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Elimination of the color discrimination impairment along blue-yellow axis in patients with hypothyroidism after treatment with Levothyroxine as assessed by the Farnsworth Munsell 100 hue test

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Abstract: Our previous study has shown that individuals with untreated hypothyroidism display significantly higher partial error scores (√PES) along the blue-yellow (B-Y) axis compared to the red-green (R-G) axis than normal individuals, using the Farnsworth-Munsell 100 hue test (FM-100 test) [J. Opt. Soc. Am. A, 37, A18 - A25 (2020)]. We wished to determine how color discrimination may change when hypothyroidism has been treated to the point of euthyroidism. Color discrimination was reassessed for 17 female individuals who had undergone treatment for hypothyroidism, and the results were compared with 22 female individuals without thyroid dysfunction. No statistically significant difference was found in the total error score (√TES) for the first and second measurement for both groups ($p > 0.45$). The √PES for the hypothyroid group improved significantly in the previously impaired color regions after the treatment. Color discrimination defects found in untreated hypothyroidism can be negated with treatment of the condition over an appropriate time period.

1. Introduction

Hypothyroidism is a condition of reduced thyroid function, which leads to insufficient synthesis or lack of thyroid hormones (THs), such as thyroxine or tetraiodothyronine (T4) and triiodothyronine (T3). Acquired hypothyroidism can cause a variety of sensory deficits, including visual ones [1-4]. THs have been shown to affect the production of the visual pigment opsin in rodents and the deficits have been observed not only during perinatal development [5-8], but also after induced hypothyroidism in adults [9]. It is known that, unlike primates (including humans), mice and rats are dichromats. Their retinas have only S and M cones which contain UV/short-wave-sensitive (S-opsin) and middle- to long-wave-sensitive (M-opsin) photopigments. The induced hypothyroidism has not affected the structural development of the retinal elements, but there has been a change in the expression of the opsin, suppressing the expression of M-opsin and activating the expression of S-opsin [e.g. 9]. Cone differentiation and cone opsin expression in mice retinal development are known to involve thyroid hormone-activated transcription factor TRβ2, which suppresses the expression of S-opsin and induces the expression of M-opsin [10,11].

Although color research in people with hypothyroidism is still scarce, it has been shown that absence of TH causes color vision deficiencies in humans [12-16], mainly expressed along the blue-yellow (B-Y) axis [13-16]. In our previous study using the Farnsworth - Munsell 100 hue (FM-100) test, color discrimination was assessed in two groups of participants – patients with untreated hypothyroidism and a control group without thyroid dysfunction. We found a

significant impairment along the blue-yellow (B-Y) axis in the hypothyroid group compared to the control group, while the total error scores (TES) were similar in both groups [16]. It is not known if this color discrimination defect would reduce after treatment when individuals reach biochemical euthyroidism. There is limited research which considers this issue. Cakir et al. [12] studied color contrast sensitivity for letters along protan (R–G) and tritan (B-Y) axes in patients before and after 3 months of treatment with levothyroxine, when the hypothyroid group had achieved biochemical euthyroidism. The baseline color contrast sensitivity was lower in the patient group relative to controls for all colors. The contrast sensitivity improved after treatment mainly for red-green stimuli, while the difference between treated patients and controls for blue-yellow stimuli still persisted. The authors pointed out that the 3 months of treatment was probably too short to fully recover patients' color deficits. In addition, the control group was not re-examined for a second time, to exclude the possibility of learning effects. In a case report [13], it was found that the area of complete spatial summation (Ricco's area) for S-cone decrements (yellow) increased by between 3 and 10 times in a patient with hypothyroidism compared to normal individuals. After a prolonged state of euthyroidism after treatment with levothyroxine (7 years) the measurement was repeated and it was found that this finding had been reversed, i.e. no increase in Ricco's area for yellow stimuli was observed compared to the other participants. However, the limitation of this study was that the patient's hormonal status was not available at the first measurement (hypothyroidism was diagnosed at a later stage), although symptoms of hypothyroidism were present. Another limitation stems from the long period between the treatment and the second measurement.

The purpose of the present study was to determine whether the initial color vision impairment remains after treatment with synthetic thyroxine for an appropriate period of time. The assessment of color discrimination with the Farnsworth Munsell 100 hue test (FM-100 test) was repeated in both groups, patients and controls, after the hypothyroid group had been treated with levothyroxine for at least one year (between 12 and 24 months), and had reached biochemical euthyroidism.

2. Methods

2.1 Subjects

This longitudinal study recruited 39 female subjects, aged between 21 and 55, divided into two groups. The first group consisted of 17 individuals (mean age 41.1 ± 9.2 yr/range 23–55 yr) who were patients diagnosed with primary hypothyroidism (hypothyroid group), including Hashimoto's thyroiditis (n=16) and postoperative hypothyroidism (n=1). The second group were 22 age- and sex-matched subjects (mean age 42.0 ± 8.4 yr/range 21–54 yr) without thyroid dysfunction (euthyroid control group) (Table 1). The patient and control groups consisted of individuals who participated in the first measurement before the treatment of the hypothyroid group (Measurement 1) and who came back for the second measurement after the treatment (Measurement 2).All patients had their thyroid-stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) measured again in the same laboratory, before being subjected to the second measurement. Only patients who had reached biochemical euthyroidism took part in the present experiment. No statistically significant difference in hormonal status between patients in the second measurement and the control group was found (Table 1).The participants all had normal color vision on the Ishihara Test for Color Deficiency, 38 Plates Edition and The City University Color Vision Test, Third Edition, 1998. The ophthalmological examination of all subjects was performed before Measurement 1, which included retinoscopy, intraocular pressure, and visual acuity. Participants with ophthalmic diseases were not considered eligible for the experiments. Subjects who needed optical correction wore lenses or glasses that did not change the color or intensity of light. Only female subjects took part in the experiment to avoid gender bias.

Table 1. Characteristics of Hypothyroid and Euthyroid Control Groups during the first and second measurements.

Parameters	Hypothyroid group first measurement	Euthyroid control group first measurement	Hypothyroid group second measurement	Euthyroid control group second measurement	p value
Number	17 female	22 female	17 female	22 female	—
Age (years)	39.7 ± 9.2 (20-53)	39.6 ± 8.4 (18-54)	41.1 ± 9.2 (23-55)	42.0 ± 8.4 (21-54)	0.937[a], 0.589[c]
Mean TSH[1] (0,3 - 4 mlU/l)	14.5 ± 9.5	2.3 ± 1.1	3.0 ± 1.7	—	0.001[a], 0.001[b], 0.129[d]
Mean FT4[2] (9-23 pmol/l)	11.8 ± 2.3	15 ± 2.3	14.6 ± 3.2	—	0.001[a], 0.001[b] 0.137[d]
Mean FT3[3] (3.5–7 pmol/l)	4.6 ± 0.73	—	4.8 ± 1.0	—	0.996[b]
Anti TPO-At[4] positive, %	70.6%	—	—	—	—
Anti Tg-At[5] positive, %	76.5%	—	—	—	—

[1]Thyroid-stimulating hormone, [2]Free thyroxine, [3]Free triiodothyronine, [4]Anti-thyroperoxidase, [5]Anti-thyroglobulin. [a]hypothyroid group first measurement vs euthyroid control group first measurement; [b]hypothyroid group first measurement vs hypothyroid group second measurement; [c]hypothyroid group second measurement vs euthyroid control group second measurement; [d]hypothyroid group second measurement vs euthyroid control group first measurement.

2.2 Procedure

Color discrimination was reassessed in both patients and controls, using the FM-100 test, after the hypothyroid group was treated with levothyroxine for at least one year and all patients had reached biochemical euthyroidism. The measurements before (Measurement 1) and after treatment (Measurement 2) were conducted under the same conditions, described in detail in our previous publication [13]. Briefly, a color vision examination box specially designed in our institute [17] was used for both measurements. The test illuminance, color temperature, the procedure and data processing adhered to the original instructions [18]. The FM-100 test consists of four boxes containing a total of 85 colored caps. Each box contains two fixed anchor caps, one at the start and one at the end of each box. The observer was asked to arrange the caps in each box to produce a gradual transition of hue between the two anchor caps. The test was performed under a color temperature near to illuminant ”C”, close to the daylight illumination (6350 K). The test illuminance was between 285 and 295 Lux. The viewing distance was 45-50 cm. Pupil size was between 2 and 3 mm in diameter. Before starting the test, participants were dark adapted for 2 min and then adapted to the test illumination for 2 min. Following the original instructions [18], the subject had 2 min to arrange each box. Accuracy was also important, so if the time was exceeded, the subject was reminded that the two minutes had passed, but was allowed to finish arranging the box. The total error scores (TES) and partial error scores (PES) were recorded and square root transformation was used to avoid violation of

normality. Blue-yellow (B-Y) and red-green (R-G) PES were calculated according to Smith and Pokorny [19].

This study was approved by the Institute of Neurobiology Bioethics Committee. Prior to the experiments, informed written consent was obtained from all subjects. The study was performed in accordance with the tenets of the Declaration of Helsinki.

3. Results

The total error scores (√TES) before treatment (Measurement 1) and after treatment (Measurement 2) were compared for both the hypothyroid and the control groups. The paired samples t-test showed that no statistically significant difference existed between the mean √TES for Measurement 1 and 2 for both the hypothyroid ($t(16)=0.53$, $p=0.604$) or control group ($t(21) = 0.768$, $p = 0.452$), indicating no training effect.

We analyzed the distribution of the error scores in different hue intervals of the FM-100 test in rectangular format [16,20,21]. Figure 1 shows the mean PES for patients and controls for the Measurement 1 (Figure 1a), and the Measurement 2, after patient treatment (Figure 2b).

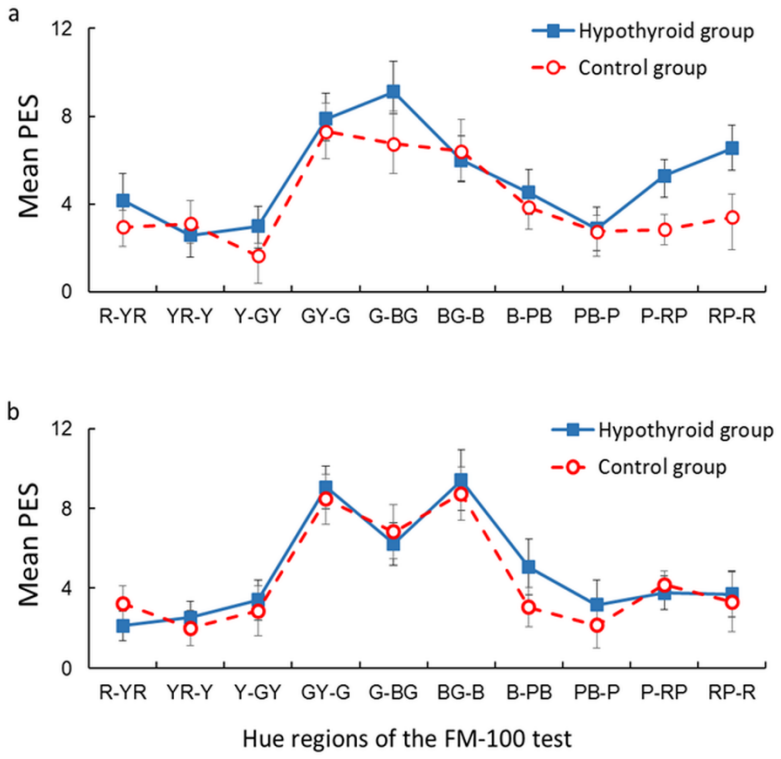

Fig. 1. Comparison between mean PES for patients and controls in different hue regions. (a) Measurement 1 and (b) Measurement 2. Vertical bars represent standard error of the mean score.

It could be seen that the effect of the treatment with levothyroxine is the improvement of the error scores in the green and blue-green (G-BG) hue regions and in the purple, red-purple and red and red-yellow (P-RP, RP-R, R-YR) hue regions which were significantly higher in the patient group. While the Measurement 1 showed well-pronounced bipolar axis formation in the

hypothyroid group, this tendency disappeared after treatment when the patients performed very similar to the controls. In fact, error score distributions overlapped almost completely over all hue regions.

As an additional illustration of the performance changes in the patient group after treatment, we analyzed the difference between the square roots of the B-Y and R-G partial error scores. The data are presented in Figure 2a for patients and Figure 2b for controls as a function of age. The graph clearly demonstrates that while the patient data lie mostly above the zero line before the treatment, indicating a formation of B-Y axis, after the treatment some of the points have shifted to form a more symmetrical distribution around the zero line. The data of the control group remain almost symmetrical around the zero line indicating similar performance along both axes in both measurements.

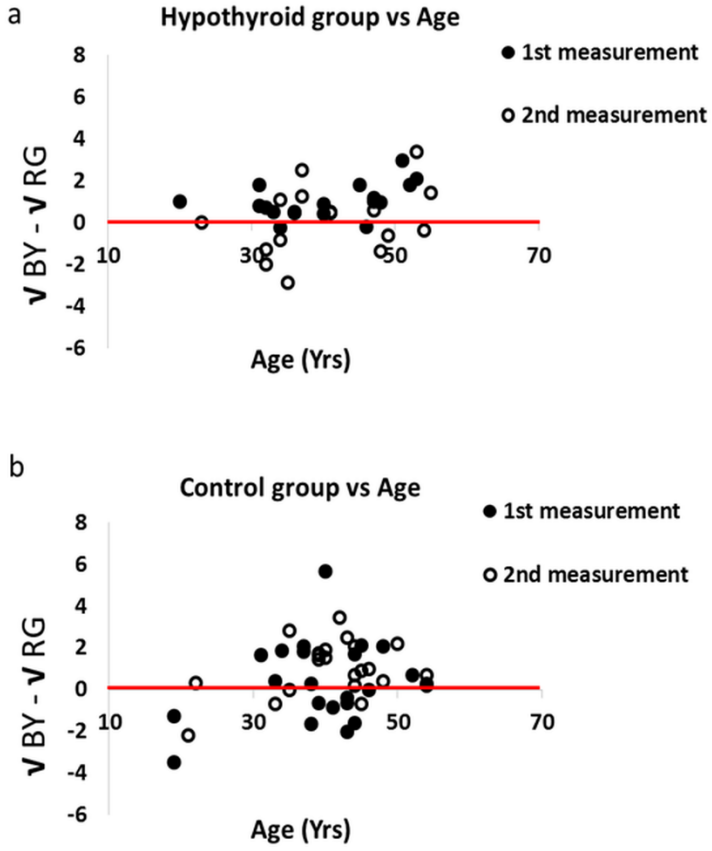

Fig. 2. The difference √B-Y -√R-G vs age for the hypothyroid (a) and control group (b) before (first measurement) and after (second measurement) treatment of the hypothyroid group.

Fig. 3 shows the original polar FM-100 diagrams for two of the patients before and after treatment. A characteristic change in the polarity of the diagrams after the treatment is seen in both subjects.

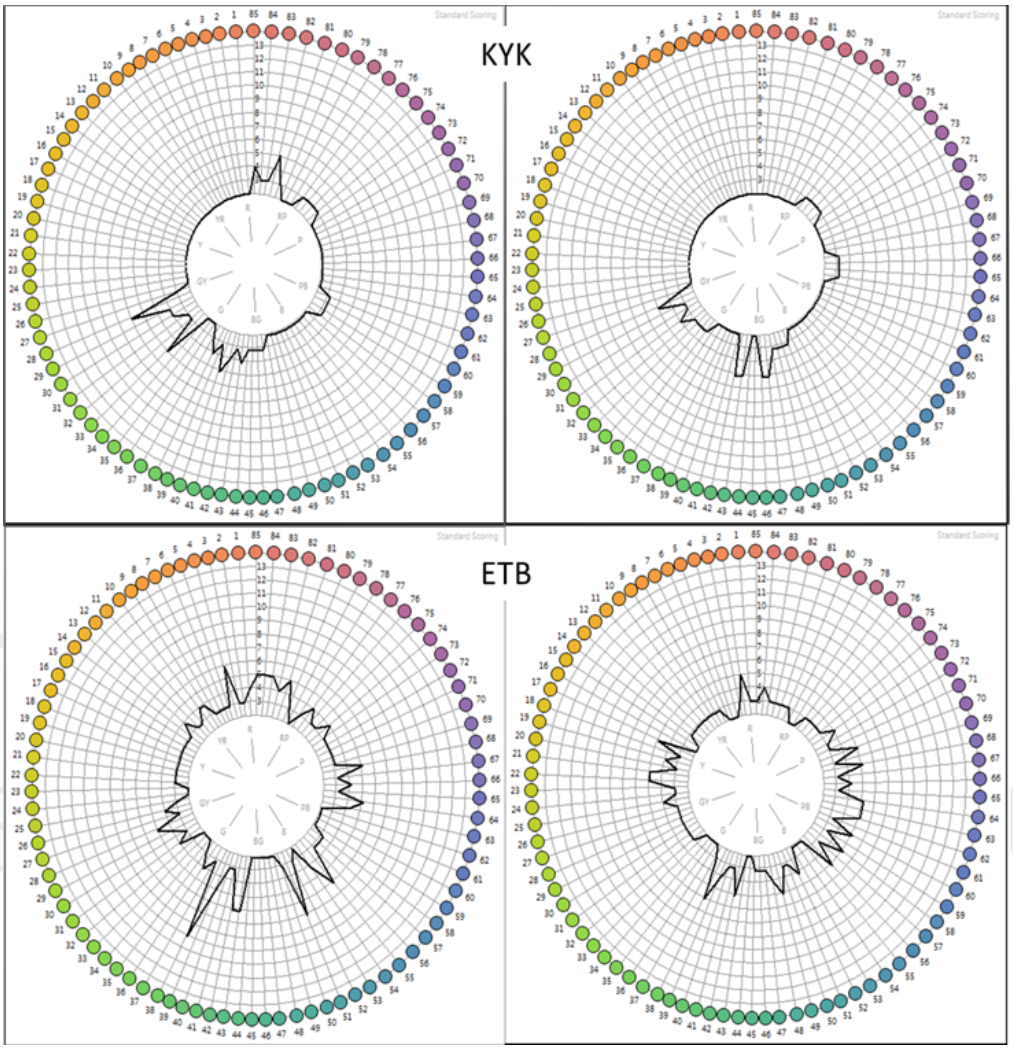

Fig. 3. Some examples of the original error score diagram of two of the patients. Left column - before treatment (first measurement); right column - after treatment (second measurement).

To test the statistical significance of the observed changes, the square roots of the partial error scores were subjected to three-way 2 x 2 x 2 repeated measure ANOVA with group, color axis (B-Y, R-G) and measurement order (Measurement 1, Measurement 2) as within-subjects factors. The analysis revealed no significant main effect of the group ($F(1,37) = 0.287$, $p = 0.595$), or color axis ($F(1,37) = 0.526$, $p = 0.473$), while the main effect of the measurement order was significant ($F(1,37) = 9.68$, $p = 0.004$), reflecting the changes observed in Measurement 2. None of the two-way interactions were significant (Group x Color axis: $F(1,37) = 0.19$, $p = 0.666$; Color axis x Order: $F(1,37) = 0.261$, $p = 0.612$; Group x Order: $F(1,37) = 0.027$, $p = 0.87$). The three-way interaction was statistically significant ($F(1,37) = 7.683$; $p = 0.009$) which indicates that some of the two-way interactions differ at the two levels of the third factor. The most notable change as it is seen in Figure 1 is that the patient performance in certain hue regions improves after the period of treatment as opposed to the lack of specific changes in the control group for both measurements.

4. Discussion

The present study demonstrates that treatment with synthetic thyroxine for at least one year significantly reduces the impairment in blue-yellow color discrimination, observed in patients with hypothyroidism to a level close to the control group performance. To our knowledge, this study is the first to show that such treatment can eliminate the observed color discrimination impairment. One previous study showed that a difference between thyroid and control group for B-Y stimuli remained after 3 months of treatment [12]. This defect appears to have been completely reduced in our study where treatment had been initiated for a significantly longer period of time. There are no data in the literature to report how long levothyroxine treatment should be in order to restore thyroid hormone levels in the human brain, but it could be that it takes longer for T3 levels to normalize in the central neural system. Based on the above suggestion and on the experimental data of Cakir et al [12], who did not observe complete recovery of color contrast sensitivity for blue and yellow after three months of hormone replacement therapy, we chose a longer treatment period for the hypothyroid patients before they were subjected to the second measurement.

It is not clear what the mechanisms underlying this reversible effect along the B-Y axis are. One possibility is that it might be related to dopamine levels regulated by the THs. Dopamine is a neurotransmitter with a key role in the retina and it is released from dopaminergic amacrine cells [22-26]. There is evidence that a relationship exists between dopamine levels and TH secretion [27]. The study examines 3 groups of subjects - with undetectable levels of dopamine in the blood, with reference levels and with increased levels of dopamine. The data show a decrease in the activity of the hypothalamic-pituitary-thyroid axis (HTPA) and a reduced peripheral conversion of iodothyronines in the first group, compared to the groups with reference and increased dopamine levels, where an elevation in the activity of the HTPA axis was observed. There are studies showing that low levels of dopamine would have a deleterious effect on the S-cones which are highly susceptible to dopamine levels. Diseases that are associated with low levels of dopamine are known to affect color vision and tend to lead to deficits in the B-Y axis, such as attention-deficit hyperactivity disorder (ADHD) [28-30], Parkinson's disease [23,25,31] and even in schizophrenia [32] and cocaine withdrawal [24,25,31]. There is evidence that the decreased dopamine levels [22-26] in hypothyroidism can be restored, since in the brain levothyroxine treatment restores the stimulatory effects of some neurotransmitters including dopamine [33]. This process might lead to restoration of the deficits along the B-Y axis.

Another possible mechanism underlying the reversible color discrimination impairment might be related to the remyelination of the neurons after treatment with synthetic thyroxine. THs are known to play an important role in the myelination of nerve cells in the central nervous system, and their low levels could lead to demyelination of axons. As an example, people with demyelinating optic neuritis (DON), a disease that damages the optic nerve, show elevation of B-Y PES while performing the FM-100 test and these deficits improve after applying treatment [34]. Multiple sclerosis is another disease that is associated with demyelination of neurons in the central nervous system [35]. High doses of thyroxine in mouse and rats with multiple sclerosis have been shown to lead to the development of oligodendrocytes (the myelinating cells of the central nervous system) and remyelination [36-38]. In addition, TH accelerates remyelination mouse models of demyelination [39-41]. There are no data to indicate the myelin status of neurons in people with hypothyroidism, but we could speculate that low TH levels lead to demyelination and that remyelination occurs after thyroid hormone levels come to normal.

It has been found previously that cone opsin levels in mice and rats are under the influence of THs, both in perinatal and postnatal development, as well as in adult organisms [5-8,42,9]. THs deficiency causes suppression of M-opsin expression and activation of S-opsin expression, which involve thyroid hormone-activated transcription factor TRβ2 [10,11]. In a mouse model of postnatal hypothyroidism, T3 treatment was found to significantly restore M-opsin

expression [42]. If we consider the hypothesis that the regulation of opsin expression in the human retina is similar to the processes in retina of mice, and that it affects color discrimination in humans, it would be expected that discrimination along L-M axes will be impaired in hypothyroid patients and will recover after treatment. This has not been observed in the present study. It is debatable whether mouse retinal models are adequate to explain human data since, apart from all other differences, mice are dichromats. Human studies have shown that in patients with resistance to TH syndrome (RTHβ) with dominant-negative TRβ mutations, there was lower L/M cones response while no differences were found in the S-cone response measured by electroretinogram [43]. Furthermore, in stem cell analysis, it has been found that during embryonic development in humans, in retinal organoids that lacked TH receptor all cones developed into S-subtype, low T3 generates S-cones and high TH is necessary to induce L/M cone fate and suppress S-cone fate [44]. Thus, both animal and human data indicate that the deteriorated action of THs leads to reduced L/M response or suppressed middle wavelength opsin expression, while S-cone responses are not affected and S-cone opsin expression is activated. The present results showed that color discrimination along the B-Y axis was impaired in hypothyroid patients and that it recovered after reaching euthyroidism, while L-M discrimination did not change. These results cannot be predicted based on the above data of opsin regulation. Further research is needed to observe the pattern of opsin expression in the cones of hypothyroid patients and to establish its association with the color discrimination function in hypothyroidism before or after its treatment.

5. Back matter

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Disclosures. The authors declare no conflicts of interest.

Data availability. Data underlying the results presented in this paper are not publicly available at this time but may be obtained from the authors upon reasonable request.

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