Chapter 4

# Thyroid Hormone Effects on Sensory Perception, Mental Speed, Neuronal Excitability and Ion Channel Regulation

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http://dx.doi.org/10.5772/48310

## 1. Introduction

Although thyroid hormone effects on the brain are most prominent in development, also in adult-acquired hypothyroidism symptoms such as sensory impairments, disagreeable smells and taste, slowness of thought and action, changes of speech, irritability, headaches, sleep disturbances, confusion up to delusions and hallucinations, impairments of memory, of vision as well as of hearing frequently occur. This involvement of the nervous system was already discussed in the first reports on myxoedema (1–3) and a systematic description included in the first extensive investigation by the Committee of the Clinical Society of London (4). Many of these symptoms have since been studied in considerable detail. The conspicuous slowing of movements of hypothyroid subjects has been shown to correlate with peripheral sensory and motor nerve dysfunctions and abnormal neuromuscular transmission (5–10). The slowing of thoughts and mental function occurs concomitant with a decrease in the frequency of the alpha rhythm of the EEG (11–15). In addition to the slowing of the alpha-rhythm increased latencies of visual, auditory and somatosensory evoked potentials in adult-onset hypothyroidism indicate a slowed conduction of information in the central nervous system (16–24). In addition to a slowing of neuronal conduction velocity, changes in the threshold of hearing (25–29) and of the sensation of smell have been reported (30, 31). Cognitive and memory tests revealed impaired performances, which could at least partially be reversed by hormone substitution (24, 32–34). The extent of the reversibility of these symptoms is still a matter of debate (35).

Since many of the neurological symptoms observed in hypothyroidism point to a conspicuous mental slowing as leading symptom of hypothyroidism, we here were

interested to test in a small sample of 6 patients, whether already a transient hypothyroid state, induced by 4 weeks of total thyroid hormone withdrawal, would result in detectable changes in the speed of sensory perception and cognitive functions. For this aim we combined different psychophysical tests shown to be sensitive in previous studies of hypothyroidism with some new examinations. While cognitive tests, such as the trail making test as well a calculation task showed a non-significant tendency toward slowing, a more complex visual- spatial performance test revealed a significant slowing of mental function after four weeks of hypothyroidism. The speed of speech was significantly reduced and a fast Fourier analysis showed a shift to lower frequencies in the hypothyroid test persons. A significant decrease in red-green colour fusion frequency was found, indicating an impaired temporal resolution of visual stimuli. Smelling of two odorants tested, odorant discrimination (Sniffin`sticks) and the hearing thresholds were slightly, but insignificantly impaired in the hypothyroid test persons. The results of these tests indicate that the most prominent and first significant clinical symptom to develop in hypothyroidism is a slowing of speech and of visual perception.

Slowing of conduction velocity can be explained by a reduced myelination. A second mechanisms is a decrease in voltage-gated sodium current density, leading to a slowed charging of the membrane capacitor thus resulting in a decreased slope of the action potential upstroke velocity which in turn decreases conduction velocity. Although several investigations support the concept that thyroid hormone affects myelination, recently evidence has accumulated, that thyroid hormone also increases sodium current density in neurons from several species. We will thus discuss reports on the regulation of voltage gated ion currents in neurons and muscle cells later in the chapter, which could offer an explanation for the observed slowing of thoughts and movements at the cellular and molecular level.

Furthermore, it has been known for a long time, that thyroid hormone regulates energy expenditure (see also Yehuda-Shnaidman et al. in this issue). Pumping of $Na^+$ out of the cells has been accounted for the expense of 40% of energy consumed at rest (36, 37). Thus an increased influx of $Na^+$ due to enhanced voltage-gated $Na^+$-influx will most likely also stimulate $Na^+/K^+$-ATPase activity, and could also account at least to some extent for the stimulation of an enhanced expression of $Na^+/K^+$-ATPase subunits in the membranes. We thus conclude the chapter by reviewing data on the regulation of $Na^+/K^+$-ATPase by thyroid hormone in the brain and its potential link to $Na^+$ current regulation.

## 2. Clinical symptoms during transient severe hypothyroidism quantified by psychophysical investigations in adult human test persons

To illustrate some conspicuous effects of thyroid hormone on brain function we studied 6 patients after total thyroidectomy for thyroid carcinoma who had discontinued taking thyroid hormone prior to routine diagnostic $^{131}I$- scanning and who thus showed a reproducible degree and duration of hypothyroidism. Symptoms described to occur a few weeks after discontinuation of thyroid hormone therapy are changes in peripheral

conduction velocity and in the EEG (15). Furthermore, subjective impairments of the quality of life (38–40) as well as changes in mood (41, 42) and decreases in working memory (43) have been reported.

## 3. Methods

*Test persons*. A test battery was developed to allow a relatively fast examination of several aspects of sensory and cognitive function. To integrate the investigation into the normal clinical examination procedures the whole testing protocol was designed to be completed within 1.5 hours. All tests were carried out on 6 patients after thyroid hormone withdrawal for 26 to 28 days and on 6 healthy volunteers which were age (maximal difference: 3 years) and sex matched (with the exception of one female control person for a male patient). Patients were retested after at least 6 weeks of hormone substitution, after obtaining low TSH values. To elaborate the optimal test parameters some of the tests had been performed in more detail on an additional hypothyroid test person, the data of which are included in the appropriate results sections. In the 7 test persons (age 42-64, 4 female, 3 male) TSH-suppressive thyroid hormone substitution after total thyroidectomy and radioiodine therapy for thyroid carcinoma had been discontinued for 26-28 days for routine diagnostic application of $^{131}$I. Thyroid hormone levels measured in hypothyroidism were FT3: < 2.0 pmol/l, FT4: <2.6 pmol/l in 6 patients and FT3: 2.6 pmol/l, FT4: 4.8 pmol/l in the remaining patient, TSH was > 80 mU/l in three patients and 48.7 ± 10.4 mU/l (mean ± SE) in the remaining four patients. After 6 - 10 weeks of hormone substitution these values were: FT3: 6.2 ± 0.5 pmol/l, FT4: 26.0 ± 3.0 pmol/l and TSH: 0.09 ± 0.04 mU/l, n=7 (normal ranges: FT3: 3.4 - 7.6 pmol/l (SPART, Amerlex MAB, Johnson & Johnson); FT4: 11 - 23 pmol/l (SPART, Amerlex MAB, Johnson & Johnson), TSH: 0.3 - 4.0 mU/l (IRMA, Dynotest, Brahms). Results are given as means ± standard error. Statistical analysis was performed using paired Student`s t-test. Informed consent was obtained from all individuals before performing the tests.

*Speed of speech*. To investigate possible changes in the speed of speech we asked the test persons to repeat four times the same word as fast as possible (in this case the word „Apfelmus"). They were asked the repeat the series of four words four times and were encouraged to accelerate their speech as much as possible. The four series of words were stored on magnetic tape with a SONY WTC-D6C stereo cassette recorder and analysed off-line using a Digidata 1200A analog-digital converter with "Axoscope" software (Axon Instruments). The time needed to pronounce the four words was then read from a digital storage oscilloscope. In addition a fast Fourier analysis was performed on the record of the second syllable ("mus") selected from the two fastest traces obtained from each test person in the hypothyroid and the euthyroid condition. The section of the record to be analysed was selected with "Axoscope" and then analysed with "Origin 5" software.

*Tests of cognitive performance*:

a. *Calculation and Correlation*. To test more complex mental performances patients were first handed a sheet of paper and asked to complete a set of 24 simple calculation tasks

of third grade difficulty (like: 23+11=?). Each result of a calculus task was assigned one of five colours (yellow, red, green, dark and light blue). After completing the calculation task the test persons were asked to fill a second form, consisting of an outline drawing containing 54 numbered areas, where each number equalled one of the results of the preceding calculus task (some numbers were used several times). The patients were handed coloured pencils and asked to assign the appropriate colour from the result of the calculus task to each of the numbers given in the drawing. This procedure finally resulted in the appearance of a meaningful picture (in this case a boat). The time taken by the patients to complete the calculus task and to assign the colours to the figures in the drawing was monitored.

b. *Trail making*. The test consisted of a piece of DIN A4 paper, containing randomly distributed numbers (24 pt size, black, surrounded by a black circle). The paper was placed on a table in front of the test persons who were asked to connect the numbers from one to 25 (version A). In version B numbers from 1 to 13 and letters from A to L were distributed randomly and the test persons asked to connect them alternating between the numbers and the succession of the alphabet, e.g., 1-A 2-B- 3-C etc. The time needed for completion of the test was recorded (44).

*Tests to determine time resolution of visual perception and colour contrast perception:*

a. *Flicker fusion frequency*. Light flashes delivered with a sufficiently high frequency fuse to give the impression of a continuous light source. The lowest frequency at which an intermittent light source is perceived as a continuous one is termed the „flicker fusion frequency". A light source containing red (660nm), green (565 nm) or blue (470nm) diodes of 1 $cm^2$ diameter with an intensity of 14 Cd $m^2$ (determined with a Minolta luminance meter) was displayed to the test persons at a distance of 52 cm (to excite a 1° area of the visual field). The screen was positioned at the back of a 50 x 50 cm wide and 52 cm deep box with black walls. The flicker frequency was generated with a square wave pulse generator with a 50% duty cycle. The frequency could be changed with a dial. Test persons were asked to focus on the light with both eyes while the frequency was increased and to give a sign when they perceived the flashes to fuse to a continuous light source. Since it turned out to be too time-consuming to test the right or the left eyes, foveal and peripheral illumination separately and to use lights of different colours and since preliminary experiments showed no qualitative differences in the results, most patients were only retested with the red colour fixed by two eyes. The average value of three determinations of flicker fusion frequency always starting from low frequencies was determined.

b. *Red-Green fusion*. Changes in the perception of chromatic flicker were tested in addition to the critical flicker fusion frequency of luminance flicker. In this test a rotating disk of 12 cm diameter was shown to the test persons. The disk was diagonally partitioned into four sections which were painted alternatively in light red (Plaka Nr. 82) and light green (Plaka No. 90; 16 – 20 $Cd/m^2$, determined with a Minolta LS 100 luminance meter). The speed of rotation was increased continuously and the number of rotations

per minute was electronically counted. Increasing the speed of rotation first gave the impression of a luminance flicker. A further increase in the speed of rotation resulted in the impression of a homogenous dark yellow colour. The patients were asked to give a sign at the frequency were they saw the first signs of a luminance flicker and as soon as they perceived the impression of a homogenous yellow colour. Each test was repeated three times starting with low frequencies and the average value of the three determinations was noted.

*Sense of Smell*. Two tests were used to detect possible changes in the sense of smell: First a test for the recognition and discrimination of 16 different odorants, including familial smells like cinnamon and rather unusual flavours, like leather, was used. Then the threshold of perception was tested using two different odours, one that tests the excitation of the olfactory nerve (phenylethyl alcohol (Phe)), smelling like rose, and one, exciting both, trigeminal and olfactory nerves (eugenol (Eu)), Sniffing´sticks, (45)). In brief, for the odorant tests, caps were removed from plastic sticks containing odorants of different concentrations filled into the sticks ending in felt tips extruding about 5 mm from the tip of the stick. A stick was gently moved at a distance of about 1 cm below the nostril of the test person. Sticks containing the test solution in ascending concentration (descending numbers on the stick) were presented to the test person in series of three sticks, two of which contained distilled water. The threshold was defined as the concentration at which the patient correctly recognised the odour in two out of three presentations.

*Hearing threshold*. Hearing thresholds were determined for 8 different frequencies using an Ascom Audiosys Maico ST20 audiometer. Changes in threshold for sinusoidal tones of 1 and 8 kHz were evaluated.

### 3.1. Experimental results

*Speed of speech.* Figures 1A and B show digitized traces of speech records of a female test person in hypothyroidism (upper trace, a) and after hormone substitution (lower trace, b). After hormone substitution this test person pronounced the four words faster. As shown in Fig. 1C, on average the test persons needed a significantly longer time to pronounce the same words in the hypothyroid condition as compared to the euthyroid control persons or after thyroid hormone substitution. Figure 1D gives a more elaborate example of the development of the slowing of speech during hormone withdrawal and resubstitution. Here an additional test person was asked to repeat a short poem in regular intervals at maximal speed and the time taken to complete this poem was recorded. During hormone withdrawal the time needed to finish the poem became increasing longer. During resubstitution with thyroid hormone the time to finish the poem gradually decreased during the following month. To find out whether the increase in speed of speech during hormone resubstitution was accompanied by an increase in pitch a fast Fourier analysis was performed on the syllable “mus” (encircled by the rectangles in Fig. 1A). The analysis of the pronounciation of this syllable, consisting with predominant amplitude of the noun “u” showed several clear frequency peaks (Fig. 1B). The records from four of the five male subjects included in the

study showed a peak between 100 and 200 Hz which was not seen in the records from any of the female test persons. Since the most prominent peak in all test persons was found between 200 and 300 Hz this peak was evaluated in hypothyroidism and after hormone substitution. As shown in Table 2 and illustrated in Fig. 1B the peak frequency was shifted by an average of about 30 Hz to higher frequencies by the hormone substitution. This shift was found in all subjects with the exception of one test person, aged 61, who suffered from paresis of the *n. recurrens*.

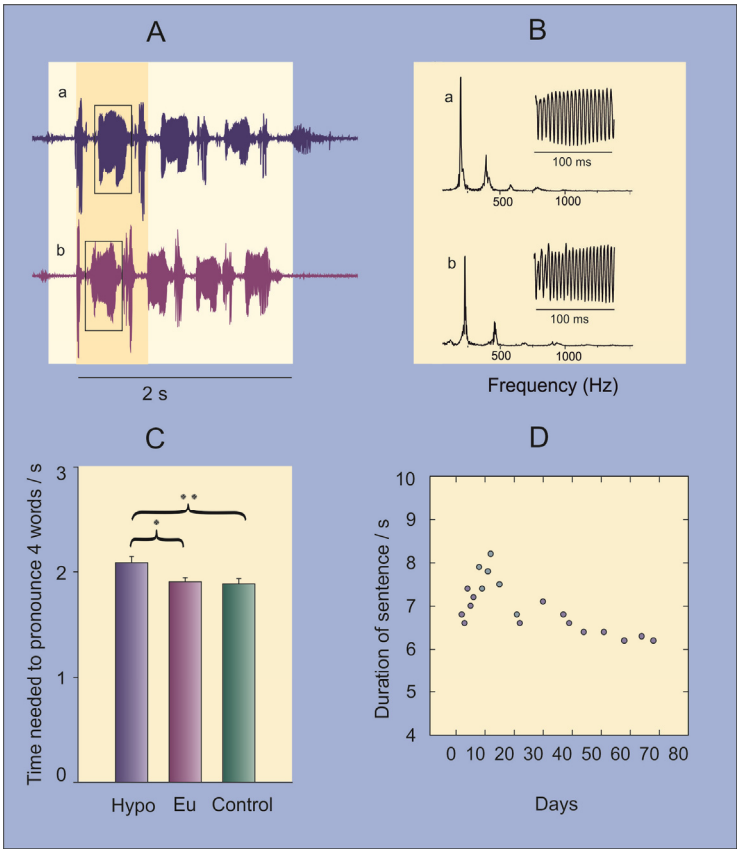


**Figure 1.** *Changes of speech during thyroid hormone withdrawal*. Original voltage traces of a record from a female test person (A) repeating four times the word "Apfelmus" as fast as possible after four weeks of thyroxine withdrawal (a) and after 10 weeks of hormone resubstitution (b). The darker yellow shadow indicates the time needed to pronounce the first word in the hypothyroid condition. B: Fast Fourier analysis of sections of the speech record shown within the squares in A. Inset: 100 ms long sections from the analysed traces. C: average time needed to pronounce the four words after hormone withdrawal (Hypo), resubstitution (Eu) and by control subjects (mean ± SE, n=6) asterisk: $p<0.05$, 2 asterisks: $p<0.01$. D: time needed to complete a short poem of an additional test person recorded daily during last 20 days of thyroxine withdrawal and during the following 60 days of resubstitution. Note the gradual decline in speed of speech with increasing time of thyroid hormone withdrawal.

*Speed of visual perception*. In hypothyroidism, the frequency, at which patients first reported to perceive a flickering light source as a continuous one was slightly but insignificantly smaller than the frequency determined in the control group. The hypothyroid group showed no significant improvement after 6 weeks of hormone therapy (Figure 2Ab). In a single test person, where the flicker fusion frequency was recorded daily for blue, green and red light and both eyes tested separately, however, a significant decrease in flicker fusion frequency was shown in the third week after the arrest of hormone substitution. After six weeks of hormone resubstitution the flicker fusion frequency had significantly recovered with respect to the last week without the hormone (Table 1 and Figure 2 Aa).

| | 6 days during first week of thyroid hormone withdrawal | | | Days 17-22 of hormone withdrawal | | | P (1st week versus 3rd week) | 40-46 days after beginning of thyroid hormone resubstitution | | | P (6 weeks after resubstitution versus 3 weeks after hormone withdrawal) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | mean | SEM | n | mean | SEM | | n | mean | SEM | |
| CFF (Hz), green 2600 Cd/m$^2$ | 12 | 37.4 | 0.4 | 12 | 36.6 | 0.6 | 0.27 | 12 | 40.6 | 0.3 | 0.000006 |
| CCF (Hz), red 100 Cd/m$^2$ | 12 | 35.8 | 0.6 | 12 | 32.8 | 0.4 | 0.0003 | 12 | 36.3 | 0.3 | 0.0000002 |
| CCF (Hz), blue 30 Cd/m$^2$ | 12 | 35.3 | 0.6 | 12 | 29.9 | 0.5 | 0.0000004 | 12 | 37.2 | 0.3 | <0.0000000001 |

**Table 1.** Critical flicker fusion frequency for three different colours (12 measurements on 2 eyes determined on 6 successive days were pooled from one test person, SEM: standard error of the mean, unpaired t-test), the original data for red light are displayed in Figure 2Aa.

The critical colour fusion frequency (CCFF), determined with a rotating wheel of alternating green and red sectors was significantly reduced in the hypothyroid test persons compared with the control subjects. The frequencies at which the rotating, red-green disk was perceived as starting to show a luminance flicker (Fig. 2 Ba) as well as the frequency at which a uniform yellow colour was reported (Fig. 2Bb) were both significantly smaller in the hypothyroid test persons as compared to the control group.

*Cognitive performance*. Since several cognitive tests have been shown to be sensitive for thyroid hormone we here tested whether hypothyroidism for 4 weeks has an effect on calculation and visual-spatial orientation. A slight but insignificant slowing of the speed with which the hypothyroid persons completed the calculation task compared with the euthyroid control group was observed (Table 2, Figure 3A). A stronger effect was seen,

however, if a more complex performance task, like the correlation of numbers with colours and finding and colouring the appropriate numbered area, had to be accomplished (visual-spatial orientation). Here the hypothyroid patients performed somewhat slower than the control subjects. After 6 weeks of hormone substitution the formerly hypothyroid persons showed a significantly improved performance (Figure 3B). Hypothyroid persons completed the trail making test insignificantly slower than the euthyroid controls or after hormone substitution, (Figure 3C, D).

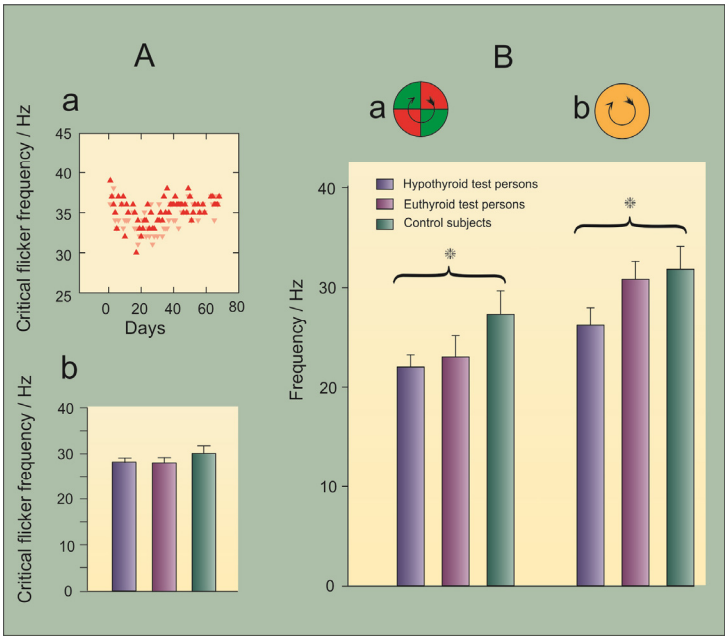


**Figure 2.** *Speed of visual perception*. Aa: critical flicker fusion frequency for a luminance flicker of red light, 100 Cd/m$^2$ measured once daily at the same time in the morning in a test person during the last 20 days of thyroxine withdrawal and during resubstitution. Note the gradual continuous decrease in CFF with increased time of thyroxine withdrawal and the gradual increase after hormone resubstitution. Dark red symbols: right eye, light red symbols: left eye. Ab: average critical flicker fusion frequency determined in six separate test persons after four weeks of hormone withdrawal (green bars), resubstitution (violet bars) and in control subjects (pink bars). B: critical colour fusion frequency in same test persons for luminance flicker of red and green sectors of a rotating disk (a) and fusion of the red-green sectors to homogenous yellow (b) (mean ± SE, n=6) asterisk: $p<0.05$.

*Hearing threshold*. Since thyroid hormone has been reported to also affect the auditory system here we tested whether thyroid hormone withdrawal for several weeks has a measurable effect on hearing thresholds. No changes in hearing threshold were obvious for frequencies below 8 kHz. Hence only the measurements at 1 kHz and 8 kHz were evaluated (Table 2). If data from both ears were pooled, the improvement of 8 dB seen after hormone substitution at the test frequency of 8 kHz just reached significance.

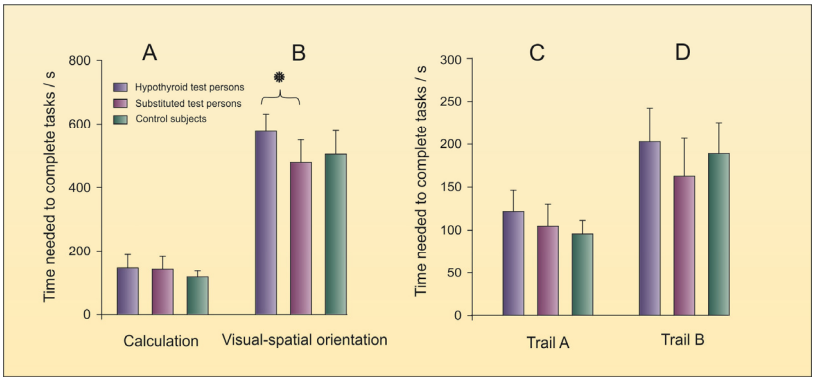


**Figure 3.** *Performance in cognitive tests.* A: Average time needed by test persons after four weeks of hormone withdrawal (light bars), thyroid hormone resubstitution for at least nine weeks (grey bars) and by control subjects (black bars) to complete a set of simple calculations. B: Average time needed by the same subjects to combine numbers in an outline drawing with corresponding colours. C: Average time needed by the same subjects to complete the Trail A test and D: the Trail B test (mean ± SE, n=6). Asterisk: $p<0.05$

*Sense of smell*. Finally, thyroid hormone might also affect the sense of smell. Of the six test persons tested one had been anosmic since childhood and a second subject did not want to repeat the smelling threshold test. Hence only 4 persons could be retested in the euthyroid state (Table 2). Using the odorant discrimination task, the hypothyroid test persons rated 66% of the presented flavours correctly. After hormone substitution they showed a slightly increased performance rating 72% of the presented flavours correctly, while the controls gave 70% correct answers. After four weeks of hypothyroidism, small but insignificant decreases in the threshold of odorant detection were found for both odorants which were still below the thresholds determined for the control subjects (Table 2).

*Age-dependence of thyroid hormone effects*

Although hypothyroid subjects performed on average slower in several tests it could have been possible that some test persons showed only a slowing of speech while others showed a slower resolution of visual signals. To find out whether some subjects were on average, slower or faster than others for each of seven tests, the speed of speech, calculation time, picture filling, Trail A, Trail B, critical flicker fusion frequency for red luminance flicker and fusion frequency for chromatic flicker, all twelve test persons were assigned numbers of 1 to 12 for each test, were the fasted was scored with 1 and the slowest with 12. If two persons showed the same speed of performance they were assigned an equal score, such that the highest value was less than 12 for several tests. For each test person the average score in the seven tests was calculated (Fig. 4). If differences in performance in the different tests were random, then the scores would scatter around a value of somewhere below 6.5 (assuming that in some tests several test persons showed the same speed). As Fig. 4 shows, this was not the case. As expected, the hypothyroid test persons were on average slower than the control subjects (Fig. 4A). As also somewhat

expected the speed of performance showed a tendency to decline with age, such that the older test persons, displayed at the right side of the series of columns in Fig 4A, scored on average higher than the younger subjects. In comparison of the performance of the test persons during hormone substitution with the control subjects an increase in overall speed of performance of the formerly hypothyroid subjects was seen, such that the average speed of the substituted test persons became indistinguishable from that of the controls (Fig. C). Interestingly, the relative increase in speed seemed to be larger in the younger than the older test persons (compare Fig. 4A with Fig. 4B).

| | Hypothyroid Test Persons (HypoTP) | | | Substituted Test Persons (SubTP) | | | P (HypoTP versus SubTP) | Controls | | | P (HypoTP versus Controls) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | mean | SEM | n | mean | SEM | | n | mean | SEM | |
| Speed of speech / s | 12 | 2.09 | 0.05 | 12 | 1.91 | 0.04 | 0.03 | 12 | 1.88 | 0.05 | 0.003 |
| Pitch of „u“ /Hz | 12 | 236 | 13 | 12 | 263 | 10 | 0.008 | 12 | 264 | 10 | 0.16 NS |
| CFF /Hz | 6 | 28.3 | 1.0 | 6 | 28.2 | 1.1 | 0.90 NS | 6 | 30.3 | 1.6 | 0.38 NS |
| CCFF I /Hz | 6 | 22.0 | 1.2 | 6 | 23.0 | 2.1 | 0.73 NS | 6 | 27.3 | 2.4 | 0.03 |
| CCFF II /Hz | 6 | 26.2 | 1.8 | 6 | 30.8 | 1.8 | 0.21 NS | 6 | 31.8 | 2.3 | 0.02 |
| Calculation time /s | 6 | 146 | 42 | 6 | 142 | 40 | 0.75 NS | 6 | 118 | 19 | 0.51 NS |
| Visual-spatial orientation/s | 6 | 576 | 56 | 6 | 478 | 71 | 0.02 | 6 | 504 | 74 | 0.44 NS |
| Trail A /s | 6 | 122 | 25 | 6 | 105 | 26 | 0.16 NS | 6 | 96 | 16 | 0.40 NS |
| Trail B /s | 6 | 203 | 40 | 6 | 163 | 44 | 0.13 NS | 6 | 189 | 36 | 0.79 NS |
| Odour recognition (%) | 5 | 66 | 6 | 5 | 72 | 6 | 0.32 NS | 5 | 70 | 6 | 0.48 NS |
| Smell threshold (eugenol) | 5 | 6.7 | 0.6 | 4 | 6.9 | 1.2 | 0.91 NS | 5 | 7.8 | 0.5 | 0.19 NS |
| Smell threshold (Phe) | 5 | 5.9 | 1.1 | 4 | 6.7 | 0.5 | 0.54 NS | 5 | 7.8 | 0.5 | 0.23 NS |
| Smell threshold (Pyr) | 5 | 5.1 | 0.5 | 4 | 5.4 | 0.8 | 0.37 NS | 5 | 5.9 | 1.1 | 0.50 NS |
| Hearing threshold for 8 kHz /-dB | 12 | 32 | 5 | 12 | 24 | 6 | 0.05 | 12 | 25 | 4 | 0.24 NS |
| Hearing threshold for 1 kHz /-dB | 12 | 22 | 3 | 12 | 21 | 4 | 0.43 NS | 12 | 23 | 2 | 0.83 NS |

Speed and pitch of speech: the two fastest measurements of each test and control persons were included. CFF: critical flicker fusion frequency, CCFF: critical colour fusion frequency, Smell thresholds: a lower threshold of smell corresponds to a higher test score: Phe: Phenylethylalcohole, Eu: Eugenol: Pyr: pyridine, hearing thresholds: data from right and left ears were pooled, SEM: standard error of the mean, paired t-Test

**Table 2.** Summary of the effects of hypothyroidism on performance in the different psychophysical tests in hypothyroid test persons, hormone substituted hypothyroid test persons and euthyroid control subjects.

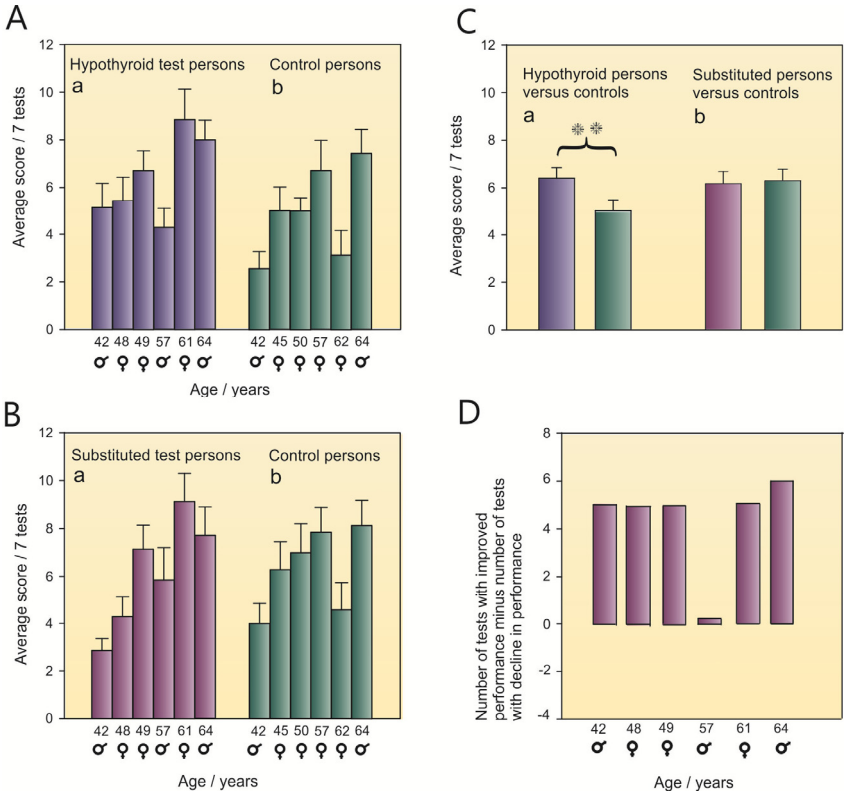


**Figure 4.** *Effects of age and thyroid status on speed of performance of individual test persons*. Mean scores obtained by the 12 test and control subjects in 7 tests. A: Comparison of speed of performance in the sum of 7 tests in hypothyroid subjects with control subjects. Smallest score: fastest person, largest score: slowest person. B: Comparison of former hypothyroid subjects after at least 6 weeks of hormone substitution (a) with controls (b). C: Mean values of scores of all six persons after thyroid hormone withdrawal compared with control subjects (a) and of test persons after hormone replacement with controls (b). Light bars: test persons after hormone withdrawal, grey bars: test persons after hormone resubstitution, black bars: control subjects.**: $p<0.01$.D: Overall improvement in speed of performance after hormone substitution. For each of the 6 test persons the number of tests in which performance was speeded minus the number of tests in which performance was slowed was determined (maximal value of improvement: 8, maximal value of slowing: -8). While 5 persons considerably increased their speed of performance (e.g. an increase in speed in 6 tests and a decrease in performance in 1 test) only 1 test person showed no average increase in speed.

To investigate whether only the younger test persons responded with an increase in the speed of neuronal information processing to thyroid hormone we evaluated the individual change in performance of each test person. For each of the 6 test persons and eight tests (the speed of speech, pitch of speech, calculation time, picture filling, Trail A, Trail B, critical flicker fusion frequency for red luminance flicker and fusion frequency for chromatic flicker) we rated an increase in the speed of performance in a test assigning a 1 to an increase in

speed, a 0 for an unchanged performance and a –1 for a slowing of performance at retesting during hormone resubstitution. If a person showed no overall change in speed of performance, a score scattering around 0 should result, if the subject slowed considerably the score should be in the negative range and if a subject speeded in all tasks, the maximal score would reach 8. As depicted in Fig. 4D out of the 6 persons tested with all 8 identical tests 5 showed a considerable speeding which corresponded to an increased performance in at least 6 out of 8 tests. Only one of the test persons, aged 57, showed an increased performance in only 4 tests and a decreased performance in 4 tests. This person was the only one who showed no increase in the speed of speech with thyroid hormone substitution. Nevertheless Fourier- analysis revealed an increase in pitch by 11% after prolonged hormone resubstitution in this test person.

Our findings, that younger persons are more impaired than older subjects after thyroid hormone withdrawal is in accordance with recent findings by Heinzel et al., who reported a stronger subjective impairment in younger patients after thyroid hormone withdrawal than in older patients (46). This is in accordance with observations of age-dependent effects on heart action potential parameters observed to parallel age-related thyroid states (47, 48). This observation might relate to a down-regulation of thyroid hormone receptors with aging (49).

## 4. Evaluation of the experimental data in the context of previous observations of the action of thyroid hormone on mental speed

Taken together, this short survey of measurable changes in sensory perception and reaction after a period of a few weeks of severe hypothyroidism indicates that the first effects of hypothyroidism to become significantly evident concern changes in the speed of speech and visual perception.

*Speed of speech*

Although slowing of speech and thinking had already been noticed in the first description of myxedema (2) and by the Committee of the Clinical Society in 1888 (4) to be one of the most prominent symptoms of hypothyroidism we are aware of only one published attempt to quantify changes in speech due to different thyroid states. This study reported a negative correlation between the basal frequency of speech and the duration of the achilles tendon reflex (50). These authors performed investigations before and after treatment of hypo- and hyperthyroidism with reported time intervals from 7 days to 17 weeks, but did not further comment on the severity of thyroid dysfunction and the time course of development of recovery of the changes in pitch. A further study observed a decrease of the fundamental frequency of speaking 4 days after thyroid ablation (51). Although the cause for the slowing of speech is difficult to interpret, increased intervals between the different words (see Fig. 1A) suggest, that in addition to a possible slowing of muscle contraction and a potential decrease in tension of the vocal cords a central slowing of neuronal information processing is likely to occur.

*Speed of processing of visual signals*

The second most prominent effect of hypothyroidism revealed by our tests is a slowing of the speed of perception of visual information. These results confirm several previous studies, one of which reported critical flicker fusion frequencies (CFF) up to 41 - 48 Hz in 23 hyperthyroid patients and a decrease in flicker fusion frequency to the normal value of 37 Hz within one month after treatment of the hyperthyroidism (52). Decreased values of the critical flicker fusion frequency as well as of the maximal speed of finger movements were shown in hypothyroid patients (53). A third study revealed an increase in CFF in hypothyroid subjects with a delay of 2-3 weeks after an increase in dose of thyroid hormone substitution (54). We could find no previous reports on influences of thyroid hormone on the critical colour-fusion frequency (CCFF) which tests the speed of processing of chromatic pathways in addition to the CFF, which tests the speed of luminance processing. CCFF occurs at a lower frequency as CFF (55). The lower frequency of colour processing compared to luminance flicker already starts to arise at the level of the retina (56).

Since thyroid hormone affects the renewal rate of the photoreceptor outer segments in the rat (57, 58) one locus of action of thyroid hormone could be the retina. This is confirmed by the finding of increased amplitudes of chiefly the b-waves of the electroretinogram in hyperthyroidism and a decrease in hypothyroidism (59, 60), suggesting that thyroid hormone influences retinal sensitivity to light. Since there is evidence that thyroid releasing hormone (TRH) in the circulation decreases the critical flicker fusion frequency (61) the effect could also be due to the enhanced TRH level in the investigated test persons. Since, however, no effects of hypothyroidism on peripheral circulating TRH values have been found (62) it seems presently more likely that the decrease in flicker fusion frequency is due to a direct effect of thyroid hormone.

Increased voltages of EEG records and a decreased duration of arousal responses to photic stimulation after administration of thyroid hormone (63) could be explained by an increased light-sensitivity of the retina, but additionally also by an increased transmission of sensory signals to the visual cortex. Substantial experimental evidence has been obtained to show that the upper frequency limit with which signals are transmitted in the visual pathways decreases with the number of synaptic stations traversed (for review see (64)). Hence a modulation of synaptic transmission at the thalamic level seems to be responsible for the increase of CFF by psychotropic stimulants and the decrease by sedatives (for reviews see (65, 66)). Furthermore, investigations of the relation between CFF and intelligence revealed only non-significant relations between different scores for intelligence and CFF (67, 68), however a decrease of 4 Hz of was found in mentally retarded persons (69) suggesting that a larger decline of cognitive function may be accompanied by decreases in CFF. In addition a correlation was found between the decline of CFF and the decline in performance on cognitive tests in old age (70).

Complementary to a reduction in CFF, flash evoked potentials showed increased latencies and reduced amplitudes in hypothyroid patients 6 weeks after thyroidectomy which were reversed after 8 weeks of treatment (16). Consistently, visual evoked potentials using

chequerboard reversal patterns showed reversible increases in latencies and reductions in amplitudes in hypothyroidism (17, 19–21, 23, 24, 71–73). However, this increase in latency is not consistently observed in all cases of hypothyroidism and thus it is still controversial after which duration and or severity of hypothyroidism significant increases in latency can be observed (74). Nevertheless, blink reflex prolongation could be consistently observed in hypothyroid patients confirming a slowing in visual pathways in adult onset hypothyroidism (75). From the available studies no definitive conclusion concerning the targets for thyroid hormone action in the visual pathways can be drawn. Thyroid hormone could already effect photoreceptor sensitivity as well as increase the speed of impulse propagation and synaptic transmission in any of the following relay stations.

*Cognitive performance*

Several reports have described mental changes in hypothyroidism, ranging from difficulties to perform simple calculations to memory impairments and finally to hallucinations (76–79). Although these impairments are probably the most troublesome symptoms for the patients, it has been difficult to quantify cognitive problems in adult-onset hypothyroidism. Daytime sleepiness as well as mental and physical fatigue are complaints in 70 - 80% of the hypothyroids (80, 81). Disturbances of sleep during thyroid dysfunction might account for some of the problems delineated above, as the different sleep stages are necessary for memory consolidation (82, 83). Sleep fragmentation in hypothyroids is not necessarily caused by nocturnal breathing disorders (sleep apnea) (84, 85).

The trail making test, which tests skills including vigilance, concentration, visual scanning and visuomotor tracking speed was shown by Reitan (44, 86) to respond to different types of organic brain damage. Later on slowed performance on the trail making test (part B) was shown in hypothyroid patients (78, 87). Subsequently Osterweil et al. (24) observed that the performance for Trail A was significantly slowed in old and very old hypothyroid patients as compared to age-matched controls and Wahlin et al. (88) reported that TSH was predictive for Trail-B in very old persons. Our finding of a non-significant slowing in the trail making tests confirms the observation of Osterweil et al., that carcinoma patients off thyroid hormone replacement show no statistically significant differences in test performance compared to euthyroid controls. However, 5 of the six persons tested showed an increase in performance when retested after hormone replacement, which escaped statistical significance because of the large scatter between the different individuals. This suggests that thyroid hormone withdrawal of longer duration is necessary before changes in this test become statistically significant.

Apart from this relatively simple test effects of thyroid hormone on more complex cognitive tasks have been investigated. The first measurement of an increase in the intelligence level by a mean of 20 I. Q. points of three adult myxedematous patients after three months of treatment with thyroid hormone has been reported by Crown (32). Especially in older hypothyroid persons, reversible decreases in the Folstein mini mental state score were found (24, 89, 90). In a double-blind study on adult persons with subclinical hypothyroidism out of 17 patients 4 showed improved performance on at least two and 7 test persons improved in

one of a reaction time, an object memory and a figure identification test after a six month period of thyroxine supplementation (33). Likewise, in subclinically hypothyroid adults the Wechsler Memory Scale indicated a significant decrease in logical memory (91, 92) as well as verbal and visual memory (93) (for a recent review see (94)) and severe hypothyroidism for a short time decreased working memory (43). Using fMRI changes in hypothyroid subjects during working memory tasks could be visualized (95). Finally also changes in the estimation of time spans have been observed in hypothyroid subjects (96). All these experiments were performed after a longer period of hypothyroidism or latent thyroid dysfunction. To be able to complete our test battery in a reasonably short time we designed a short tests for calculation and visual-spatial performance. Our present results indicate that a severe hypothyroidism of a short duration already causes significantly slowed performance in a visuo-spatial orientation task. This is in line with findings of increased latencies of event-related evoked potentials in hypothyroidism (97, 98).

*Perception of smells*

Although perversions of taste and smell during myxoedema have already been noticed in the first descriptions of this disease (99, 100) there have only been a few investigations on this subject, which provided no clear answers concerning the prevalence of olfactory disorders during hypothyroidism. Reversible increases in the threshold of smell and taste have previously been found in hypothyroid subjects (30, 31, 101). In addition to the reduced threshold, hypothyroid persons rated bitter and salty tastes as more agreeable than euthyroid control persons in the latter study. Interestingly, a more general study concerned with smell and taste disorders reported a more than average complaint of patients taking levothyroxine about a loss of the sense of taste. The investigation of these patients revealed, in contrast to their subjective impressions, higher scores on a taste-identification test. Additionally, the patients taking thyroxine perceived a test concentration of coffeine as having a greater intensity as the other patients, without showing significantly different taste thresholds (102). The discrepancy between subjective impression and test results could have resulted from increases in thresholds of taste preceding hormone substitution resulting in an increased awareness of the sense of smell. A study of taste thresholds, measured in 11 hypothyroid subjects after total thyroid ablation, which had stopped taking replacement for 4-8 weeks prior to a $^{131}I$ scan showed no increases in recognition thresholds to NaCl and urea (103). These patients showed, however, a decrease in intensity rating for the two tastants and less dislike to both substances at higher concentrations as compared to control subjects. Although the authors conclude that hypothyroidism probably has to persist for a longer time in order to develop more pronounced changes in taste, the preference and intensity rating tests could indicate the beginning of changes in taste after this period. Our present findings of an insignificant tendency towards a higher threshold of smell for both odours in the hypothyroid compared with the euthyroid subjects are in line with the assumption of a beginning loss of taste and smell after 4 weeks of hypothyroidism. In contrast, however, a study by Lewitt et al. (104) found no significant changes in the thresholds for taste and smell even in longer standing hypothyroidism. Since this study, in addition, reported no increase in the latencies of visual evoked potentials, in contrast to seven other available reports, it could

be possible, that the discordant findings of this report were due to the high median age of the investigated subjects (61 ± 16 years) which could already have displayed age-dependent declines in sensory function. In addition, the possibility exists, that only a fraction of the hypothyroid subjects shows changes in taste thresholds (105).

Possible causes of a loss in smell during hypothyroidism have also been investigated in rats. Here prolonged hypothyroidism has been shown to result in deficits in migration of olfactory receptor neurones while the mitotic rates of basal cells remained unaltered in postnatal (106) as well as in adult rats (107). The effects of propylthiouracil (PTU) – induced hypothyroidism were reversed by thyroxine therapy. Further experiments could, however, not confirm increases in the threshold to olfactory and taste stimuli in adult rats rendered hypothyroid with PTU for 5 weeks (108, 109) in which only changes in taste preferences for sour, bitter and salty, not of detection threshold were found. Additional confusion arose from several case reports describing thyreostatic drugs to also induce decreases in the sense of taste and smell in patients (methylthiouracil, - (110); methimazole - (111); thiamazol and carbimazol, (112–114). Sometimes, only the sensation of taste, sometimes also olfaction was impaired. Some patients could have actually become hypothyroid, but in some patients no other symptoms of hypothyroidism were noted and the symptoms did not reappear during thyroidectomy-induced hypothyroidism (110). A histological examination showing destruction of the olfactory epithelium, sparing the basal cells already after 32 hours of methimazol administration to rats further substantiates the possibility of toxic effects of antithyroid medication (115), which lead to apoptosis of rat olfactory receptor neurons (116). However, in studies of methimazol toxicology effects of hypothyroidism should be carefully excluded. Likewise, we cannot presently exclude, that changes in taste, which have been reported to occur frequently in patients as side effects of a high dose $^{131}$I therapy (117) could also have resulted to some extent from the accompanying hypothyroidism, which also has been reported as a potential cause of a "bourning mouth symptom" (118).

*Hearing*

Impairments of hearing have long been reported to occur in hypothyroidism (for reviews see (27, 119)). The incidence of decreases in hearing threshold observed in hypothyroid patients varies from study to study, ranging from 85% (28), 80% (29), 62% (120), 55% (121) 43% (122), 31% (80) to as low as 12% [98].

The only study showing no evidence of reversible hearing losses in hypothyroid patients (123) was performed on old patients between 61-92 years, in which the effects of presbyacusis may have a stronger effect on hearing threshold than those of thyroid hormone. The most dramatic hearing impairments arise if the thyroid hormone supply is insufficient during development, where irreversible structural impairments in the cochlea, presumably a disruption of the smooth fit of the tectorial membrane to the hair cells occurs (see e.g. (124–126). While a thyroid-hormone induced selective expression of neurotrophin-receptors could underly the morphogenetic changes shaping the inner ear (127) the acceleration of the expression of a fast potassium conductance (128) and the development of rapidly activating $Ca^{2+}$- and voltage-activated K+ (BK) conductances in inner hair cells (129)

could be necessary for the proper development of cochlear sensory transduction. Furthermore, hypothyroidism causes delays in the development of synaptic inhibition in the auditory brainstem (130). In line with a larger susceptibility of the immature auditory system to thyroid hormone deficiency Heinemann (131) reported no case of hearing impairment in 23 patients with primary hypothyroidism if treated in time but in 4 out of 7 cases if hormone substitution had been delayed. Besides the irreversible effects of thyroid hormone on the development of inner ear function, reversible changes of hearing acuity have already been described in early reports on the symptoms of adult-onset hypothyroidism (132, 133). Improvements of hearing threshold with treatment in some patients with hypothyroidism have since been shown with pure tone audiometric testing (25, 28, 29, 134, 135). Especially noteworthy in this context is the finding, that in 7- 11 year old, normal, but latently hypothyroid schoolchildren living in endemic areas of severe iodine deficiency iodine prophylaxis led to an average improvement of hearing (30 children tested in each village) by 15 db over the course of three years (136). Smaller changes in hearing threshold were reported after a total thyroid hormone withdrawal for a few weeks: 6 - 12 weeks after hormone withdrawal Post (137) reported 26 normal audiograms, decreased hearing thresholds which did not reverse after 3- 12 months of treatment in 5 patients and small, partially subjective improvements with hormone substitution in 4 patients from a total of 35 patients. No acute changes in hearing were also found by Mra and Wax (138) in 10 patients 2-6 weeks after total thyroidectomy. In contrast, Rubenstein et al. (120) described a case of a reversible hearing loss of 20 dB in a 5 year old child, that had been induced by stopping thyroid hormone therapy for four weeks. Another case report, where audiometric investigations were available 2 months before thyroidectomy a high frequency hearing loss started on the 40$^{th}$ day of hormone withdrawal, which was partially reversible after hormone substitution (139). These inconsistent findings correspond to our results of borderline significant increases in hearing thresholds of about 8 dB for high frequencies after 4 weeks of thyroid hormone withdrawal.

Animal experiments showed that in guinea pigs thyroid ablation caused decreased amplitudes of cochlear microphonic potentials (140) and cochlear action potentials of decreased amplitudes and increased delay when recorded four to eight months after administration of an ablative dose of radioactive iodine (124). Likewise, increased hearing thresholds have been observed in adult guinea pigs (125) at high frequencies of 8kHz (141) after 120 days of hypothyroidism. In contrast, Ritter (26) measured only deafness in five out of 166 experimental rats rendered hypothyroid on the 21st day of life. Interestingly, changes in the number of spines/per shaft of pyramidal neurones (indicating synaptic densities) could be shown in the auditory cortex of adult rats thyroidectomized at 120 days of age and investigated 120 days later (142). The authors note that in auditory pyramidal cells these changes develop much more slowly than in pyramidal cells of the visual cortex, which could indicate that the adult auditory system may respond to hypothyroidism on a slower time scale than the visual system. Perhaps these considerations could also explain why, in contrast to visual evoked potentials which consistently show slowing in hypothyroidism, some authors found no changes in auditory evoked potentials (24, 143) while other studies (18, 21, 22) found reversible increases in latencies of auditory evoked potentials in hypothyroidism.

Taken together, the auditory system may lose its sensitivity to thyroid hormone with increasing age and this may also depend on an individual susceptibility. In addition, effects on hearing may develop only after a thyroid hormone withdrawal for more than five weeks in the adult.

*Effects of thyroid hormone on sensory perception and brain function*

The present tests performed on a small number of patients indicate that the most prominent symptom after 4 weeks of thyroid hormone withdrawal is a beginning decline in the speed of central neuronal information processing, which was reflected in decreases in the speed of visual perception, speed of speech as well as of visual-spatial orientation. Hearing and smelling thresholds were only slightly changed, and in the context with the publications discussed above this indicates that auditory and olfactory perception may change only with thyroid dysfunctions of longer duration or are more sensitive to thyroid hormone in development. The experiments illustrated here complement previous findings, that hypothyroidism slows peripheral conduction velocity (144), reduces EEG frequencies and increases latencies of evoked potentials (73). The conception that thyroid hormone deficiency causes a general decrease in neuronal excitability was recently supported by the observation of a decreased cortical excitability and increased motor thresholds using transcranial magnetic stimulation in adult patients (145). Accordingly, in a small percentage of epileptic seizures in humans (146) thyrotoxicosis was identified as sole cause of the seizures and the seizures were found to fully subside after restoration of euthyroidism, again indicating an effect of thyroid hormone on cortical excitability. An increased susceptibility to seizures was also noticed in hyperthyroid animals such as cats (147) and mice (148).

## 5. Explanations of thyroid hormone effects on the brain at the molecular and cellular level

Owing to the complex actions of thyroid hormone there is currently no concluding explanation concerning the molecular mechanisms underlying the effects of thyroid hormone on cortical excitability. At the morphological level, in the mature brain thyroid hormone excess (149) as well as deficiency (150) have been reported to decrease the number of dendritic spines, assumed to represent postsynaptic endings, already after 5 days in adult rats. Even more dramatically, hypothyroidism leads to a reduction of the neuropile in CA1 and CA3 hippocampal areas and in addition to a loss of pyramidal cells in the CA1 area (151). Thus it seems possible that adult-onset hypothyroidism may actually cause neuronal degeneration, as already occasionally observed in autopsies of early cases of patients who had died with myxedema (152, 153). A reversible shrinkage of neuropile could also explain the findings of reversibly widened ventricular spaces in the brains of hypothyroid subjects (154, 155).

The development of cholinergic terminals in rat forebrain, hippocampus and amygdala is regulated to a considerable extent by thyroid hormone (see e.g. (156)). Although smaller and more localized effects are reported in adults, several lines of evidence suggest that acetylcholine -release may be enhanced by thyroid hormone and decreased in hypothyroidism in the adult nervous system as well (157, 158). A decrease of cholinergic activity could perhaps

also explain the occurrence of slow EEG waves (159) as well as the cognitive impairments frequently seen in hypothyroid subjects. A regulation of cholinergic function also fits to the observation of a regulation of nerve growth factor which has been suggested to be involved in maintaining the function of cholinergic hippocampal projections by thyroid hormone in adult rat brain (160). Thyroid hormone, however, does not seem to interfere exclusively with cholinergic forebrain neurons but to regulate the balance of a variety of other neurotransmitters in a region-specific manner. Hence dopamine levels were found to be increased in the midbrain of hyperthyroid rats (161) and decreased in hypothyroid rats (162). Also the dopaminergic input into striatal neurons could be upregulated by thyroid hormone (163). Furthermore, a differential regulation of serotonin levels (162, 164) as well as 5-$HT_2$ receptors have been found (165). Regulations of various adrenoceptors as well as GABA-receptors have been described see e.g. (166–168). In addition T3 could act as a cotransmitter to modulate noradrenergic action (169) or as a modulator of endogenous benzodiazepine action (170). While it is believed that thyroid hormone exerts its effects predominantly via nuclear receptors possible direct effects on membrane receptors further complicate the picture (157, 171, 172). In addition to a membrane action via $\alpha V\beta 3$intergins, high doses of 20 μM T3 or T4 have been shown to directly act on GABA receptors to down-regulate GABAergic postsynaptic currents in cultured hippocampal neurons (173, 174), which could explain acute increases in neuronal excitability induced by iontophoretecally injected T4 and T3 (171). Although the regulatory influences exerted by thyroid hormone are complex it seems that T3 regulates to some extent the release of neurotransmitters such as acetylcholine, dopamine, 5-HT and noradrenalin in specific pathways as well as the density of the corresponding receptors (166).

A stimulating effect of thyroid hormone on transmitter synthetic enzymes or precursor-uptake systems as well as the protein synthesis of the receptors could in principle explain the decrease in cerebral responsiveness in hypothyroid subjects. Furthermore, a down-regulation of postsynaptic inhibitory currents in hyperthyroidism, as suggested by Puia and Losi (174), could account for the increased irritability seen in hyperthyroid subjects. A diminished postsynaptic current density due to a decrease in transmitter release or receptor density or activation could also explain some of the increased latencies since a smaller current density would lead to a delay in the charging of the membrane capacitance. However, investigations using transcranial magnetic stimulation provided evidence that in hypothyroid patients the cortical excitability as such is decreased (145). Furthermore, experiments on peripheral nerves of hyperthyroid rats indicated enhanced afferent spikes and a drop in the chronaxia for direct activation of action potentials in rat peripheral nerves (175). Hence thyroid hormone could also influence neuronal excitability directly, which could secondarily result in a decrease in transmitter release.

*Changes in conduction velocity, action potential waveform and the regulation of voltage-gated ion currents by thyroid hormone*

Changes in Achilles tendon reflexes and the slowing of peripheral conduction velocity in hypothyroidism have so far mostly been explained by a reduction in myelination, and the gene for myelin basic protein is, in fact, regarded as one of the few genes known to be directly regulated by thyroid hormone (for review see (176)). However, a decrease in

sodium current density could as well explain the decreases in peripheral conduction velocities and increases in latencies of evoked potentials found in hypothyroidism (16–24) and reversely the increased amplitudes in hyperthyroidism (177, 178). Since there seems to be an optimal density of sodium channels that ensures maximal neuronal conduction velocity (179), beyond which no further increase or even a slowing of conduction velocity occurs, an upregulation of sodium currents by thyroid hormone could also explain the inconsistent findings concerning latencies of evoked visual potentials in hyperthyroidism, where some authors found decreases in latencies (180) or even increases with increases in thyroid hormone (21, 71, 177, 178). Because of the temperature sensitivity of the activation of sodium and calcium currents the fall in core temperature during hypothyroidism and its increase in hyperthyroidism could further exacerbate the symptoms (19).

*Influences of thyroid hormone on action potentials and underlying ion currents in the heart*

Evidence that thyroid hormone could indeed change action potential waveforms became available from electrical recordings performed in ventricular cells from guinea pig hearts, that showed decreases in action potential length in the course of hours after application of thyroxine, which then gradually recovered over the course of days (181). In line with these observations, prolongations of action potential durations were observed in hypothyroid rat heart cells (182) and guinea pig ventricular myocytes (183). That thyroid hormone directly effects the electrical properties of heart cells, and not just alters sympathetic receptors was shown by Valcavi et al. (184), who demonstated an increase in the intrinsic activity of the sinus node in hyperthyroid patients that persisted after chemical blockage of autonomous innervation. Patch clamp recordings revealed that in heart cells from neonatal rats (185, 186) and in cat atrial myocytes (187), acute applications of 5-20 nM T3 increased voltage activated sodium currents. Single channel recordings revealed that the application of 5-50 nM T3 induced bursting of $Na^+$-channels in rabbit ventricular myocytes (188). Later studies showed, that T3 increases the sodium channel open probability by binding directly inside the membrane and that the interaction with a pertussis toxin sensitive G-protein greatly enhances this effect (189). More recent experiments by Schmidt et al. (190), confirmed rapid effects of T3 on human hearts, however, suggesting a contribution of the sympathetic nervous system. After a period of prolonged hyperthyroidism in rats, in contrast to acute effects, no changes in $Na^+$current density as well as of inward potassium currents were found. At that time increased rates of rise of the action potentials could be rather explained by an increase in $Ca^{2+}$-currents and a shortened action potential duration by an increase in a delayed rectifier current (191). Although it is presently not completely understood, which channel regulations exactly determine short and long term effects of thyroid hormone, it is safe to conclude, that an upregulation of voltage activated $Na^+$-, $Ca^{2+}$ and $K^+$-currents plays a pivotal role in decreases in action potential duration, the acceleration of the heart beat and modulation of contraction amplitude by thyroid hormone.

*Influences of thyroid hormone on action potentials and underlying ion currents in the central nervous system*

The influence of thyroid hormone on the electrical properties of neurons has been studied in less detail. The first experiments using whole cell patch clamp recordings were carried out on cultured postnatal rat hippocampal neurons and showed an upregulation of voltage-

gated $Na^+$-currents ($I_{Nav}$) by T3 (192). An upregulation of the density of voltage-gated $Na^+$ currents was also found in acutely isolated neurons from the occipital cortex of hyperthyroid rats and a down regulation observed in cells from hypothyroid rats. The changes in $Na^+$current density led to increased action potential upstroke velocities as well as to enhanced discharge rates in thyroid hormone treated cells in response to identical stimulus strengths (193). Similarly, increases in voltage-gated $Na^+$ currents were observed in human neuroepithelial cells as well as mesenchymal stem cells after incubation with 1 nM T3 for 72h to 6 days in culture. Neuroepithelial cells additionally responded with increases in $Ca^{2+}$ currents to prolonged T3-treatment (194). In the in *vivo* situation thyroid hormone effects seem to be more complex: Thus in CA1 neurons of the rat hippocampus changes in the bursting pattern have been observed, which could be explained by an upregulation of a low-threshold $Ca^{2+}$ current (195). Furthermore, consistent with Hoffmann and Dietzel, 2004, decreases in action potential depolarization rate and decreases in discharge rate were observed by thyroid hormone withdrawal. In contrast to the action of thyroid hormone in the heart these authors additionally observed a shortening of action potental duration upon thyroid hormone withdrawal, that could be explained by the upregulation of an A-type potassium current (196). Finally in a somewhat distant animal, in Rohon-Beard neurons from the embryonic zebrafish rapid increases of voltage-gated $Na^+$currents by thyroxine were found (197). This $Na^+$current regulation was shown to be essential for the further development of the embryo and depended on $\alpha V\beta 3$ integrin activation and the MAPK (p38) pathway (198). An increase in voltage-gated $Na^+$current density by thyroid hormone would cause a general speeding of mental functions as illustrated in figure 5:

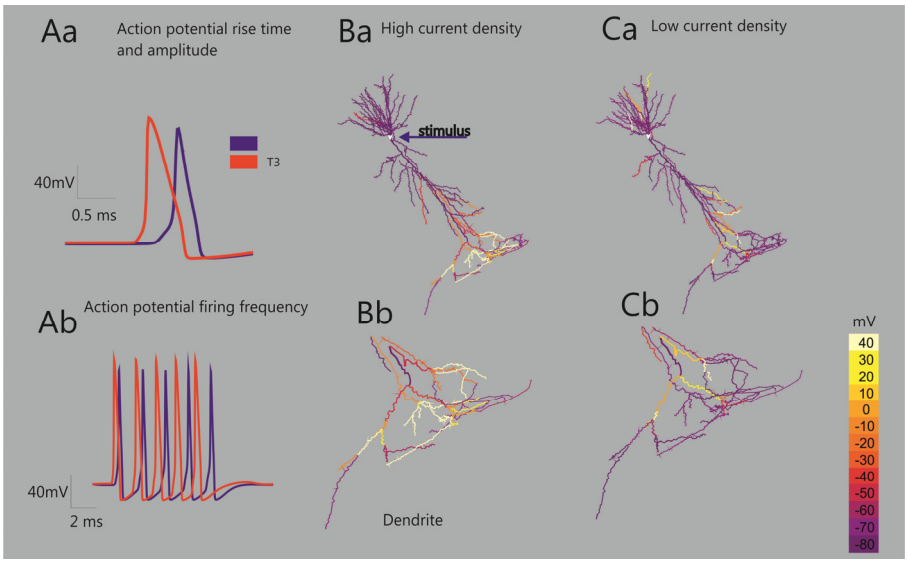


**Figure 5.** Simulation of action potential spread in a hippocampal model neuron, for action potential with high (A-red) and low (A-blue) $Na^+$-current density. A an increase in $Na^+$current density increases action potential depolarization (Aa), amplitude and discharge frequency (Ab). B. Simulation of action potential spread in a ramified neuron 1 ms after application of a stimulus at t=1ms.

B shows the spread for the neuron with high current density and B for the neuron with low current density. The magnified inserts (Ba and Cb) clearly show, that the overshoot of the action potential (light colours) reaches the synapses much earlier in the cell with high current density than in the cell with lower current density (Cb). Simulations performed using the Hodgkin-Huxley equations and the program Neuron version 3.2.3 (199).

Hypothyreosis also affects a prominent EEG pattern, namely the alpha rhythm (11–15). This may be also related to altered $Na^+$ channel function, since TTX-insensitive $Na^+$ currents of cortical bursting neurones have been implicated in the generation of the alpha rhythm (200). Subsequently, the presence of SCN5A mRNA, encoding the TTX-resistant $Na^+$ channel had been demonstrated in the mammalian brain (201, 202).

It is noteworthy that the mental symptoms observed with the psychophysical tests used in the present study developed gradually, as most prominently demonstrated in the continuous observations on a single person and only recovered with a similar slow time course in the first weeks of hormone resubstitution (see Fig. 1D and 2A). Prolonged recovery phases for the reversal of several of the symptoms accompanying hypothyroidism have been described (20, 84, 203–205) and subjective improvements of well-being, quantified with a "Quality of life-Thyroid scale" were found only after four weeks compared to one week of thyroid hormone replacement (38).

This corresponds to the observation of a lack of acute effects of T3 in hippocampal slices (206) and the observation of a slow upregulation of $Na^+$current density in hippocampal cultures (207). In the later study the $Na^+$current regulation was shown to depend on the presence of glial cells in the culture medium. Thyroid hormone has been shown to induce protein secretion from glial cells (208), including *basic fibroblast growth factor* (FGF-2) (209) and *epidermal growth factor* (210). Furthermore, thyroid hormone has been shown to elevate *nerve growth factor*, *neurotrophin-3* and *brain derived neurotrophic factor* (BDNF) in the brain (see e.g.(211)). A first indication that intermediate steps, including growth factors could be involved in the regulation of $Na^+$currents by thyroid hormone were experiments, that showed, that the effect of T3 on $Na^+$ currents could be reduced by a simultaneous incubation of cultures with antibodies against FGF-2, leading to the hypothesis depicted in Figure 6.

Concerning the action of thyroid hormone on neuronal excitability there seems to be a common finding that the density of voltage-gated $Na^+$currents is up-regulated by thyroid hormone rendering the cells more excitable. This mechanism would explain many of the symptoms observed in thyroid disease, such as slowed peripheral conduction velocity and decreased excitability of the hypothyroid brain. In other tissues, such as various epithelial cells, thyroid hormone could, likewise, play an essential role in the regulation of the expression of amiloride sensitive, epithelial $Na^+$channels (see e.g. (212)). The molecular mechanisms, leading to $Na^+$current upregulation, may however, differ in different species and tissues and warrant further elucidation.

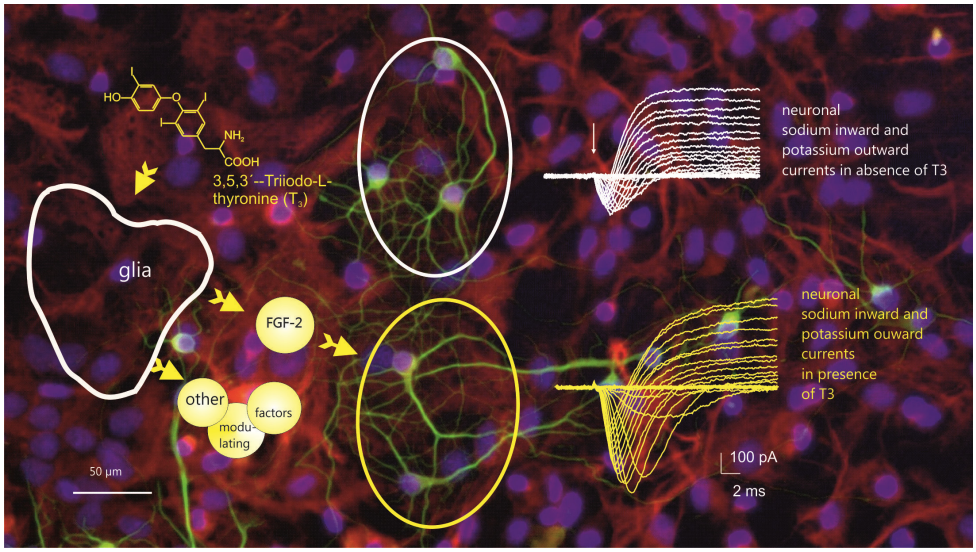


**Figure 6.** Illustration of a potential mechanism leading to $Na^+$-current regulation in the hippocampus of rats: T3 stimulates glial cells (stained red by antibodies against GFAP) to secrete growth factors (such as FGF-2) which in turn up-regulate $Na^+$currents in neurons. (stained green by antibodies against βIII tubulin). Thus in addition to regulating the neuronal environment and stimulating synapse formation glial cells could also be involved in modulating neuronal excitability.

*Regulation of $Na^+/K^+$-ATPase expression by thyroid hormone*

Since thyroid hormone has long been known to increase energy expenditure, and about 40% of energy at rest is consumed by activity of the $Na^+/K^+$-ATPase (36, 37, 213) many researchers focused on studying effects of thyroid hormone on $Na^+/K^+$-ATPase activity and expression. The $Na^+/K^+$-ATPase is a heterodimeric membrane spanning protein complex composed of three catalytic alpha subunits (α1, α2 and α3) with molecular weights of ~97-116kDa and two glycosylated β subunits (β1 and β2 of ~35-55kDa). While the α subunits contain the $Na^+$, $K^+$ and the intracellular ATP binding site, the β subunits are required to insert the catalytic α subunits into the appropriate locations of the cell membrane (214). An intracellular $Na^+$ load of the cell leads to binding of three Na-ions to their intracellular binding sites, thus triggering phosphorylation of the α subunit and inducing a conformational change of the pump to expose the Na-ions to the extracellular surface at the expense of ATP (see e.g. (37)). Thus an increased intracellular $Na^+$-load, as induced by a larger or longer $Na^+$ influx will increase energy consumption by stimulating the demand for ATP. Interestingly, the $Na^+/K^+$-ATPase shows a 10-12 fold increase in expression during postnatal development of the brain (215) which parallels the postnatal increase in $Na^+$ current density (216).

The different isoforms of the $Na^+/K^+$-ATPase were reported to be distributed in a cell and tissue dependent manner. Thus in brain tissue the α3 isoform transcript is expressed abundantly in comparison with the mRNA for the α1 and α 2 subunits. The α3 expression

increases 10 fold within the first 7 days after birth and remains at this elevated level until the 55th day of age in the rat. In contrast, the mRNA for the $\alpha$1, $\alpha$2 and $\beta$ isoforms reach their maximal expression levels only after the rats are at 25 days old (215).

In general, thyroid hormone was found to up-regulate $Na^+/K^+$-ATPase activity and expression in many tissues: For instance, in rat cardiomyocytes, T3 was observed to increase the mRNA pattern of $Na^+/K^+$-ATPase $\alpha$1 and $\beta$1 subunits 4fold after 48hrs and the $\alpha$2 mRNA expression even 7fold after 72hrs of treatment (217). A similar effect of T3 was found in a rat liver cell line. Here, a non transformed continuous cell line derived from adult rat liver treated with T3 showed a 1.3 fold increased activity of $Na^+/K^+$-ATPase. More specifically, the mRNA expression of the $\alpha$1 and $\beta$1 isoforms of the $Na^+/K^+$-ATPase increased 1.5 and 2.9 fold respectively compared with controls maintained in T3 free (hypothyroid) media (218).

In rat brains thyroid hormone has been shown to up-regulate $Na^+/K^+$-ATPase activity and protein expression in synaptosomes only in the first two postnatal weeks (219). In addition Schmitt *et al.,* in 1988 showed that the hypothyroid condition reduces the expression of the mRNA for $Na^+/K^+$-ATPase $\alpha$ isoforms in rat brain (220). However, observing thyroid hormone effects in identified brain regions in the adult rat indicated, that hypothyroidism could down-regulate $Na^+/K^+$-ATPase activity in specific brain regions, such as the adult hippocampus (221, 222). Further experiments showed that the predominant brain cell specific $\alpha$3 isoform of the $Na^+/K^+$-ATPase decreased in hypothyroid rat brain as well and that the relative sensitivity of the different $Na^+/K^+$-ATPase $\alpha$ subunits in brain cells for thyroid hormone is $\alpha3>\alpha1>\alpha2$ (223). The expression of all $Na^+/K^+$-ATPase isoforms and their regulation by T3 was also observed in primary neuronal cell cultures of rat brain at the mRNA and protein level using northern and western blot techniques (224). In contrast to neurons, glia cells express $\alpha$1, $\alpha$ 2 and $\beta$1, 2 not $\alpha$3. The mRNAs as well as the proteins of the four subunits expressed in glia cells showed an upregulation when the cells were grown with the supplement of T3 for 5 and 10 days respectively (225).

Although a T3-responsive element has been found in the promotor region of the $\alpha$3 subunit (226) two reports on muscle cells indicate, that the regulation of the $Na^+/K^+$-ATPase by thyroid hormone might be at least to some extent secondary to an enhanced sodium influx. Thus Brodie and Sampsom (227) observed that a blockage of $Na^+$-influx by tetrodotoxin to block the voltage-gated $Na^+$currents or by amiloride to block further $Na^+$transport routes both reduced the T3-induced increase of $^3$[H]-ouabain binding sites, which represent membrane inserted $Na^+/K^+$-ATPase in cultured myotubes. These results were confirmed by Harrison and Clausen (228) in skeletal muscle, who showed that an increase in saxitoxin binding (reflecting $Na^+$channel density) preceded an increase in $^3$[H]-ouabain binding (reflecting membrane inserted $Na^+/K^+$-ATPases). These experiments indicate a link between $Na^+$ current regulation and the regulation of the $Na^+/K^+$-ATPase by thyroid hormone. This is in agreement with other experiments in chick skeletal muscle that suggested that the activation of voltage-gated $Na^+$channels by veratridine leads to an increased biosynthesis of $Na^+/K^+$-ATPase in chick myogenic cultures (229). Whether these findings also apply to neurons, or whether some subunits are regulated directly by thyroid hormone receptors and others are regulated by the sodium load of the cells remains, however, to be clarified.

## 6. Conclusions

Thyroid hormone deficiency leads to a general slowing of many body functions, including a slowing of heart rate, a slowing of intestinal movements as well as of thoughts and movements. As demonstrated here in an exemplary fashion on a small sample of patients the most conspicuous symptom to develop during a short period of severe hypothyroidism is a gradual, quantifiable slowing of speech and of critical flicker fusion frequency. Although several explanations at the cellular and molecular level are feasible an intriguing hypothesis is, that a central aspect of the origin of many of these symptoms might be a regulation of the sodium current density that is a key player of neuronal and cellular excitability. In fact, some effects of thyroid hormone can to some extent be blocked by the sodium channel blocker TTX: Thus the upregulation of the membrane $Na^+/K^+$ATPase expression in myotubes (227) and skeletal muscle (228) as well as of soma growth in L-GABAergic neurons (230) by thyroid hormone were all to some extent blockable by TTX, suggesting that some effects of thyroid hormone occur downstream of sodium channel regulation. In future it will be exciting to elucidate the full signal cascade involved in the regulation of the different sodium channel subunits as well as to conclusively sort out the primary and the secondary targets of thyroid hormone action. It will be interesting to study whether some of these thyroid hormone actions decline in the aging brain.

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## 7. Acknowledgement

V. Niederkinkhaus and S. Mohanasundaram were supported by fellowships from the International Graduate School of Neuroscience (IGSN) at the Ruhr University. We want to thank U. Eysel, the Physiological Institutes of the Universities of Bochum and Würzburg for lending us a luminance meter and audiometers, N.E. Meyer for help with the design of the visual-spatial orientation test, and H. Schatz, R.A. Deisz, M. Kreissl and B. Igelhorst for many helpful discussions.

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