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40 Hz Invisible Spectral Flicker and its Potential Use in Alzheimer's Light Therapy Treatment

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ABSTRACT

Alzheimer's disease (AD) not only takes an emotional toll on the individual with the disease, their families, relatives, and caretakers, it also has immense socioeconomic consequences on the health care system and society. Moreover, the socioeconomic consequences are expected to increase significantly, thus reducing the social and economic cost of AD is of high importance. Recently, exposure to 40 Hz stroboscopic light therapy, for one hour a day, resulted in slowing the progression of AD in mice and has a considerable potential for treatment in humans. However, exposure to such stroboscopic light carries its own consequences being that it is difficult to implement in a patient's daily routine, irksome to use, and can cause visual discomfort which may result in a lack of patient adherence.

Here, we demonstrate a novel technology based on controlling multiple single-color LEDs to produce white light where its spectral composition alternates at a given modulation frequency without visible flicker. We coin this technique as Invisible Spectral Flicker (ISF). We present 40 Hz invisible spectral flicker light as a potential alternative in reducing discomfort compared to 40 Hz stroboscopic light, whilst still entraining oscillations in various areas of the brain. Furthermore, we demonstrate a distinct way to generate a 40 Hz metameric light source with the presented color mixing scheme, and validate that the CIE 1931 (x, y) coordinates match for two different spectral power distributions. Finally, we illustrate the light characteristics of seven 40 Hz color fusion light sources and two 40 Hz stroboscopic light sources. The technology presented here will lead to new, and hopefully improved, designs of light therapy systems for the treatment of Alzheimer's and dementia.

Keywords: Invisible Flicker, 40 Hz, Light Therapy, Flicker, Alzheimer's Disease, Metamerism, Color, Chromaticity.

1. INTRODUCTION

Alzheimer's disease (AD) is one of the greatest global health challenges of today that will only worsen in the next decade as the world population and life expectancy continue to increase[1–6]. Currently, there are no cures or treatments for the disease[7]. Unfortunately, the few drugs that are approved by the U.S. Food and Drug Administration (FDA) are for the symptomatic treatment of AD only[8], and in 15 years no new drug has been developed to successfully pass the clinical trials, leading many to consider AD drug development as a graveyard with frequent "failures"[9,10]. Therefore, there is a need for the development of non-pharmaceutical therapies that can tackle AD long before symptoms arise. This goal can only be accomplished through cross-disciplinary collaborations and understanding of science, engineering, technology, and medicine to fully create therapeutic intervention treatments that can ameliorate the negative effects of the disease. Identifying novel technology that can induce changes in the brain will help advance our knowledge of neurodegenerative diseases that are impacting millions of patients and families globally. AD is characterized as a progressive cognitive

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decline, pathologically defined by the accumulation of amyloid-β (Aβ) protein in extracellular senile plaques and of tau proteins in intracellular neurofibrillary tangles[11,12]. These changes lead to neuron death in brain structures critical for cognitive functioning, beginning in the entorhinal cortex and spreading to the hippocampus and surrounding areas, and eventually to the neocortex[13]. The neuronal changes resulting from AD are associated with the disruption of high-frequency neural gamma oscillations (30-80 Hz) required for typical cognitive functioning[14,15]. Novel solutions to Alzheimer's treatment and prevention are attracting significant interest due to the lack of effective pharmaceutical interventions. Recently, new research shows considerable potential in slowing the progression of AD by use of daily 60-minute therapy with 40 Hz stroboscopic light[16], for one hour a day, in addition to improving cognition by decreasing amyloid-β (Aβ) and increasing microglia recruitment[17–19]. Recent pilot studies have investigated some important aspects of the light stimulation on humans with electroencephalography (EEG) among others, however, no conclusions are drawn on the long term feasibility, safety or efficacy on patients with AD[20–23]. In these studies, gamma oscillations at 40 Hz are successfully observed in humans as with mouse models, but it is still unknown whether the same treatment result can be translated to humans with AD when requiring an hour of daily exposure. The evident question that arises is whether AD patients can tolerate the flickering 40 Hz stroboscopic light for long periods of time. The 40 Hz stroboscopic light may be disturbing (especially long term) to the users and may result in side effects such as discomfort, headache, nausea, migraine and photosensitive epilepsy[24]. Exposure to 40 Hz stroboscopic lights is also irksome and hard to implement in the patient's daily routine. Therefore, creating targeted light therapy devices that can still entrain gamma oscillations, in the same manner as a stroboscopic flicker light, while improving symptomatology (cognitive function and circadian rhythm), and slowing disease progression, are vital to increasing our understanding of how to treat AD and its symptomologies.

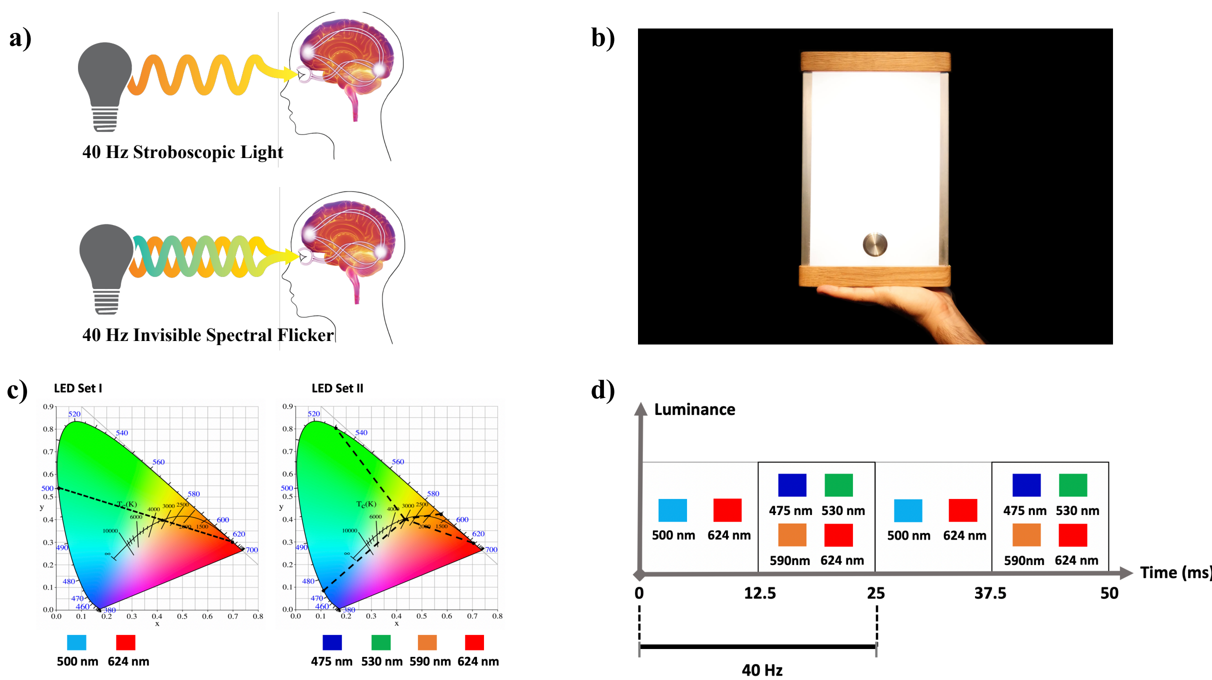

Figure 1. Novel technology platform to generate invisible spectral flicker. a) Illustration of the concept of invisible spectral flicker at 40 Hz that you get by temporally mixing two different spectral profiles matched in time, color property and luminance. **b)** An investigational device that can generate invisible spectral flicker, built in order to investigate the neuronal response weighted against the experience of discomfort of flicker. **c)** LED Set I composed of a cyan and red LED intersecting at 3100 K in the CIE 1931 color diagram defined by the chromaticity (x, y) coordinates. LED Set II is composed of four LEDs, a blue, green, amber and red. Matching these we can intersect the same point as with LED Set I in the chromaticity diagram. Note: Ideal case with monochromatic light. **d)** Temporal and luminance matching of chromaticity coordinates. Here, we take the 3100 K white light source as an example of how we match in time two sets of LEDs switching at 40 Hz with a 50% duty cycle. Not only do we have to match the chromaticity coordinates in time, but also with respect to the luminous flux. Note: We can temporally match a 6000 K white or any other mixed color in a similar fashion.

In this proceeding, we present a novel technology for impending investigational use, tunable in such a way, that it can be used to examine various types of light on neuronal entrainment at 40 Hz. Here, we will differentiate between three types of light sources. A 40 Hz metameric light source, a 40 Hz color fusion light source, and a 40 Hz stroboscopic light source. All light sources are composed to appear white or near white. Note: for both the metameric light source and color fusion light source, the flicker is merely perceivable, and both are built on the methodology of invisible spectral flicker presented below. The metameric and color fusion light sources can be composed with various polychromatic combinations of LEDs. For future use, one will be able to investigate the effects using EEG SSVEP, and be able to fine tune and determine which combination of single-color LEDs are required to develop the optimal light source that is not only comfortable to treat with, but can still result in close to similar effects as 40 Hz stroboscopic light.

1.1 Overview of color fusion, metamerism and EEG SSVEP

Color fusion is found when two different colored lights are presented simultaneously and fused to be perceived as one new color by the observer[25]. Color fusion can also appear by alternating the two lights at a frequency above the critical flicker frequency (CFF) resulting in flicker fusion, in which the observer no longer perceives the flicker. Metamerism is the term used when two light stimuli are perceived similarly by the human eye, despite having different spectral power distributions (SPD). The effect is caused by the lights triggering the same response in the photoreceptors of the eye[26].

Flickering lights are found to induce a clear response in regions of the brain related to the vision, like the occipital area in the back of the head. The measured EEG response will match the frequency of the stimuli. This is referred to as Steady State Visual Evoked Potential (SSVEP) which is widely known and used within the field of Brain Computer Interface (BCI)[27,28]. The SSVEP response is even present when using stimulation that is perceived as invisible by the observer, typically shown with stimulation flickering above the CFF (50 Hz)[29]. The study by Hermann et al.[28] also suggest a resonance phenomenon at 10, 20, 40 and 80 Hz meaning that these frequencies induce a stronger signal than others.

1.2 Why discomfort is important to test for different polychromatic combinations of single-color LEDs

40 Hz stroboscopic flicker is not comfortable to observer nor it is given that stimulation with 40 Hz ISF will be either. However, it is to be assumed that the masking of the flicker will reduce the level of discomfort experienced by the observer. It is therefore important to investigate this issue in terms of different color combinations and intensities in order to develop therapeutic tools that live up to the expected usability. It is furthermore interesting to explore the EEG response of the different color combinations and intensities in order to maximize the response in relation to minimal discomfort.

1.3 Why EEG SSVEP is important to test for more advanced polychromatic combinations of single-color LEDs

Only simple color combinations have been measured using EEG with regards to the SSVEP responses. The black and white color combination (stroboscopic) is widely studied and its effect is well known[27,30]. Invisible flicker using green and blue LED's also showed good results when used to control a Brain-machine Interface (BMI) system[29]. Furthermore, red and green combination together with yellow and blue has also been studied[31,32]. However, none of the present studies focus on minimizing the perceived flicker, which can be achieved using a more advanced combination of colors that are offered by this LED platform.

1.4 Overview of 40 Hz light sources presented in the proceedings

We illustrate ten different light sources generated with the technology platform. One light source is the 40 Hz metameric light source which is generated by adjusting colorimetrics and lumens inside an integrating while matching in real-time the chromaticity coordinates in an associated CIE 1931 chromaticity diagram.

Seven of the light sources are built on the principle of making the flicker as invisible as possible for the user by simply letting four researchers from the research group agree that the flicker is approximately imperceptible. Here, we note that we are aware that the flicker is perceivable to some, and subjects tend to not agree on the tuning of the colorimetrics and lumens values for the matching.

Finally, the last two light sources are white 40 Hz stroboscopic light, where one has a relatively high brightness and the other a relatively low brightness.

The invisible spectral flicker technology will be utilized in future pilot studies, to improve our understanding and discovering the effects of various types of 40 Hz invisible spectral flicker on EEG responses weighted up against the discomfort of flicker. This can provide insight towards the selection of treatments that show feasibility and EEG performance to go into clinical trials.

2. METHODOLOGY OF INVISIBLE SPECTRAL FLICKER (ISF)

Here, we illustrate the methodology behind the color mixing scheme in order to compose 40 Hz invisible spectral flicker. Invisible flicker is defined by IEEE as "A temporal instability in illumination (flicker) above the critical flicker fusion frequency (CFF)"[24]. The CFF for color fusion is around 25 Hz and the CFF for stroboscopic light is around 50 Hz[33]**.** See fig. 1a for the concept of minimizing the experience of flicker while keeping a 40 Hz component, and a simple illustration of an investigational device on fig. 1b with the invisible spectral flicker methodology integrated. Within this proceeding we define 40 Hz invisible spectral flicker to be a light source, that alternates between two different spectral profiles at 40 Hz, such as between two metameric profiles or between two different color profiles in the case of color fusion.

In order to demonstrate how the color mixing scheme works out, let's focus on an example where we wish to produce a white color flickering at 40 Hz, however, making the flicker as imperceivable as possible. The chromaticity of the combined light must end up in the vicinity of the Planckian Locus (the curved black line in the center as seen in fig. 1c) and as such the color combination of 500 nm and 635 nm will only be able to create one white at around 3100 K, see LED Set I in fig. 1c. Another LED configuration, Set II, generates a white by combining blue, green, amber and red as shown. Because we are using four different single-color LEDs, we are now able to produce any color in between them (the gamut area) on the diagram, and as such it is simply a matter of matching the white light generated with the earlier set of cyan and red.

By adjusting the individual light intensities of the LEDs, it's possible to match the chromaticity of the combination of the first two, hence it will make them indistinguishable from each other, and as such flickering between the two will produce a perceived constant white light in the eyes of a person standing in front of it.

Refer to fig. 1a for an illustration of the concept of minimizing the experience of flicker while keeping a 40 Hz modulation component in the light. An investigational device example can be seen on fig. 1b used to test the light output of the ISF controller with a diversity of LED color configurations.

2.1 Luminance matching is paramount

When matching two sets of white to each other it is not enough to match their chromaticity. The human eye, especially in the peripheral vision, is very good at observing and noticing small changes in luminance (cd/m^2). As such, if our two sets of light are not matched in luminance, a flicker will be perceived with dependency on both the observation angle and the luminance mismatch, which in the worst case leads to perceived flicker when directly looking into the light.

To closely match the two white compositions in intensity while keeping the set chromaticity values, we rely on the linearity of the ISF LED controller and manual configuration with aid of a light spectrometer as well as a luminance meter to help detect minor deviations.

The chromaticity is configured first with aid of the spectrometer and the luminance is set for one of the light sources which is used as reference for the other. At this point, one light source is fully configured and only the luminance needs to be adjusted for the second light source. The luminance is incrementally adjusted while both lights are alternating at the desired frequency and the perceived flicker becomes unnoticeable. A more concise procedure is also exposed in this section.

2.2 Procedure for Manual Matching Prior to Measurement

The invisible spectral flicker light sources are matched by a human operator by adjusting two LED sets: LED Set I and LED Set II. The procedure for matching two light sets to produce invisible spectral flicker has been stablished as follows.

1. Set I and Set II are defined initially by their single-color components and their Planckian Loci calculated
2. A nominal distance and minimal distance for the observer are defined. (Greater than 20 cm)
3. Set I is configured to its corresponding Planckian Locus with aid of an optical spectrum analyzer

4. Set I is configured to the brightness value desired to the nominal observer distance
5. Set II is configured to its corresponding Planckian Locus with aid of an optical spectrum analyzer
6. Set II brightness is configured to a lower level than Set I (at least noticeable to the operator)
7. Alternation between the two sets is initiated at 40 Hz or another target frequency
8. Set II is uniformly increased in brightness over several steps until any flicker and artefacts are not perceived
9. At this point a check is done by moving slightly away from the light, the masking should be maintained. Then moving slightly closer without breaking the minimum distance some flicker should appear.
10. Increase the brightness of Set II by steps less than 1% duty cycle until the flicker or artefacts are not perceived and check that the masked point is kept at the nominal distance.
11. If the masked point is reached, the light is considered matched. Otherwise, Set II should be reduced in brightness again and repeat the incremental brightness approximation from steps 8 to 10

3. TECHNOLOGY DEVELOPMENT

One challenge in generating invisible spectral flicker from multiple high-power color LEDs, is that the flicker tuning at 40 Hz is on the limits of flicker perceptibility and working at this limit makes accurate control of the light paramount because small deviations from the intended stimulation may deteriorate the perceptibility or show an undesired flickering. At the same time, the threshold of human vision for stimulation with more advanced polychromatic LED compositions and temporal modulation waveforms, is not well understood and requires more experimentation for its characterization. In order to carry out the experimentation, a flexible controller was needed, one that could manage a wide variety of LED and independently control each LED channel. A custom LED controller was developed for the purpose of being able to finely tune six independent channels in brightness as well as allowing forward current control and synchronous timing control for the different channels turning on/off.

Precursor work on invisible spectral flicker showed that large dimming ratios are needed to match the brightness of different color channels, this requirement is even more stringent at lower luminance levels where the human eye is more sensitive to changes in light. Furthermore, constant current driving was needed to minimize wavelength shift and thus maintain the linearity of the system. This led to the design of a Pulse Width Modulation (PWM) based driver with six channels and independent forward current control and dimming duty cycle control. This driver can control the forward current in fine increments up to 1000 mA allowing the use of a large range of LEDs and to compensate for wavelength shifts related to heat. The brightness is then dimmed linearly by the duty cycle of the PWM in fine increments.

3.1 Custom LED controller for invisible spectral flicker

In order to produce invisible spectral flicker, tight control of light intensity across 5 or more LEDs is needed, which is handled by custom-made hardware. The LEDs must change their light output 40 times per second in a synchronized manner, such that the perceived light output has no visible and undesirable flicker. Despite rapid changes in light output per LED, the electric current through each LED should be constant when they are on in order to minimize the wavelength drift of the light output. A stable color output, independent of perceived intensity, simplifies calibration. This requirement introduces the need for a separate constant current LED driver.

A conceptual schematic of the hardware is seen in fig 2a, where the main signal flow goes from the microcontroller (MCU) on the bottom left to the LED assembly on the right. Notice that the schematic is conceptual and in practice it is replicated for as many color channels as needed.

To understand the circuits operation, it is easiest to start at the end of the signal flow, with the LED on the left. Each LED's light intensity and current draw is controlled individually, with the analog control governed by a multi-channel constant current LED driver. This LED driver is supplied with input signals for both intensity and constant current setting, arriving from the PWM generator and digital-analog converter (DAC), respectively.

To switch between the LED intensities in a synchronized fashion, a multiplexer selects between two PWM signals, for each single LED. As seen in the plots of fig. 2a, the signals going into the multiplexer are two PWM signals of potentially differing duty cycle; in the case of the figure, they are 50 % and 0 %. The multiplexer has a 40 Hz square wave on the switch input, which produces the changing duty-cycle on the output. As a result, the LED will be modulated with different duty cycles.

a) **b)**

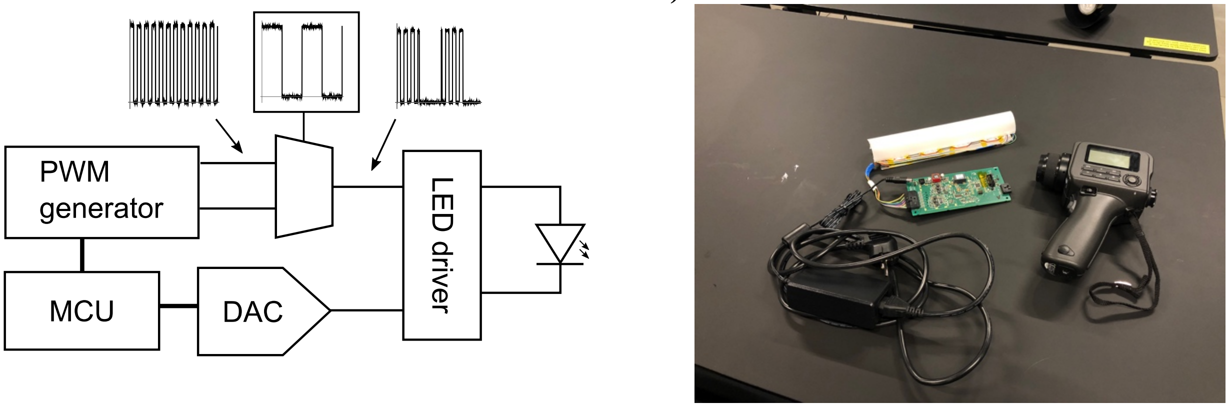

Figure 2. LED Control a) Conceptual schematic of the LED control. **b)** Developed LED Controller circuit board with a LED module consisting of 6 channels with 4 series LEDs per channel.

The PWM signals are generated by a multi-channel PWM generator. The switching signal is a square wave set to 40 Hz, which is generated using voltage-controlled oscillator. A microcontroller is included on the hardware for configuration, monitoring and communication.

The system affords a selection of duty cycle with a resolution of less than 0.05 % point and a constant current resolution of 0.5 mA, which can all be controlled from a computer for specific test programs or calibration.

3.2 LED Controller Performance

Linearity and fine adjustment are the main drivers for the ISF controller design. On fig. 3a, 3b, and 3c we demonstrate the essential LED controller performance of the individual LED channels for each single-color LED. The individual channels meet the requirements as expected as we have approximately a constant peak wavelength and linear lumens output versus duty cycle.

a) **b)** **c)**

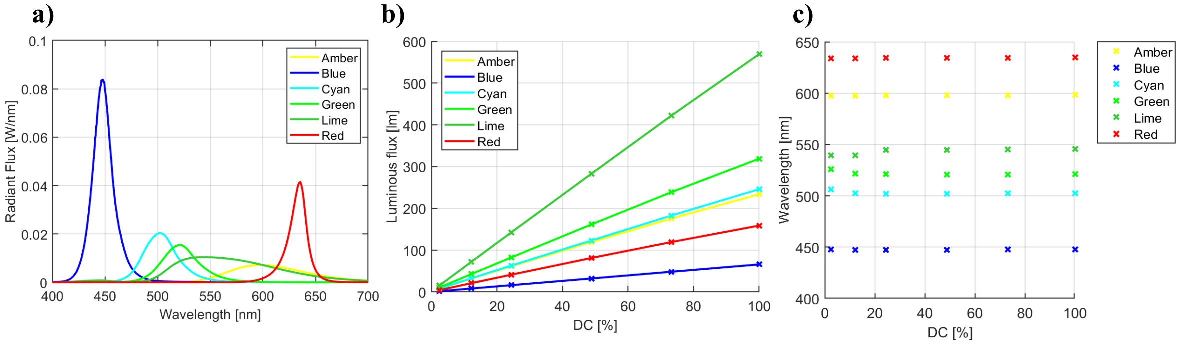

Figure 3. LED Technology Verification. a) Power spectral density plots of all six single-color LEDs. **b)** Linearity of luminous flux output versus duty cycle. **c)** Wavelength stability plot versus duty cycle.

4. LIGHT SOURCE CHARACTERISTICS

Once the LED controller is developed, the light source was characterized in the DOLL Quality Lab facility at the department of photonics engineering at DTU. The photometric measurements were done in a 1900 mm integrating sphere (ISP 2000, Instrument Systems), connected via a fiber bundle to a spectrometer (CAS140 CT Instrument

Systems), see fig. 4b. This enables us to measure the total luminous flux output from the lamp (measured in lumen, lm) and spectral power distribution of the light, which gives colorimetric information such as correlated color temperature (CCT), color rendering index (CRI) and chromaticity data. For the flicker measurements, a multi measurement device BTS256-EF Wi-Fi from Gigahertz-Optik was used, see fig. 4a.

4.1 Metameric lumens matching inside integrating sphere

To measure the amount of light, we measure the luminous flux (unit lumen, lm). The luminous flux is the radiant flux, weighted against the sensitivity of the human eye. Note: we match in lumens and not luminance as they are almost equivalent in this measurement setting. Then, when changing between two sets of LEDs the light intensity distribution of the light source stays the same when using a uniform diffuser plate for the color mixing. Thus, the relationship between the luminance and the luminous flux stays the same. Therefore, the luminous flux can be used when matching two sets of settings with each other.

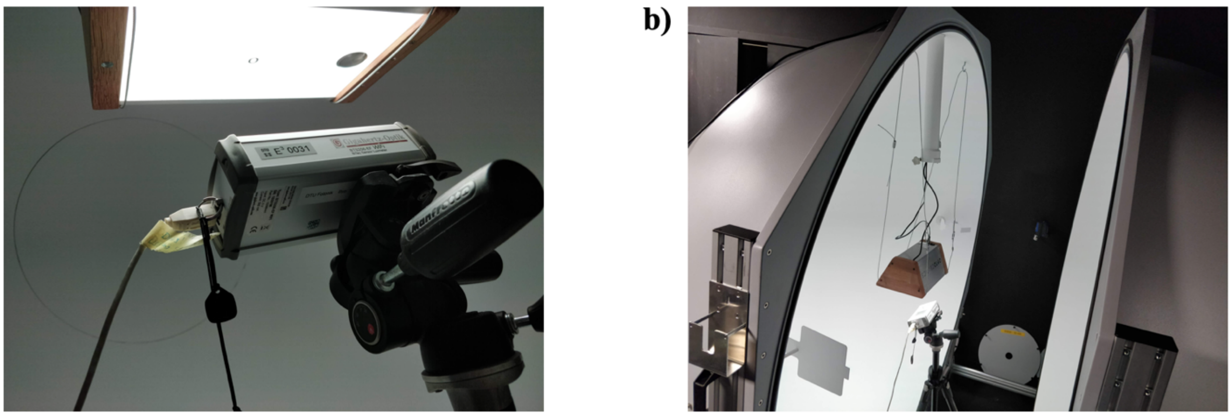

Figure 4. Measurement devices for light characteristics. **a)** BTS256-EF for flicker measurements. **b)** Integrating sphere for light measurements, and for adjusting colorimetric and lumens values when generating the 40 Hz metameric light source.

4.2 Temporal Light Artifacts (TLA)

Temporal light artefacts (TLAs), which include flicker, stroboscopic effect and phantom arrays, are caused by temporal light modulation (TLM) of a light source. Under most circumstances, these artifacts are undesired visual perception effects. E.g., for normal illumination, these effects could compose a threat to wider solid-state lighting (such as LED lighting) adoption. Sometimes, for example in cases where one wants to attract attention, TLA could be desired.
TLAs are per definition perceptual effects, i.e. observable. However, TLM can also cause effects on human that are not observable, e.g. cognitive or neurobiological. These could have both negative and positive outcome, and more research is needed in the field. The work described in the proceeding deals with a possible positive neurobiological effect on Alzheimer’s disease.

There are no measures of assessing the degree of cognitive or neurobiological effect from TLM[35]. There have been, however, in recent years, developed metrics for two TLAs: flicker (Pst) and stroboscopic effects (SVM).

4.3 Pst and Stroboscopic Visibility Measure (SVM)

The short-term flicker severity measure (Pst) and the Stroboscopic Visibility Measure (SVM) are two recently developed standards[36] for measuring TLAs. Flicker is defined as perception of unsteadiness of light intensity, for a static observer in a static environment, i.e. neither the light source nor the observer or the eyes of the observer are moving. Due to this definition, flicker is observable only below a light modulation frequency of about 90 Hz. Stroboscopic effect is defined as perception of unsteadiness of light intensity, for a static observer in a non-static environment, i.e. the light source or any object in the light are moving. This then causes observation of stroboscopic patterns. Such effects can be visible for light modulation frequencies up to 2000 Hz[36]. A third effect is the phantom array effect, for which no measure exists. This is defined as perception of unsteadiness of light intensity for a non-static observer in a static environment. This means that the effect becomes visible due to eye movements. Since the eyes can move very rapidly, the effect can be observed up to very high light modulation frequencies, up to 11 kHz[37].

The measures for flicker and stroboscopic effect using Pst and SVM are done by mathematically analyzing the temporal light intensity waveform. For Pst, 180 s of the waveform needs to be assessed, and for SVM 1 s. The BST256-EF device used in this work records and present the Pst and SVM value after a light intensity signal has been recorded.

Both Pst and SVM are normalized such that a resulting value of Pst or SVM value equals to 1, there's a 50% probability of observation by a standard observer. Higher values indicate a higher probability. In order to make a "flicker-free" light source, the Pst and SVM values should thus be as low as possible. For lower modulation components in the intensity waveform contains, the closer to "flicker-free" the light source will be.

Ideally, in the case of the investigational device used in this work, a modulation free waveform is achieved by alternating between two color fusion sets with the same total luminance intensity and same chromaticity, thus a 40 Hz metameric light source.

Table 1. Measured light characteristics of the four different types of generated light sources. (* orthogonal at 20 cm).

	Metameric Source	**CF 1**	**CF 2**	**CF 3**	**CF 4**	**CF 5**	**CF 6**	**CF 7**	**Stroboscopic 1**	**Stroboscopic 2**
CCT (K)	4835	3379	4591	7558	3669	4458	4889	4185	8428	10212
Illuminance (lux)*	3454	2296	2346	1896	2408	2570	3505	3043	237	3878
CRI	66	60	69	39	58	81	41	56	81	73
Pst	3.0	8.0	6.8	4.2	5.2	2.6	1.6	2.2	54	44
SVM	0.6	1.2	1.2	1.4	1.1	1.1	0.61	0.8	2.4	2.3

As can be seen in table 1, the Pst and SVM values are considerably lower for the metameric and color fusion light sources, compared to the both cases of stroboscopic light. Even though the values are not below 1 in all cases, there's a clear indication of potential in the methodology. However, more work has to be done investigating Pst an SVM values for various types of light sources, while weighting it up against the discomfort of flicker and the EEG SSVEP neuronal entrainment results. This would result in finding an optimal light source for potential therapeutic use. We don't draw any sharp conclusions in this characterization, as the light sources for this proceeding are chosen for practical convenience. In future work, one should consider fixating illuminance values and color temperatures to be similar for the various types of light sources.

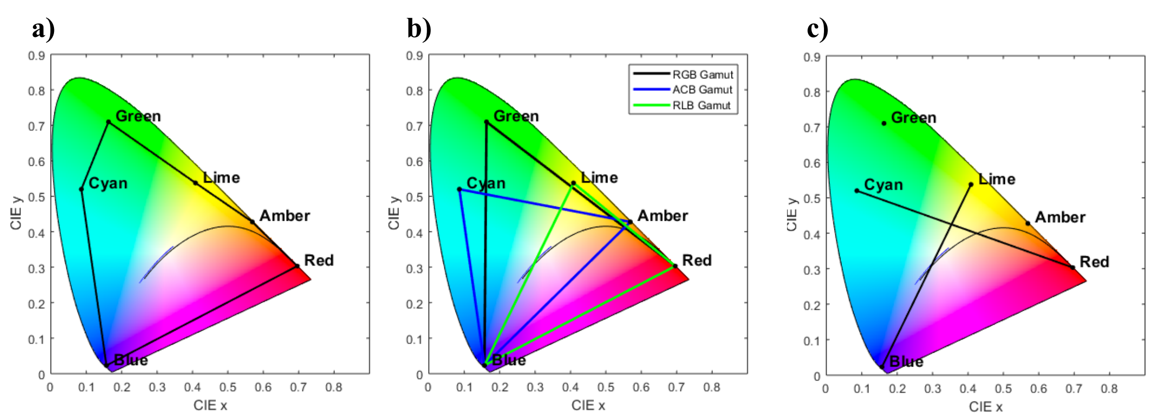

Figure 5. Measured color gamuts for the LED system. a) Mapping of full color gamut with all six LEDs representing all possible polychromatic colors (gamut area) that can be generated **b)** Three different color gamuts utilized to generate the seven different color fusion light sources. **c)** Metameric light source with crossing between a B-L and C-R LED composition. The thin black curve in the diagrams are the Planckian locus and the smaller blue curve is the daylight locus.

With the integrating sphere setup, we measured the full color gamuts of the single-color LEDs, see fig. 6a, where the color gamut is represented in the CIE 1931 chromaticity diagram. In fig. 5b we show the individual color gamuts we used to generate the different kinds of color fusion light sources. Whereas in fig. 5c we illustrate the metamerism chromaticity point, where the manual tuning of the light sources was conducted until a lumens and chromaticity match was achieved.

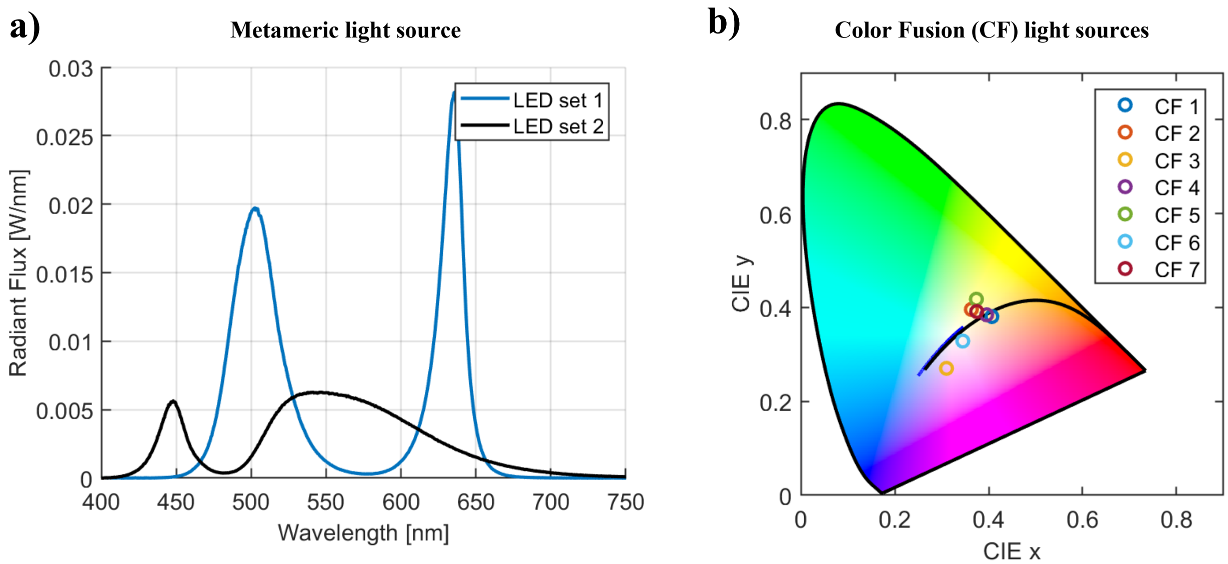

Figure 6. 40 Hz invisible spectral flicker light sources. a) Power spectral density plots of the two LED sets that are chromaticity and luminance matched (the 40 Hz metameric light source). **b)** All seven 40 Hz color fusion light sources plotted in the CIE 1931 chromaticity diagram. Note: the points are derived from the combined spectra measured with an integration time covering a whole period in a 40 Hz signal (25 milliseconds).

In fig. 6a, we illustrate the spectral power distribution of the individual iso-luminance and iso-chromaticity LED sets used to generate the 40 Hz metameric light source. The measured values of luminous flux are 348 lm for LED Set I and 347 lm for LED Set II. Additionally, the measured chromaticity coordinates are (0.358, 0.433) for LED Set I and (0.357, 0.430) for LED Set II. In fig. 6b we plot the CIE 1931 chromaticity coordinates with the seven 40 Hz color fusion light sources superimposed to give the reader an overview of the colors examined and where they lie around the Planckian locus points. Thus, we have here demonstrated that the technology we have built can be used to generate simple and more advanced polychromatic combinations of single-color LEDs, modulated in time such that the visibility of flicker becomes practically invisible compared to that of white 40 Hz stroboscopic light sources. A more throughout investigation is necessary to determine how much less and conclude a difference, however, the results shown here indeed shows a tendency that it is plausible the case.

5. DISCUSSION

Development of solutions to tackle AD is of high importance, and medical device solutions to Alzheimer's treatment and prevention are attracting significant interest due to the lack of effective pharmaceutical interventions. New research shows considerable potential for treatment using chronic 40 Hz stroboscopic light therapy, for one hour a day, in slowing the progression of Alzheimer's disease. However, exposure to 40 Hz stroboscopic light is irksome and hard to implement in the patient's daily routine. For this reason, we presented invisible spectral flicker as an alternative solution utilizing simple color mixing theory. We are mindful, that a proper color space is important for the colorimetric and luminance matching when generating the 40 Hz metameric light source. An alternative to the CIE 1931 diagram was suggested in 1960 with the CIE 1960 (u, v) diagram. However, this diagram only involves scaling factors compared to CIE 1931, and a pair of chromaticity points with the same coordinates in the CIE 1931 diagram will also have the same coordinates in the CIE 1960 diagram. We are also aware that the CIECAM02 model has been shown in the literature to be a more decent model of activity in the primary visual cortex, when compared to former CIE color models such as the CIE 1931, CIE 1960 and CIELAB[38]. However, for the purpose of merely demonstrating the technology, and for eye matching; the

CIE 1931 model was practically working if one made sure to match in luminance continuously while moving around the chromaticity diagram.

Furthermore, during the measurements with the integrating sphere, we experienced that it is considerably difficult to eye match colors and get the luminance matched between different sources at the same time with this number of single-color LEDs, and there is room for improvement in future work on how to automate this process.

Entraining 40 Hz oscillation in different cortical regions depends on the spectral composition of light, however, with the tunability of the spectral composition and the amount of different types of light that can be generated inside the color gamut is enormous. Therefore, we have planned future investigations to figure out the entrainment versus assessment of the subject experience of flicker discomfort. The entrainment can be measured using a simple EEG setup recording the SSVEP response at the visual cortex. The results will give an indication of how the stimulation is inducing a 40 Hz signal. The EEG measurements can however not conclude any entrainment in deeper brain regions which would be relevant for the treatment of AD. The EEG recordings can be performed both in clinical setting and at home, which is of great advantage when dealing with cognitive impaired patients. These future studies will provide an insight, so far unknown, on how more complex polychromatic color combinations induce neuronal responses.

We are aware that Pst values don't measure discomfort directly, but merely whether the flicker is visible or not to the observer. The same is true for SVM with regards to visibility of stroboscopic effects. Therefore, future studies will also focus on investigating the subjective measures of the perception of this kind of light stimulation. These measures shall be put in relation to both the Pst values and the SSVEP response to validate the assumptions about flicker perception dependent on the spectral compositions. Another variable to study is the waveforms used, where a sinusoidal based stimulation could show different levels of discomfort or visible flicker as well as different SSVEP response. The studies will hopefully aid in optimizing the spectral composition and visible flicker in order to attain an effective treatment with high usability and patient adherence.

Finally, a larger modulation depth poses an increased risk of photosensitive epileptic seizures[24]. Potentially 40 Hz invisible spectral flicker decreases this risk, considering it has a lower modulation depth than 40 Hz stroboscopic light.

6. CONCLUSIONS

Here, we presented a novel technology utilizing multiple single-color LEDs to generate invisible spectral flicker at 40 Hz with the potential of entraining 40 Hz oscillation in different cortical regions depending on the spectral composition of light. We also illustrate a 40 Hz metameric light source and 40 Hz color fusion light sources. The 40 Hz metameric light source is built by designing two different spectral distributions with the same chromaticity coordinates around the Planckian locus. Then the two spectral distributions will appear almost identical to human perception when keeping the luminance, the same for both spectral distributions, and using the CIE 1931 diagram for color matching of chromaticity coordinates. Measuring temporal light artifacts on ten different 40 Hz light sources, we see that there is a plausible reason for investigating Pst and SVM values for various types of light sources, while weighting it up against the discomfort of flicker and the electroencephalography response. The technology presented here will lead to new, and hopefully improved, designs of light therapy systems for treatment of Alzheimer's and dementia.

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