroidism and medication history and grouped as follows:

- group 1: Controls with no history of thyroid dysfunction
- group 2: Newly diagnosed cases with TSH levels ≥2.5mU/L and presenting with neuropsychological symptoms but no past history of thyroid dysfunction
- group 3: Patients with the current history of hypothyroidism symptoms (TSH levels ≥4.0 mIU/L) who were currently undergoing L-T4 treatment
- group 4: Euthyroid patients (TSH levels ≤4.0 mIU-/L) and currently undergoing LT-4 treatment

Objective depression and cognitive function assessment

Global cognitive status was evaluated using the Mini Mental State Examination (MMSE). The maximum score on the MMSE is 30. There are three categories for cognitive impairment severity: 0–17 represents severe cognitive impairment, 18–23 represents mild cognitive impairment, and 24–30 represents no cognitive impairment.[15] Participants were eligible for recruitment if they achieved a score of 24. Depression was assessed by Hamilton depression rating scale (HDRS) that is a specific scale for assessment of depressive symptoms, consisting of 17 items. Eight items are scored on a 5-point scale, ranging from 0=not present to 4=severe. Nine are scored from 0–2.[16] Total score of 0–7=normal, 8–13=mild depression, 14–18=moderate depression, 19–22=severe depression, >23=very severe depression were considered.

Socioeconomic status was assessed using the Kuppuswamy scale.[17] The total score ranges from 3 to 29 and it classifies families into 5 groups, "upper class (I), upper middle class (II), lower middle class (III), upper lower (IV) and lower socio-economic class (V) on the basis of a) occupation of the head of the family, b) education of the head of the family, c) total monthly income of the family."

SWM function task

All the recruited subjects were administered the computerized neuropsychological test for SWM from the Cambridge Neuropsychological Test Automated Battery (CANTAB). It is a fair neuropsychological authenticated and reliable computerized test battery, used to assess executive functions.[18,19] The extensive subsets of CANTAB allow measuring various cognitive subdomains of executive functions such as SWM, new learning, short-term memory, attention through a single battery, in comparison to traditional neuropsychological tests. In current study, it is believed that the use of CANTAB battery for the assessment of SWM function would accurately document changes.

The evaluation of the battery performance was conducted in a controlled and noise free environment, specifically a quiet room.

Participants were instructed to search through a number of boxes on the screen to find which hid a yellow token. There was a guideline to govern this search, which said that if a token was found inside a specific box, it would not be found there again during that trial. As a result, as they moved through each trial, the participant needed to remember which boxes the tokens had already been located in. Trials increased in difficulty according to the number of boxes (4, 6 and 8). Following performance indices were recorded:

1. Spatial working memory between error (SWMBE): The number of times the subject incorrectly revisits a box in which a token has previously been found. Calculated across all assessed four, six and eight token trials.
2. Spatial working memory between errors SWMBE4 boxes: The number of times a subject revisit a box in which a token has previously been found. Calculated across all trials with 4 tokens only.
3. Spatial working memory between errors SWMBE 6 boxes: The number of times the subject revisits a box in which a token has previously been found. Calculated across all trials with 6 tokens only.

4. Spatial working memory between errors SWMBE8 boxes: The number of times the subject revisits a box in which a token has previously been found. Calculated across all trials with 8 tokens only.
5. Spatial working memory double error (SWMDE): The number of times a subject commits an error that is both a within error and a between error. Calculated across all assessed four, six and eight token trials.
6. SWM Strategy (6-8 boxes): The number of times a subject begins a new search pattern from the same box they started with previously. If they always begin a search from the same starting point, we infer that the subject is employing a planned strategy for finding the tokens. Therefore, a low score indicates high strategy use (1=they always begin the search from the same box), a high score indicates that they are beginning their searches from many different boxes. Calculated across assessed trials with 6 tokens or more.
7. Spatial working memory total error, SWMTE: The total number of times a box is selected that is certain not to contain a token and therefore should not have been visited by the subject, i.e., between errors + within errors - double errors. Calculated across all assessed four, six and eight token trials.
8. Spatial working memory total errors SWMTE4 boxes: The number of times a box is selected that is certain not to contain a token and therefore should not have been visited by the subject, i.e., between errors + within errors - double errors. Calculated across all trials with 4 tokens only.
9. Spatial working memory total errors SWMTE6 boxes: The number of times a box is selected that is certain not to contain a token and therefore should not have been visited by the subject, i.e., between errors + within errors - double errors. Calculated across all trials with 6 tokens only.
10. Spatial working memory total errors SWMTE8 boxes: The number of times a box is selected that is certain not to contain a token and therefore should not have been visited by the subject, i.e., between errors + within errors - double errors. Calculated across all trials with 8 tokens only.
11. Spatial working memory within errors (SWMWE): The number of times a subject revisit a box already shown to be empty during the same search. Calculated across all assessed four, six and eight token trials.

The level of education was recorded for each participant in CANTAB, (level 1, left formal education before age 16; level 2, left formal education at age 16; level 3, left formal education at age 17–18; level 4, undergraduate degree or equivalent; level 5, Master's degree or equivalent; level 6, PhD or equivalent).

Statistical analysis

The sample size estimation was conducted using G* Power (3.1.9.2). The average proportion of exposed cases (i.e. TSH mean value influencing cognition process in hypothyroidism) was ρ=0.27, with a desired absolute error of d=0.05 and a power of β=0.90.[20] Further analysis were done by using SPSS version 27.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Descriptive statistics were used to describe the basic characteristics of the study population. The normality of the cognitive data was assessed using the Kolmogorov-Smirnov test. Due to the violation of the assumptions of normality of variance, non-parametric tests (the Kruskal-Wallis test and Spearman correlation test) were employed. Between-group comparisons were conducted using the Kruskal-Wallis test. General linear models (GLM) and repeated measures factorial ANOVAs were used to investigate the effect of working memory load for conditions to demonstrate overall group effects. Greenhouse-Geisser corrected statistics were used to report the repeated measures ANOVAs. Confounding factors such as age, gender difference, level of education, and socioeconomic were controlled for in the overall group effects using a linear regression model, we inspected whether these factors influenced the dependent measures. Additionally, to explore the potential impact of the duration of LT-4 treatment on SWM with the reduction in TSH levels, group 4 (euthyroid patients, n=35) was divided into two subgroups: 4a (ongoing LT-4 for 1 or more than one year, n= 29) and 4b (ongoing LT-4 treatment for 10 or more than ten years, n=6). These subgroups were then analyzed for analysis of one of the key parameters of the SWM task: SWMTE.

Results

The present study analyzed data from 136 subjects, including 100 patients and 36 controls. Descriptive values of the clinical characteristics and demographics of the study population (as shown in Table 1). Between group differences were found in total error, between errors, and double error, which are the key parameters of the SWM task (Table 2). Further analysis was conducted to determine if there was a significant effect of load on between search errors. A repeated measures ANOVA with a 3 load (4, 6, 8 boxes) by 3 group designs showed a significant effect of load ($F(2, 1.32)=141.21$, $p\leq0.001$). However, the interaction between group × load result was not significant ($F(6,3.9)=1.26$, $p=0.27$). This effect was observed in all groups was due to the increase in load from 4 to 6 boxes rather than from 6 to 8 boxes (Fig. 1). Socioeconomic status was found as a predictor variable and influenced the measures of dependent variables: SWM Total errors ($F=5.49$, $p=0.02$) and SWM strategy scores ($F=7.23$, $p=0.008$), as assessed by a linear regression model. This was suggesting that socioeconomic status has an impact

on working memory. Another aspect we investigated was the effect of the duration of LT-4 treatment on SWM in the euthyroid group. A notable trend was observed (Fig. 2), the group 4b making fewer errors compared to group 1, indicating better performance in SWM function after 10 or more years of LT-4 treatment.

Table 1. Clinical characteristics and demographics of the study population*

Variable	Group 1 n=36	Group 2 n=33	Group 3 n=32	Group 4 n=35
Age (years)	36±9.2	36.9±0.65	38.6±11.1	38.9±9.79
Gender	M=6; F=30	M=4; F=29	M=1; F=31	M=2; F=33
Level of education	3.8±0.77	3.6±0.65	3.6±1.03	3.51±0.81
Socioeconomic status	20.5±3.24	19.75±3.77	20.8±4.29	18.9±4.84
MMSE	29.4±0.73	29.18±2.06	28.09±2.05	27.57±2.44
HDRS	1.97±1.62	5.09±3.71	4.28±3.21	2.68±2.24
TSH (mIU/L)	1.6±0.72	4.04±1.40	13.30±20.99	2.94± 0.94
T3 (pmol/L)	1.57±1.43	1.16±0.58	1.04±0.56	1.07±0.50
Free T4 index (µg/dL)	7.71±2.42	8.47±1.69	8.95±1.65	9.09±1.41
Years of medication	–	–	4.62±3.69	3.85±3.25
Neuropsychological and other symptoms				
Fatigue	52.78%	72.72%	87.5%	57.14%
Weight Gain	16.6%	33.3%	68.7%	11.4%
Insomnia	22.4%	42.4%	59.3%	48.5%
Memory loss	08.3%	78.78%	81.2%	42.8%
Cold intolerance	05.5%	27.2%	31.2%	25.7%
Dry skin	11.1%	21.2%	34.3%	31.4%
Hearing loss	5.5%	18.1%	43.7%	11.4%

* M – male, F – female, MMSE – Mini Mental State Examination, HDRS – Hamilton Depression Rating Scale, TSH – Thyroid Stimulating Hormone, group 1 – controls, group 2 – newly diagnosed cases, group 3 – patients with elevated TSH levels (on going-LT-4), group 4 – euthyroid (but on LT-4)

Table 2. Comparison of Spatial working memory (SWM) task parameters among all groups*

Variables	Group 1 (n=36), mean rank	Group 2 (n=33), mean rank	Group 3 (n=32), mean rank	Group 4 (n=35) mean rank	p
SWMTE	56.35	74.26	80.73	64.39	0.05
SWMBE	55.78	74.64	81.02	64.36	0.04
SWMWE	70.25	69.18	75.25	59.89	0.22
SWMDE	67.96	70.80	77.56	58.60	0.04
SWMTE4 boxes	57.61	67.33	77.03	73.00	0.11
SWMBE4 boxes	57.61	67.33	77.03	73.00	0.11
SWMTE6 boxes	61.14	76.00	80.53	58.00	0.04
SWMBE6 boxes	60.29	76.20	80.47	58.74	0.04
SWMTE8 boxes	57.79	71.61	77.11	68.71	0.21
SWMBE8 boxes	56.11	72.53	75.06	71.44	0.16
SWMS	67.19	67.83	78.31	61.50	0.36

* SWM – spatial working memory, TE – total error, BE – between error, WE – within error, DE –double error, group 1 – controls, group 2 – newly diagnosed cases, group 3 – patients with elevated TSH levels (on going-LT-4), group 4– Euthyroid (but on LT-4)

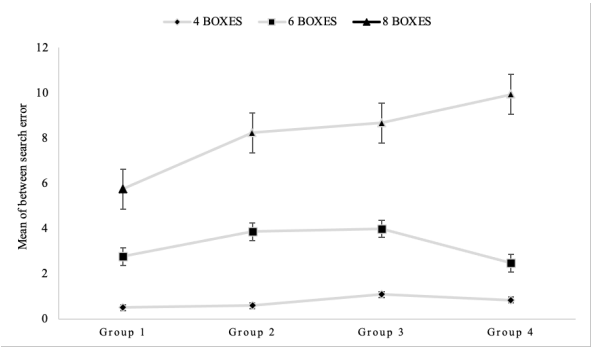

Fig. 1. Shows mean of between search error with load (4 to 6; 6 to 8 boxes) within groups, group 1 – controls, group 2 – newly diagnosed cases, group 3 – patients with elevated TSH levels (on going-LT-4), group 4 – euthyroid (but on LT-4)

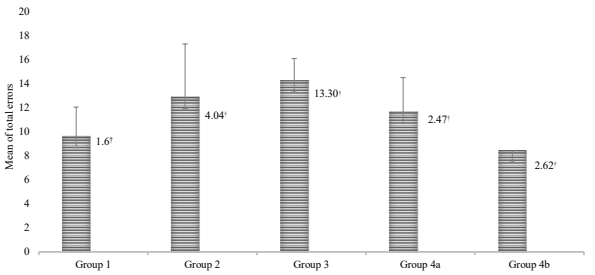

Fig. 2. Shows the mean values and standard deviation of total error in spatial working memory task among all groups, † – mean value of TSH, group 1 – controls, group 2 – newly diagnosed cases, group 3 – patients with elevated TSH levels (ongoing LT-4), group 4a – euthyroid (on LT-4 for 1 or more than one year but less than 5 years), group 4b – euthyroid (on LT-4 for 10 or more years)

Discussion

The specific impairment in WM in individuals with SCH is not well understood. Previous research has consistently shown that patients with SCH exhibit significant impairments in SWM performance.[21,22] However, the exact range of TSH levels at which memory impairment occurs is still unclear.

Our clinical observations indicate that patients on LT-4 can be broadly categorized into three groups:

1. Newly diagnosed patients reporting symptoms.

2. Diagnosed patients who are either noncompliant or poorly compliant with their dosage, resulting in poorly controlled TSH levels.

3. Compliant patients who regularly follow up with their clinician to regulate medication dosage and maintain TSH levels within normal limits.

Based on this clinical picture, patients with subclinical hypothyroidism (SCH) were classified into these three categories. Therefore, the present study aimed to investigate deficits in SWM function in patients with SCH who are currently on LT-4 treatment, as well as newly diagnosed cases, and compare them to a control

group. To objectively assess SWM function, we utilized a computerized battery with touchscreen technology. Our results, confirmed by psychological testing, showed that the patient groups had statistically significant differences ($p \leq 0.05$) in key parameters of the SWM task when compared to the control group.

We discovered that group 4 (with a mean TSH level of 2.94 mIU/L) performed better with fewer errors in the SWM task compared to group 3 patients (with mean elevated TSH levels of 13.3 mIU/L). This enhancement in memory skills can be attributed to the decrease in TSH levels resulting from appropriate treatment. These findings suggest a connection between TSH and WM. However, we also found that SWM deficits were more prevalent in group 4 compared to group 1, indicating that this memory domain does not fully recover to a euthyroid state.

Interestingly, we found that out of 35 euthyroid cases of group 4, 6 patients had been administered LT-4 for a duration of 10 or more years. These patients of group 4b showed a notable reduction in total errors compared to group 4a (who had been on LT-4 for one or more than one year but less than 5 years). Contrary to this, a clinical trial conducted by a study in patients with SCH found that there was an improvement in SWM function in the Wechsler memory scale after 6 months of LT-4 treatment with a reduction in TSH value with a mean and standard deviation of 3.96±1.23 mIU/L.[21] Also, Correia et al. reported that there was improvement in SWM function in the n-back task after 6 months of LT-4 treatment in patients with SCH.[23] One study conducted on animal models found that the administrating LT4 daily for three months significantly improved spatial memory in older mice.[24] The varying results among studies on the impact of LT-4 treatment on SWM in the SCH population may be attributed to differences in assessment methods or study design.

On the other hand, group 2 made more between search errors (SWMBE) and double errors (SWMDE) but fewer errors than group 3. This might be because mild SCH impairs memory and causes neuropsychological symptoms in these patients. It is important to determine whether the observed enhancement in WM among patients is a direct result of restoring of normal endocrine function or an indirect consequence of alleviating neuropsychological symptoms. Though beyond the scope of this study, this area may be the target of future neuroimaging studies. In contrast to the impairment for between search errors and double errors, the patient groups taken entirely did not make more within search errors (SWMWE) than controls ($p \geq 0.05$). This may be because the patients experience a lack of short-term memory but can retain information from a previous search to avoid between search errors. However, they may struggle to maintain information during the same search, resulting in within search errors.[25] Furthermore, the error rates increased with load, with the greatest impairments occurring with the initial increase from 4 to 6 boxes within all groups. Working memory had 'capacity constraints', meaning performance deteriorated with increased task load, indicating it was close to or surpassed its capacity.[26] Leung et al. found similar results on the correlation between spatial memory networks and memory load.[27]

We found that group 3 was less likely to use an efficient strategy (scores of SWMS), compared to the other three groups. However, patients in group 4 patients were more likely to use an efficient strategy compared to group 1 and group 2. The CANTAB SWM task measures executive WM, and it is believed to reflect planning ability and the ability to choose effective response sequences by integrating information.[25] Our findings, suggests that the participants' specified socioeconomic status had an impact on the dependent variable's measurements of SWM task. A total of 61% of our study participants had an undergraduate or equivalent level of education, and 78.5% of participants belonged to the upper middle class (II) socioeconomic status. After reviewing the literature, we found a relevant explanation for these results. According to Leonard et al., socioeconomic status may have a selective impact on WM, which relies on the hippocampus and prefrontal cortex, while having only a minor effect reliant on procedural memory which is dependent on striatum.[28] It is important to note that the subjects in our study were limited to individuals who had completed graduate education exclusively. In previous literature, it has been reported that individuals who have achieved higher levels of education often exhibit a tendency to dedicate more time and effort to intellectually demanding activities.[29] This prolonged exposure to cognitively stimulating environments is believed to have a positive impact on brain structure and function, leading to enhanced neurological development, such as an increase in synaptic density, or a more efficient utilization of existing brain networks.[30] In addition, these neuroprotective effects, the continued practice of cognitive skills may facilitate the development of compensatory strategies that help maintain cognitive abilities.[31] However, we did observe a trend of enhanced strategy implementation across all study groups. Notably, among the euthyroid patients receiving LT-4 treatment for a duration of 10 or more years, lower scores for strategy used were recorded compared to the control group, indicating a heightened utilization of strategic approaches in these patients. This suggests that prolonged administration of LT-4 in these patients positively influenced their performance on the SWM task, implying improved WM in conjunction with TSH levels.

Our findings suggest that early and regular screening for SWM function, along with TSH evaluation, is necessary for individuals who experience symptoms such as insomnia, depressive mood, fatigue, mental fogginess and apathy, it may be appropriate to initiate LT-4 treatment for patients with SCH at a TSH level of ≥2.5 mIU/L. In such cases, an initial dose of LT-4 may be beneficial.

Some limitations of the study: First, the subjects were not evaluated for their dosage of LT-4 medication, which could potentially affect their cognition. This is an important factor to consider in the study. Second, the mean value of the HDRS scale was 5.09 in newly diagnosed patients with SCH (group 2), indicating that depression was not diagnosed in these patients. However, it is worth noting that a high percentage (81.8%) of these patients pronounced depressive symptoms, as shown in Table 1. This could potentially have an impact on their performance in SWM task. Unfortunately, due to limitations, we were unable to analyze the effect of depressive symptoms on the SWM task performance.

To summarize, this is the first study to demonstrate that euthyroid patients who have been taking medication (LT-4) for a decade experience more significant enhancement in their SWM function compared to those who have been on the medication for one or more years. Additionally, recent research has established a more appropriate threshold for initiating medication for hypothyroidism. Our study clearly indicates that the patients with TSH levels ≥2.5 mIU/L exhibit impairments in SWM function. Therefore, instead of adopting a "wait and watch" for neuropsychological symptoms, treatment could be initiated earlier at a threshold value of 2.5 mIU/L.

Conclusion

The results of current study demonstrates that in patients with SCH, the performance of SWM exhibits enhancement as a result of the decrease in TSH levels subsequent to LT-4 treatment. However, there was a significant reduction in SWM function among newly diagnosed patients with SCH having TSH levels of 2.5 mIU/L or higher. Our research indicates that a TSH level of 2.5mIU/L may be the optimal point to begin LT-4 treatment for patients with SCH. Further well-designed randomized controlled trials with longer follow-up periods are needed to gain a deeper understanding more insights of the pathogenesis and natural history of SWM in SCH across these ranges of TSH included in the current study. These trials should also investigate the effectiveness as well as the efficacy of LT-4 treatment.

Declarations

Funding

This research received no external funding.

Author contributions

Conceptualization, S.S. and S.K.; Methodology, S.K.; Software, S.K.; Validation, S.S., S.K., A.P. and A.S.; Formal Analysis, S.K.; Investigation, A.P.; Resources, A.S.; Data Curation, S.K.; Writing – Original Draft Preparation, S.K.; Writing – Review & Editing, S.S.; Visualization, S.K.; Supervision, S.S.; Project Administration, S.K.; Funding Acquisition, A.S.

Conflicts of interest

No conflict of interest was reported by the author(s).

Data availability

Data files are available with the first author of the article.

Ethics approval

This study was approved by the Institutional Ethics Committee of Guru Nanak Dev University, Amritsar (302/HG).

References

1. Gold MS, Pottash L, Extein I. Hypothyroidism Evidence From complete thyroid function evaluation. *JAMA*. 1981; 245(19):1-4. doi: 10.1001/jama.245.19.1919
2. Constant EL, Adam S, Seron X, Bruyer R, Seghers A, Daumerie C. Anxiety and depression , attention, and executive functions in hypothyroidism. *J Int Neuropsychol Soc.* 2005:535-544. doi: 10.1017/S1355617705050642
3. van Vliet NA, van Heemst D, Almeida OP, et al. Association of Thyroid Dysfunction With Cognitive Function: An Individual Participant Data Analysis. *JAMA Intern Med*. 2021;181(11):1440-1450. doi: 10.1001/jamainternmed.2021.5078
4. Alfwaress F, Muhammad M. Language and Neurocognitive Impairments Associated with Hypothyroidism. *Folia Phoniatr Logop*. 2023;75(3):149-157. doi: 10.1159/000527803
5. Kuryłło M, Mojs E. The impact of hypothyroidism on cognitive processes, with particular emphasis on attention and memory issues. *Neuropsychiatr Neuropsychol Neuropsychol*. 2023;17(3):194-200. doi: 10.5114/nan.2022.124706
6. Samuels MH. Cognitive Function in Subclinical Hypothyroidism. *J Clin Endocrinol Metab*. 2010;95(8):3611-3613. doi: 10.1210/jc.2010-1242
7. Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health Status, Mood, and Cognition in Experimentally Induced Subclinical Thyrotoxicosis. *J Clin Endocrinol Metab*. 2008;93(5):1730-1736. doi: 10.1210/jc.2007-1957
8. Diamond A. Executive functions. *Annu Rev Psychol*. 2013;64:135-168. doi: 10.1146/annurev-psych-113011-143750
9. Pasqualetti G, Pagano G, Rengo G, Ferrara N, Monzani F. Subclinical Hypothyroidism and Cognitive Impairment: Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab*. 2015;100(11):4240-4248. doi: 10.1210/jc.2015-2046

10. Yin J jing, Liao L min, Luo D xue, Xu K. Spatial Working Memory Impairment in Subclinical Hypothyroidism: An fMRI study. *Neuroendocrinology*. 2013:260-270. doi: 10.1159/000343201
11. Li M, Zhong N, Lu S, Wang G, Feng L, Hu B. Cognitive behavioral performance of untreated depressed patients with mild depressive symptoms. *PLoS ONE*. 2016;11(1). doi: 10.1371/journal.pone.0146356
12. Esposito Mark D, Detre John A, Aisop Dvid C, Shin Robert K, Scott Atlas GM. The neural basis of the central executive system of working memory. *Nature*. 1995;378:279-281.
13. Zhu DF, Wang ZX, Zhang DR, et al. fMRI revealed neural substrate for reversible working memory dysfunction in subclinical hypothyroidism. *Brain J Neurol*. 2006;129(11):2923-2930. doi: 10.1093/brain/awl215
14. Talaei A, Rafee N, Rafei F, Chehrei A. TSH cut off point based on depression in hypothyroid patients. *BMC Psychiatry*. 2017;1-5. doi: 10.1186/s12888-017-1478-9
15. Ong HL, Subramaniam M, Abdin E, et al. Performance of Mini-Mental State Examination (MMSE) in long-stay patients with schizophrenia or schizoaffective disorders in a psychiatric institute. *Psychiatry Res*. 2016;241:256-262. doi: 10.1016/j.psychres.2016.04.116
16. Trajković G, Starčević V, Latas M, et al. Reliability of the Hamilton Rating Scale for Depression: A meta-analysis over a period of 49years. *Psychiatry Res*. 2011;189(1):1-9. doi: 10.1016/j.psychres.2010.12.007
17. Saleem SM, Jan SS. Modified Kuppuswamy socioeconomic scale updated for the year 2021. *Indian J Forensic Community Med*. 2021;8(1):1-3. doi: 10.18231/j.ijfcm.2021.001
18. Green R, Till C, Al-Hakeem H, et al. Assessment of neuropsychological performance in Mexico City youth using the Cambridge Neuropsychological Test Automated Battery (CANTAB). *J Clin Exp Neuropsychol*. 2019;41(3):246-256. doi: 10.1080/13803395.2018.1529229
19. Wild K, Howieson D, Webbe F, Seelye A, Kaye J. The status of computerized cognitive testing in aging: A systematic review. *Alzheimers Dement J Alzheimers Assoc*. 2008;4(6):428-437. doi: 10.1016/j.jalz.2008.07.003
20. K Parsaik et al. Hypothyroidism and Risk of Mild Cognitive Impairment in Elderly Persons - A Population Based Study. *JAMA Neurol*. 2015;71(2):201-207. doi: 10.1001/jamaneurol.2013.5402.
21. Yin JJ, Liao LM, Luo DX, et al. Spatial working memory impairment in subclinical hypothyroidism: An fMRI study. *Neuroendocrinology*. 2013;97(3):260-270. doi: 10.1159/000343201
22. Allam M, Helmy S, Fathy S, et al. Screening for Cognitive Dysfunction in Patients with Hypothyroidism. *Egypt J Neurol Psychiat Neurosurg*. 2008;45(1):175-184.
23. Correia N, Mullally S, Cooke G, et al. Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2009;94(10):3789-3797. doi: 10.1210/jc.2008-2702
24. Fu A, Zhou R, Xu X. The synthetic thyroid hormone, levothyroxine, protects cholinergic neurons in the hippocampus of naturally aged mice. *Neural Regen Res*. 2014;9(8):864-871. doi: 10.4103/1673-5374.131602
25. Van Asselen M, Kessels RPC, Wester AJ, Postma A. Spatial working memory and contextual cueing in patients with Korsakoff amnesia. *J Clin Exp Neuropsychol*. 2005;27(6):645-655. doi: 10.1081/13803390490919281
26. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*. 2005;25(1):46-59. doi: 10.1002/hbm.20131
27. Leung HC, Seelig D, Gore JC. The effect of memory load on cortical activity in the spatial working memory circuit. *Cogn Affect Behav Neurosci*. 2004;4(4):553-563. doi: 10.3758/CABN.4.4.553
28. Leonard JA, Mackey AP, Finn AS, Gabrieli JDE. Differential effects of socioeconomic status on working and procedural memory systems. *Front Hum Neurosci*. 2015;9(OCT):1-9. doi: 10.3389/fnhum.2015.00554
29. Parisi JM. Engagement in Adulthood: Perceptions and Participation in Daily Activities. *Act Adapt Aging*. 2008;34(1):1-16. doi: 10.1080/01924780903552246.
30. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. 2003;14(2):125-130. doi: 10.1111/1467-9280.t01-1-01430
31. Scarmeas N, Stern Y. Cognitive reserve: Implications for diagnosis and prevention of Alzheimer's disease. *Curr Neurol Neurosci Rep*. 2004;4(5):374-380. doi:10.1007/s11910-004-0084-7