Sensitivity of the human visual system to amplitude modulated light

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Preface

This work was conducted as a degree project for Amanda Johansson in Engineering Biology, Institute of Technology, Umeå University. It was performed at NIWL-North, Department of Work and the Physical Environment, Umeå.

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Monica Sandström

Contents

Abbreviations and Definitions

Flicker: Periodic luminance variation
CFFT: Critical flicker fusion threshold
AT: Ascending Threshold
DT: Descending Threshold
Frequency: Variation rate with time; unit Hz
Background: Immediate background of light source
Surrounding: Area surrounding experimental set-up
LED: Light Emitting Diode
L/D-ratio: Light/dark-ratio
LCD: Liquid Crystal Display
VDT: Video Display Terminal

ANOVA: Analysis of Variance
MANOVA: Multivariate Analysis of Variance

CNS: Central Nervous System
EEG: Electroencephalography/ Electroencephalogram
ERG: Electroretinography/ Electroretinogram
EHS: Electrical Hypersensitivity

Sammanfattning

Amanda Johansson, Monica Sandström. Sensitivity of the human visual system to amplitude modulated light. *Arbetslivsrapport* 2003:4.

Den kritiska flimmerfrekvensen; på engelska Critical Flicker Fusion Threshold, CFFT, beskriver den frekvensmässiga gräns när ett flimrande ljus övergår till att uppfattas som ett kontinuerligt ljus. Denna parameter används ofta för att uppskatta det centralnervösa tillståndet hos en person. Såväl individuella som yttre faktorer kan påverka CFFT. Syftet med den föreliggande rapporten är att ge en beskrivning av företeelsen CFFT samt de mätmetoder för CFFT som finns. För att uppnå detta har en genomgång av litteraturen på området företagits, samt en pilotstudie där en vanlig mätmetod, den s.k. Method of Limits, användes. Syftet med pilotstudien var att undersöka några av de parametrar som kan tänkas påverka CFFT, både sådana som är relaterade till individfaktorer och sådana som är relaterade till yttre omständigheter.

En genomgång av litteraturen på området ger en divergerande bild av värdet av att använda CFFT vid neurofysiologiska försök. Ett flertal mätmetoder står till buds, och de är i princip alla möjliga att använda, under förutsättning att man tar hänsyn till faktorer som kan påverka testresultaten. Pilotstudien bekräftar att det finns ett antal individuella faktorer som påverkar resultaten vid mätning av CFFT. Astigmatism tycks vara en viktig faktor, liksom ålder och i viss utsträckning kön. Vidare föreligger skillnader mellan resultat från försök utförda vid olika tid på dagen samt ett beroende på i vilken riktning frekvensförändringen sker vid försöken. Värdet på CFFT blir i allmänhet högre när frekvensen sänks (övergång från icke visuellt till visuellt flimmer) än när den höjs (övergång från visuellt till icke visuellt flimmer). Denna skillnad är mer uttalad hos äldre försökspersoner.

CFFT kan ha ett värde som deltest vid neurofysiologiska undersökningar. Det är dock viktigt att de ovannämnda faktorerna tas i beaktande när en studie skall genomföras, t.ex. vid matchning av försökspersoner och tolkning av resultat.

Summary

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The Critical Flicker Fusion Threshold, CFFT, is often used as a measure of the current state of the central nervous system of an individual. As such it may be affected by several factors; internal as well as external. The aim of the present study was to give a description of the CFFT phenomenon, its value as a diagnostic tool and the available methods of CFFT measurement. The literature in the area was reviewed and a pilot study using one of the described methods of measurement, the continuous Method of Limits, was undertaken. The purpose of the experiments was to investigate some of the factors with a possible impact on CFFT, including both subject characteristics and experimental conditions.

A review of the literature gives a divergent picture of the value of the CFFT in neurophysiological testing. Several methods of measurement are available, and basically, any of them may be used as long as variables with a possible impact on the result are considered.

The pilot study confirms that there are a number of individual parameters affecting the test results. Astigmatism seems to be an important factor, together with age and possibly also sex. Further, there are differences between tests performed at different times of day and between ascending and descending threshold values. Descending threshold values are generally higher than ascending values, especially among older subjects. The CFFT also tends to be higher in the morning than in the afternoon, although subjects of the age <40 display only minor differences.

The CFFT appears to be a useful component of the neurophysiological test battery, but it is necessary to consider the factors mentioned above when undertaking a study, e.g. when matching subject groups and interpreting data.

1. Introduction

People experience and are affected by their environment in different ways. The sensitivity to disturbances of the environment also differs between individuals. There are numerous causes of individual variation, among which genetic differences can be mentioned, as well as differences caused by previous experiences and immediate life circumstances. An important question when dealing with the effects of environmental factors on human beings is how we are affected by sensory impressions which are not consciously perceived.

Modulated light (light with periodic time variations of intensity) is in everyday speech referred to as “flicker”. The perception of flicker is essentially a visual phenomenon, that is, it is detected and processed by the visual system. If the modulation frequency is high enough, a flickering light will be perceived as continuous. This detection limit between “visible” and “invisible” flicker can be described as the Critical Flicker Frequency Threshold, CFFT. The threshold value in a particular case is affected by several factors, i.e. the characteristics of the flickering light per se, the characteristics of the exposed individual and various external conditions (Görtelmeyer et al., 1982; Sandström et al., 2002).

2. Aims

The overall aim of this work is to increase the knowledge about the CFFT, and the limitations and advantages of using the concept as part of a neurophysiological test battery.

Part I: to describe the CFFT method from a biological as well as a technical point of view and furthermore to compile a review of the literature in this area of research.

Part II: to use one of the commonly used CFFT methods in a pilot study in order to investigate certain individual characteristics with an impact on the CFFT.

3. Part I: The CFFT concept

When a person is exposed to flickering light, the neuronal activity of the retina and the occipital cortex synchronizes with the flicker (Curran et al., 2000; Curran et al., 1998; Küller et al., 1998; Sandström et al., 2002; Simonson et al., 1952; van der Tweel et al., 1965). The activity of retinal neurons, recorded with electroretinogram (ERG), displays synchronization at higher frequencies than that of cortical neurons, measured by electroencephalogram (EEG) (Ott, 1982; Simonson & Brozek, 1952). This difference gives rise to the hypothesis that the limit of the temporal resolution of visual input, and thereby the CFFT, is set by the cerebral cortex (Curran & Wattis, 1998). The CFFT obtained by subjective visual judgment varies roughly between 25 and 55 Hz depending on the methods of measurement and experimental situation (Ott, 1982).

The CFFT is regarded as a function of the activity of both the eye and the cerebral cortex. The highest degree of cortical response that is registered when a subject is exposed to flicker is found in the occipital lobe. However, activity is also present in many other parts of the brain, and a particular site for the processing of flickering stimuli cannot be localized (Curran

& Wattis, 2000; Curran & Wattis, 1998; Hindmarch, 1988b; Küller & Laike, 1998; Simonson & Brozek, 1952). The fact that several cerebral functions are involved in the processing of flicker and affected by exposure to it, is further illustrated by the observation that CFFT values change as a result of damage to several different parts of the brain, not only to those primarily concerned with vision (Curran et al., 1990; Curran & Wattis, 1998; Simonson & Brozek, 1952).

3.1 CFFT determinants

There are different opinions about the determinants of the CFFT. The threshold is at the same time regarded as a stable, individual trait, as a pure representation of the instantaneous state of the central nervous system (CNS), and as a reflection of the impact of various external or internal stressors on an individual "baseline" threshold. Values are often used to estimate arousal/vigilance of subjects or the current CNS processing capacity. However, the correlations between the CFFT and subjective ratings of alertness are weak, which implies that the threshold value is not a function of CNS arousal only (Curran & Wattis, 1998). Regardless of the exact nature of the CFFT, actual threshold values are obviously influenced by a large number of variables, related to the subject, the applied stimulus and the experimental situation.

A review of the literature on the CFFT reveals a wide range of actual threshold values (Appendix I). The large span may be attributed to the use of different measurement methods, e.g. differences regarding the source and the nature of the stimulus signal. Methods that are all considered reliable yield very different results, even when experiments are performed on the same test population (McNemar, 1951; Simonson & Brozek, 1952). This makes it difficult to compare results from different studies, especially as the description of the experimental conditions often is incomplete (Fichte, 1982; Görtelmeyer & Zimmermann, 1982).

The CFFT can be separated into two threshold values. The descending threshold (DT; also designated flicker threshold) is the limit below which a seemingly continuous light starts to flicker. The ascending threshold (AT; also fusion threshold) is the limit above which flicker fuses into a steady light (Curran & Wattis, 1998; Ott, 1982; Simonson & Brozek, 1952). The CFFT may also be divided into a subjective and a neuronal threshold. The subjective threshold value is set by subjective, visual judgment. The neuronal threshold is obtained from direct measurements of neuronal responses in the brain (EEG) or the retina (ERG) and is defined as the frequency limit above which neurons start giving off a continuous response, even though the stimulus is intermittent (Görtelmeyer & Zimmermann, 1982).

Some methods of measurement yield different values for descending and ascending thresholds, while some do not. The difference between the threshold values is sometimes used as an argument for the hypothesis that the processing of visual input with decreasing or increasing rate of change is governed by different functions. However, it is sometimes also viewed as a mere artefact of the method used (Aufdembrinke, 1982).

The differences in the CFFT are large between individual subjects (Küller & Laike, 1998; Sandström et al., 2002), but become normally distributed for large populations (Curran & Wattis, 2000; Lachenmayr et al., 1994). Studies reveal intraindividual differences both with time of day and between different days (Frewer et al., 1988; McNemar, 1951). In some cases the day-to-day variations are large enough to make the authors question the value of one-day measurements (McNemar, 1951). However, the intraindividual variability is lower than the interindividual variability, which supports the view of the CFFT as an individual trait that is modified by external factors. Intraindividual variability is said to decrease further with an increased flicker frequency (van der Tweel & Verduyn Lunel, 1965). Among the subjective characteristics proposed as CFFT determinants are the state of the visual system, age, sex and congenital or acquired cerebral defects. Other factors might be for example fatigue, psychological or physiological stress, disease, drugs and medication etc. (Kuller & Laike, 1998). The impact of the different CFFT determinants varies among individuals. When the experimental conditions are changed, or the CFFT is measured with respect to different factors, the distribution of subjects changes, even in the same test population (McNemar, 1951).

3.2 Subject characteristics

Differences in individual CFFTs are likely to be caused by a combination of genetic differences and differences regarding former experiences and the immediate life situation, e.g. stress level (Sandström et al., 2002).

3.2.1 The eye

The sensitivity to flicker differs between different locations on the retina, since the different types of neurons are not homogeneously distributed. Apart from the photoreceptors (rods and cones) the retina contains a number of other neurons, which also participate in the process of vision. A recorded ERG-response is the summation of the total neuronal activity (Aufdembrinke, 1982; Görtelmeyer & Zimmermann, 1982; Simonson & Brozek, 1952; Wu et al., 1995). The importance of each photoreceptor type for the detection in particular measurements partly depends on the experimental lighting conditions. Rod activity is said to dominate over cone activity if the degree of illumination in the environment is low, and/or the background of the test object is dark, and vice versa if the illumination and/or the test object background is bright (Aufdembrinke, 1982; Simonson & Brozek, 1952).

Maximum flicker sensitivity is not reached on the fovea centralis, the actual site of central vision, but in the area surrounding it (Curran & Wattis, 1998; Lachenmayr et al., 1994; Simonson & Brozek, 1952). This could, together with the recruitment of a greater number of neurons, be a reason for the fact that a flicker source with a larger area generally gives a higher CFFT than a smaller one (Görtelmeyer & Zimmermann, 1982; McNemar, 1951; Simonson & Brozek, 1952). However, the reports about the flicker sensitivity of different points on the retina vary, and the main opinion seems to be that the most accurate and useful results are obtained with a signal small enough to be located directly on the fovea (Curran & Wattis, 1998). Among other things, the location of the stimulus directly on the fovea, for which a visual angle of a maximum of 2° is needed, makes it easier to ensure that all responses are recorded from the same site (McNemar, 1951; Simonson & Brozek, 1952).

A comparison of the different cone types (blue, red and green respectively; designated according to their wavelength of maximum sensitivity) reveals a lower temporal resolution of blue cones, compared to the red and green types (Görtelmeyer & Zimmermann, 1982; Stockman et al., 1993). Under conditions where the resolution of red and green cones may exceed 50 Hz, blue cones resolve flicker only up to frequencies in the range of 18-28 Hz (Stockman et al., 1993). This difference seems to have its origin not in differences between cone types, but in a confinement of the postreceptoral processing of visual input from blue cones to low-rate neuronal pathways. However, the effect of this on the CFFT is small, since all the cone systems are active in normal vision, unless they have been eliminated by overstimulation. This means that the importance of the difference between cone types is small, as long as the stimulus color is not changed during an experiment (Curran & Wattis, 2000; Curran & Wattis, 1998). Flickering blue light, with a frequency above the detection limit (above the AT), “superimposed” on a steady red or green light may give an illusory experience that the steady light flickers, without itself being registered (Stockman et al., 1993).

The pupil of the eye changes its size synchronously with modulation of light, as long as the modulation frequency does not exceed 3 Hz (Brundrett, 1974). A larger pupil permits more light to reach the retina, and therefore results in a higher CFFT (Curran & Wattis, 1998; Smith et al., 1973). The use of an artificial pupil is sometimes recommended to avoid interindividual variation due to differences in pupil size (Aufdembrinke, 1982; Simonson & Brozek, 1952). However, the differences between CFFT values obtained in measurements using artificial and natural pupils respectively have usually proven to be small (McNemar, 1951).

As regards the importance of the amount of light permitted to enter the eye, there are different opinions. It has been proposed that the CFFT should decrease with a decrease in the transparency and the light-scattering characteristics of the eye, for example through increased lens absorption or accumulation of eye pigment (Aufdembrinke, 1982; Lachenmayr et al., 1994). On the other hand it is also asserted that the refraction index of the lens has no effect on the CFFT as long as a flickering stimulus is used and the visual angle is kept small enough to let the light fall perpendicularly into the eye, since the CFFT does not depend on the quality of the picture on the retina (Lachenmayr et al., 1994).

Some studies present results indicating differences in the CFFT between individuals with different iris color. Blue eyes are said to be more sensitive than brown, with green as an intermediate stage (Smith & Misiak, 1973). A possible reason for such an effect is unknown, but the extent of iris pigmentation may correspond to the pigmentation in the rest of the eye, and therefore with the filtering of scattered light. Heavily pigmented irises could possibly correspond with an extensive pigmentation in other parts of the eye, and thereby to a greater extent of “filtering out” of penetrating light. This hypothesis is further supported by experimental results showing a decrease in the CFFT with increasing age, since non-photosensitive pigment is known to accumulate in the ageing eye (Lachenmayr et al., 1994; Smith & Misiak, 1973).

3.2.2 The cerebral cortex

The cerebral cortex is considered to be the part of the visual system that limits the temporal resolution of visual input(Curran et al., 1990; Curran & Wattis, 1998; Simonson & Brozek, 1952). This is indicated by the fact that the maximum frequency of the brain waves recorded by EEG upon flicker exposure is lower than the maximum frequency of ERG waves registered in the same situation (Curran et al., 1990). However, EEG flicker response is also present at frequencies above the CFFT of subjective judgment (Brundrett, 1974; van der Tweel & Verduyn Lunel, 1965). The presence of intraocular transmission, i.e. the transfer of visual impressions from one eye to the other, is a further sign of the importance of postreceptoral processing for the final perception of flicker (Curran et al., 1990; Moulden et al., 1984). If one eye is exposed to flicker, the same signals will be recorded from the unexposed eye (Curran et al., 1990; Curran & Wattis, 1998; Moulden et al., 1984; Simonson

& Brozek, 1952). In the same way, a reduction of the CFFT caused by fatigue or adaptation of the exposed eye is accompanied by a similar reduction in the unexposed eye. Exposed and unexposed eyes are not separable on the basis of experimental data (Moulden et al., 1984).

CFFT values are significantly lower under monocular than under binocular conditions (Ali et al., 1991; Aufdembrinke, 1982). This is probably caused by a loss of important visual cues, for example binocular disparity and convergence, as is the case for other types of one-eyedness. Fatigue due to a higher degree of eyestrain when viewing an object monocularly may also be a source of CFFT reduction. If an eye is blindfolded, the CFFT is decreased relative to the original value (Ali & Amir, 1991). The decrease is greater the longer the time of deprivation. When different stimuli are used for each eye, the use of in-phase signals raise the CFFT, while out-of-phase signals lower it (Simonson & Brozek, 1952).

There are two possible routes for the signals from the optic nerve to the brain, via the lateral geniculate nucleus or via the superior colliculus. The signal routes have different characteristics, but it is still unknown what determines the way of a given signal, or if both routes are active at the same time. It has been proposed that the difference between the AT and the DT reflects a different processing of the transition from flicker to continuum and from continuum to flicker respectively. The presence of different pathways for high- and low-frequency flicker has also been proposed (Moulden et al., 1984). However, these do not seem to map onto the neuronal composition of the retina, nor do they seem to be identical to the geniculate and collicular signal routes previously mentioned.

Upon prolonged exposure to flicker there is a gradual attenuation of the cortical response, i.e. the response for a given stimulus decreases (Küller & Laike, 1998). Attenuation of alpha and delta waves is interpreted as a sign of elevated cortical arousal, particularly if the attenuation mainly affects the pattern of alpha waves. The diminished response is thought to be the result of a targeted elimination of annoying stimuli.

A high CFFT is in some cases said to correlate with high scores in intelligence tests (Aufdembrinke, 1982). However, the results upon which this opinion is based must be regarded as dubious, keeping in mind the difficulties in measuring intellectual capacity. CFFT values have also been brought in connection with different personalities, for example in some studies which reveal relations between a low CFFT and an asocial or psychopathic personality (Ali et al., 1988; Ali & Amir, 1991; Amir et al., 1991). Data from CFFT experiments performed in the area of psychology vary considerably, and several attempts to use the CFFT in order to confirm previous hypotheses have failed (Ali & Amir, 1988; Amir & Ali, 1991; Aufdembrinke, 1982). For example extroverts are regarded as having a constantly elevated level of arousal, which would render them high CFFT values compared with those of normal controls, but in fact they have displayed remarkably low as well as high CFFT values (Ali & Amir, 1988; Amir & Ali, 1991; Sandström et al., 2002; Simonson & Brozek, 1952).

Congenital brain dysfunction or damage may also affect CFFT. Most often the effect is a reduction, as is seen e.g. in Down’s syndrome and sometimes in dyslexia (Curran & Wattis, 1998).

3.2.3 Sex

Several studies demonstrate differences in the CFFT between male and female subjects, but the data are highly inconsistent (Amir & Ali, 1991; Simonson & Brozek, 1952). The number of studies revealing higher CFFT values for men than for women is somewhat larger than the number with the opposite result, but in many cases the differences fail to reach significance

(Amir & Ali, 1991; McNemar, 1951; Simonson & Brozek, 1952). In some cases even the same research group demonstrates contradictory results from different experiments (Ali & Amir, 1988; Amir & Ali, 1991). A hypothesis regarding the reasons for a possible sex dependency of the CFFT has not been proposed to date.

3.2.4 Age

The CFFT seems to be affected by the age of the subject, but the exact nature of the relation and its causes are less evident (Curran et al., 1990; Küller & Laike, 1998; Sandström et al., 2002; Simonson & Brozek, 1952). Several studies have been performed, but the differences between single experiments, i.e. regarding the conception of the CFFT, makes it difficult to compare the results (Curran et al., 1990; Hindmarch, 1988b; Lachenmayr et al., 1994).

The CFFT of children rises prominently with increasing age, which is likely to be the consequence of development and maturation of the CNS (Curran & Wattis, 1998; Sandström et al., 2002). The values peak somewhere between the ages of 16 and 20, and then begin to drop (Curran & Wattis, 1998; Lachenmayr et al., 1994). The threshold values vary greatly among children under 16, probably due to differences in the rate of development. It is still unclear whether the age related decline proceeds gradually after the age of 20, or accelerates at a particular age (Simonson & Brozek, 1952). However, many results speak in favour of a steady, gradual change (Amir & Ali, 1991; Lachenmayr et al., 1994). Histological studies also suggest a linear loss of neuronal elements with ageing of the tissues (Lachenmayr et al., 1994).

Some authors report decreased threshold values for both DT and AT with increasing age. Others report asymmetric changes of the thresholds; either increases or decreases in the gap between the DT and the AT (Curran & Wattis, 2000; Curran & Wattis, 1998; Lachenmayr et al., 1994; Sandström et al., 2002). In most cases ascending values decrease more than descending, which results in a larger difference between the thresholds (Lachenmayr et al., 1994; Sandström et al., 2002). There are also some investigations where age related changes are not shown (Curran et al., 1990; Lachenmayr et al., 1994; McNemar, 1951). These striking variations may probably be explained by variations of the method and the performance of the experiments (Lachenmayr et al., 1994).

The exact causes of a possible age dependent CFFT reduction are uncertain, but age related changes of both the visual organs and the cerebral cortex have been proposed. A suggested explanation is a reduced inlet of light into the eye, caused by reduced pupil elasticity, increased optic density of the lens and accumulation of non-photosensitive pigment in the eye (Aufdembrinke, 1982; Lachenmayr et al., 1994; Simonson & Brozek, 1952). This hypothesis is supported by the fact that the differences between younger and older subjects in many studies decrease with increased luminance of the stimulus. Other possible reasons may be degeneration or loss of retinal or cortical neurons, and/or a slower rate of information processing in the older cerebrum (Aufdembrinke, 1982; Lachenmayr et al., 1994; Sandström et al., 2002). Older individuals are also more susceptible to fatigue, both visual and general, and therefore more likely to experience a CFFT decrease during the course of the day (Aufdembrinke, 1982; Hindmarch, 1988a; Hindmarch, 1988b). An increasing reaction time with increasing age may also contribute, especially when using certain experimental methods (Hindmarch, 1988b).

3.2.5 Physiological/medical state of the subject

In many cases, physiological changes involving the CNS also have an impact on the CFFT (Sandström et al., 2002). For example, the threshold value is decreased by starvation, dehydration, hypoxia, sleep deprivation and by impairment of the general condition of patients with diseases affecting the CNS (Ali & Amir, 1991; Amir & Ali, 1991; Simonson & Brozek, 1952). The effects on the CFFT seem to be related to the exceeding of individual thresholds rather than to absolute physiological values, e.g. values of oxygen saturation (Simonson & Brozek, 1952). A lowering of the CFFT caused by cerebral hypoxia is only slowly restored, which points to the change being caused by an accumulation of deleterious metabolites, which are sluggishly removed.

Concerning the effects of fatigue various results are presented. Investigations of CFFT variability during the working-day at normal work loads have not shown any significant changes among workers with tasks not involving Visual Display Terminals (VDTs) (Murata et al., 1996). Investigations of the effects of VDT-related work reveal both decreased and unaffected CFFT values (Murata et al., 1996; Takahashi et al., 2001). Where changes were observed, the differences also seemed to increase during the week (Murata et al., 1996). Causes of the decreasing CFFT values may be e.g. a diminished inlet of light into the eye due to eyestrain, with a concomitant decrease in pupil size, or a more general CNS fatigue. However, a comparison of different tasks only reveals small differences. As has been mentioned, older workers are thought to be more susceptible than younger ones in this respect (Simonson & Brozek, 1952). Estimating of the effects of fatigue is a problem, since an exact definition of mental/visual fatigue, which is considered as more important than physical/general fatigue, is missing. Criteria for the estimation of visual fatigue have also not been established (Simonson & Brozek, 1952). Subjective judgment cannot be used, since the subjective experience of fatigue does not always correlate well with the results from physiological measurements. Different types of fatigue are also most likely superimposed on each other to give a total effect on the CFFT.

Diseases that may cause changes in the CFFT are e.g. migraine, Alzheimer’s Dementia and different states of depression (Curran et al., 1990). Among patients with migraine, lower CFFT values than those of healthy controls are usually encountered (Coleston et al., 1995). Patients with migraine without aura display lower threshold values than do those with migraine with aura. It is not known whether a difference in visual processing between individuals with and without migraine is really present. General symptoms of headaches and eye discomfort have also been brought in connection with deviations in the CFFT, but since these symptoms often appear together, it has usually not been possible to conclude which one of them is responsible for the CFFT changes (Brundrett, 1974; Wilkins et al., 1989). There are experimental results indicating that subjects with a very high CFFT would score lower in performance tests when exposed to flickering light, than would subjects with a lower original CFFT (Küller & Laike, 1998).

Among subjects those are negatively affected by flicker exposure, a lower extent of alpha wave attenuation than among unaffected individuals is often observed (Küller & Laike, 1998). The difference is most obvious at high flicker frequencies. However, a connection between CFFT and the extent of subjective discomfort has not been established. This phenomenon is thought to depend on a subjective threshold of discomfort rather than on direct physiological effects. Patients with Electromagnetic Hypersensitivity, EHS, have also shown high thresholds compared to healthy controls, both of subjective and neuronal CFFTs (Hansson

Mild, K. et al. 1998; Lyskov, E. et al. 2001a; Lyskov, E. et al. 2001b; Sandström, M. et al. 2002). However, the threshold values have not proven to be affected by the presence of electromagnetic fields (Lyskov, E. et al. 2001b). Different states of depression seem to give decreased values in many cases (Curran & Wattis, 1998).

In patients with Alzheimer's Dementia the descending threshold is reduced to values below the ascending threshold, which is an inversion of the case for normal ageing (Curran & Wattis, 2000; Curran & Wattis, 1998).

3.2.6 Drugs and medication

Variations in the CFFT are often used in order to measure the impact of certain substances on the CNS, particularly the effects of drugs like analgesics, sleeping agents and psychoactive drugs (Curran & Wattis, 1998; Hindmarch, 1988b; Simonson & Brozek, 1952). Sedative and sleeping agents tend to decrease the CFFT, as do betablockers, antihistamines and anticonvulsants (Ali & Amir, 1991; Curran & Wattis, 1998; Sandström et al., 2002; Simonson & Brozek, 1952). However, an exact interpretation of the effects of a certain drug on the CFFT is usually impossible, since drugs affecting the CNS usually have impact on many CNS functions other than the targeted one (Curran & Wattis, 1998; Kranda, 1982a; Ott et al., 1982). Antidepressants decrease or increase CFFT values, or leave them unaffected, depending on the exact nature of the drug (Curran & Wattis, 1998). Treatment with antidepressants may in some cases increase threshold values that have been reduced by depression, but will not make them reach the original level.

Consumption of alcohol results in a CFFT decrease, which persists also when subjective sensations have ceased (Aufdembrinke, 1982; Curran & Wattis, 1998; Sandström et al., 2002; Simonson & Brozek, 1952). The impact on the CFFT of a certain dose is greater with individuals using alcohol more frequently and/or in large amounts. Long-term consumption, on the other hand, leads to neurological damage and therefore to permanently reduced threshold values (Amir & Ali, 1991)

Central stimulating agents, like coffee, nicotine and amphetamine, raise the CFFT (Ali & Amir, 1991; Bruce et al., 1986; Curran & Wattis, 1998; Hindmarch, 1988b). However, to achieve appreciable effects from coffee or nicotine, large doses are needed (Bruce et al., 1986; Curran & Wattis, 1998). The effect of habitual use is especially large for nicotine; to achieve significant effects on CFFT the subject must refrain from smoking for 18 hours or more prior to the experiment (Aufdembrinke, 1982). There seems to be no simple relationship between the dose and the effects on the CFFT (Bruce et al., 1986).

The variability among patients is large, both concerning the nature of the symptoms and the response to treatment (Ott et al., 1982). This makes it difficult to reach general conclusions about the effect of different drugs on the CFFT and about the significance of observed effects (Aufdembrinke, 1982; Görtelmeyer, 1982; Ott et al., 1982). The interpretation is further complicated by the fact that most pharmacological studies are performed on young, healthy subjects (Curran & Wattis, 1998; Hindmarch, 1988b).

3.2.7 External factors

Since the CFFT is said to represent the actual state of the CNS it seems reasonable to assume that external factors that changes the load on the organism will affect the threshold values (Aufdembrinke, 1982; Hindmarch, 1988b; Sandström et al., 2002; Simonson & Brozek, 1952). Factors such as starvation, anoxia et c., which cause a general impairment of the condition of an individual, will generally result in a CFFT decrease.

Noisy surroundings have proven to give increased threshold values (Takahashi & Sasaki, 2001). The degree of impact seems to be related to the subjects attitude to the source of the noise, which gives rise to the assumption that the causes of the CFFT elevation are psychological as well as physiological in nature (Simonson & Brozek, 1952). The high degree of CNS interaction in the processing of sensory stimuli indicated by this introduces considerable difficulties in the interpretation of the effects of these stimuli on the CFFT. Sensory stimuli other than auditory stimuli have also proven to affect the CFFT. For example, exposure to flickering light results in decreased threshold values if the flicker is coarse enough to be consciously perceived, while exposure to flicker with a frequency above the threshold of visibility may result in an elevation. The increased CFFT is interpreted as the consequence of an elevated level of arousal. Some studies reveal decreasing CFFT-values following exposure to high-frequency flicker, but with smaller differences than after exposure to coarse flicker. These smaller decreases are thought to be caused by visual fatigue. When combined, the findings are regarded as a support for the hypothesis that the CFFT is influenced by visual fatigue as well as by general CNS fatigue.

Psychological stressors seem to produce effects in either direction, depending on the nature of the specific stressor and probably also on the situation (Ali & Amir, 1988; Aufdembrinke, 1982; Hindmarch, 1988a; Hüneke, 1982). An elevation of the CFFT is regarded as a sign of elevated alertness, while a lowering is interpreted as a consequence of dissipated attention. Performance anxiety is thought to greatly affect experimental results and in many experiment instructions, it is emphasized that it is of great importance that the subjects receive the correct instructions and are reassured that CFFT values are not a matter of “good” or “bad” performance (Hüneke, 1982; Simonson & Brozek, 1952). More general anxiety in many cases results in decreased threshold values, the reasons for which remain speculative (Curran & Wattis, 1998; Hindmarch, 1988a).

3.3 Stimulus

The possibility of detecting flicker is mostly affected by the frequency of modulation of the used stimuli, but also by a number of other characteristics, e.g. area, wavelength and persistence of the signal, visual angle and pulse shape.

3.3.1 Modulation

When flicker with different waveforms are compared, rectangular waveforms in some cases seem to give lower CFFT-values than sine waves. The effect is proposed to be caused by the complicated harmonics of the rectangular wave (Aufdembrinke, 1982). At low flicker frequencies, the frequency of the third harmonic of the rectangular wave may become low enough to interfere with the first harmonic, which is intended to be the single stimulus (Görtelmeyer & Zimmermann, 1982). However, the difference is comparatively small if the modulation is large enough, and it decreases with increasing signal frequency. There are also results that indicate the opposite effect (Simonson & Brozek, 1952).

The duration of the pulse is also of importance (Amir & Ali, 1991; McNemar, 1951). CFFT values are higher for short and intense pulses, i.e. for a low light/dark-ratio (McNemar, 1951). An increase of the dark period produces an effect comparable to that of an increase in the signal area (Simonson & Brozek, 1952). However, the rectangular waveform most often chosen is the square-wave, i.e. one with a light/dark-ratio of 50/50. There is no simple relation between the CFFT and the light/dark-ratio, and the effects of the light/dark-ratio vary in different experimental situations.

3.3.2 Luminance, intensity and area

The CFFT increases with an increased contrast between the stimulus and the surrounding (Curran & Wattis, 1998; McNemar, 1951). The contrast effect declines for larger signal areas, but for stimuli of all sizes, the highest CFFT values are obtained if the experiment is performed under dark conditions (Curran & Wattis, 1998). The CFFT also increases linearly with the logarithm of the stimulus area on the retina and the stimulus luminance in a relatively large frequency range (Görtelmeyer & Zimmermann, 1982; McNemar, 1951). However, the neuronal composition of the retina is heterogeneous, and the relation between the CFFT and stimulus characteristics is not the same for all parts of it. Mathematical processing of CFFT data using present methods can only be applied on data from exposure of the fovea centralis (with a visual angle below 20°).

The CFFT increases with the logarithm of the intensity up to an individual maximum, above which the threshold values begin to drop again, as an effect of glare (McNemar, 1951; Simonson & Brozek, 1952). Too high intensities will also cause difficulties for the subject to focus on the test stimulus, since the effects of the increased intensity is larger on the peripheral parts of the retina than on the fovea centralis (McNemar, 1951). The relation between the CFFT and intensity does not hold for data from peripheral parts of the retina, just as for the relations to the luminance area (in this case with a visual angle above 15°). If the stimulus area becomes too large, individual CFFT values will become highly variable, in this case also because of difficulties in focusing (McNemar, 1951; Simonson & Brozek, 1952).

3.3.3 Wavelength

Some results indicate a variation of the CFFT with the wavelength of the stimulus (Curran & Wattis, 1998; Sandström et al., 2002), with lower values for red than for green or white light (McNemar, 1951; Sandström et al., 2002). The differences are regarded as small, though, particularly if the signal intensity is adjusted to corresponding levels (absolute values will differ) (McNemar, 1951; Simonson & Brozek, 1952). Which wavelength is actually used often seems to depend on the signal source utilized: White light is most commonly used for stroboscopes, while red is the standard color for light emitting diodes (LEDs). The choice of diode wavelength is in most cases probably a financial matter, since red LEDs are cheaper than those of other colors.

The significance of the stimulus wavelength, which is thought to be larger for the neuronal CFFT than for the CFFT of subjective visual judgment, is partly determined by the contrast between the stimulus and the surrounding (Simonson & Brozek, 1952). If the surrounding is completely dark, the CFFT is assumed to be independent of the wavelength (Aufdembrinke, 1982; Curran & Wattis, 1998). However, the threshold values are always lower with broadband stimulus light than with light of a single wavelength.

3.4 The use of the CFFT

Since the CFFT at least partly depends on external loads on the organism, the entity is valuable in evaluating the effects of certain stimuli on the CNS (Hindmarch, 1988b; Simonson & Brozek, 1952). This has made it an established tool in pharmacological studies, especially of psychoactive drugs. The variable can be rapidly measured, which, apart from the advantages concerning time and financial aspects, means that systemic changes of the subjects during the performance of the experiment will usually not affect the outcome (Curran & Wattis, 1998). As a direct physiological response, it is also not affected by cultural, social or educational differences among the subjects (Curran & Wattis, 1998). The results change only little with repeated experiments, which indicates that no learning effect is present (Curran & Wattis, 1998; Simonson & Brozek, 1952). The results usually improve somewhat in the beginning of a test series (McNemar, 1951), but the effect ceases as the subjects become familiar with the test situation (Simonson & Brozek, 1952). However, there are different opinions regarding the possible presence and effect of learning (Aufdembrinke, 1982; Curran & Wattis, 1998; Simonson & Brozek, 1952).

The main argument against the use of the CFFT is perhaps the dubious element of using a variable, which itself is a function of numerous other variables, to characterize the state of an individual (Aufdembrinke, 1982; Görtelmeyer, 1982; Simonson & Brozek, 1952). It is questionable how the CFFT actually should be related to the physiological state and performance of the CNS in a more general way, since the alertness and performance required in a particular experiment vary greatly between different methods and designs (Curran & Wattis, 2000; Görtelmeyer, 1982). CFFT changes also do not correlate equally well with all other measurements of physiological and intellectual activity/capacity (Curran et al., 1990). The great differences between individuals also make the interpretation of results from small subject groups a problem (Sandström et al., 2002).

3.5 Methods of measuring the CFFT

The choice of a method of measurement depends on the factors or characteristics evaluated in the study. The range and size of actual CFFT values differ markedly between the methods. Interindividual variations are large for all methods (Görtelmeyer & Zimmermann, 1982; Sandström et al., 2002). The principal methods are the following:

The Method of Limits
The Method of Constant Stimuli
The Method of Adjustment

All methods are available as adjusted variants. Those most commonly used are the Method of Limits and the Method of Adjustment (Curran & Wattis, 1998). The measurements can be performed in a one-dimensional way, in which only one parameter (signal frequency or amplitude) is varied (Kranda, 1982a; Sandström et al., 2002), or in a two-dimensional way, where both parameters are varied simultaneously.

The different methods also yield different CFFT-values. The CFFT is usually reported as the mean value of several runs in both directions, where a minimum of three ascending and descending runs, respectively, is recommended (Hindmarch, 1988b). Values from runs in different directions should not be merged when using a method that gives separate ascending and descending thresholds, but still this is sometimes done.

3.5.1 The Method of Limits

In the Method of Limits the flicker frequency is varied consecutively over a wider range (Aufdembrinke, 1982; Ott, 1982). The method is also referred to as the Method of Minimal Change or the Method of Serial Exploration. The CFFT is defined as the point between the last “flicker response” and the first “continuous response”, or as the point between the average values of the DT and the AT; i.e. the midpoint of what is designated as the “interval of uncertainty”(Curran & Wattis, 1998). The method has a continuous and a discontinuous variant (Ott, 1982). In the continuous method the flicker frequency is varied consecutively in steps of equal size, while in the discontinuous variant breaks of about 1,5 seconds are introduced between the frequency changes in order to separate them. This makes the discontinuous method more time-consuming, but gives it the advantage of decreasing the exposure time of the test subject to continuous, visible flicker. This in turn decreases the degree of adaptation, and due to this also the risk of changes in the CFFT during the experiment. A third variant, the Stair-case Method is also available, in which the direction of the frequency change is altered with each change of the subject’s response (flicker – continuous light) (Aufdembrinke, 1982).

When the Method of Limits is used, different values are usually obtained for descending and ascending thresholds (Aufdembrinke, 1982; Curran et al., 1990). In most cases, the value of the AT is lower that that of the DT (Curran & Wattis, 2000; Curran & Wattis, 1998), and AT values also display a larger intraindividual variability (Curran et al., 1990; Ott, 1982). The main reason for the lower AT value is assumed to be temporal adaptation. The primary causes of this adaptation are exposure to coarse flicker during the experiment and a summation of afterimages, caused by persistence of the signal amongst other things (Aufdembrinke, 1982; Curran et al., 1990; Ott, 1982). None of these phenomena are present at descending runs, since these start from a level where the flicker is perceived as continuous light (no adaptation is possible). As mentioned above, it has also been proposed that the origin of the threshold difference should be the processing of flicker with descending and ascending frequency by different cortical functions.

A higher speed of frequency change will diminish the space between the AT and the DT. This may result from less time for adaptation, but perhaps mainly from the fact that the frequency change during the response lag of the subject will be larger at a higher speed (Aufdembrinke, 1982). The difference is also smaller with the use of the discontinuous method, probably because of decreased adaptation. CFFT values are sometimes presented as an average of DT and AT values, a procedure that must be considered highly dubious, as long as the cause of the difference between the threshold values has not been established (Ott, 1982).

The CFFT values obtained with the Method of Limits also change with the starting point chosen (Aufdembrinke, 1982; Curran & Wattis, 1998). A low starting frequency for the ascending runs will give lower AT values than if the starting frequency is high, and a high starting frequency for the descending runs will give a higher DT value than a lower starting frequency. The differences are more prominent for flicker sensitivity of the peripheral parts of the retina, but in general they are small.

A problem with the Method of Limits is whether there is a physiological mechanism behind the gap between the AT and the DT, or if it is just an artefact (Aufdembrinke, 1982). Nor does the method distinguish between CFFT changes caused by changes in sensory characteristics of the subject and those caused by response bias such as changes in behaviour of the subject due to anticipation or to how the test situation is experienced (Curran & Wattis, 1998; Ott, 1982). Differences in reaction time among subjects are also likely to produce variations of CFFT values. In addition, there is always the risk that the subjects more or less unconsciously learn when (after which time or after how many changes) the threshold value is reached (Curran & Wattis, 1998). This risk may be avoided, or at least diminished, if the starting frequency is changed for different runs.

The main advantage of the Method of Limits, both for subjects and investigators, is that it is fast and easily performed (Curran & Wattis, 1998). The short time needed also makes it less likely for physiological changes during the tests to affect the results.

3.5.2 The Method of Constant Stimuli

In this method, also called the Method of Randomly Assigned Frequencies or the Cybernetic Method, flickering stimuli with frequencies in the transition zone between continuum and perceived flicker are presented in a random order (Aufdembrinke, 1982; Curran & Wattis, 1998; Görtelmeyer, 1982; Ott et al., 1982). The CFFT is defined as the frequency at which flicker is detected in 50% of the cases, which is also the midpoint of the interval of uncertainty (Curran & Wattis, 1998). The random order decreases the risk of the CFFT to be influenced by adaptation or expectations of the subject, as might be the case when the frequency is continuously changed in a known direction. A variant of the method, the Method of Restricted Frequencies only uses flicker frequencies within a narrow, pre-defined "critical band". When this method is employed it is important that the right critical band is used, with the CFFT well within its limits.

An adjusted method, the Forced Choice Method, presents a continuous and a variable stimulus at the same time, and the subject is asked to decide whether the variable signal is flickering or not (Aufdembrinke, 1982; Curran & Wattis, 1998).

All types of this method give only one CFFT value, and are said to measure sensory sensitivity only, i.e. to be free from response bias. There is also thought to be less risk of learning effects with repeated measurements, and less variation between experiments performed at different occasions. A drawback of the method is that it is very time-consuming, since very large amounts of data need to be collected.

3.5.3 The Method of Adjustment

When this method, also known as the Method of Average Error is employed, the subject varies the flicker frequency until he or she finds the highest detectable frequency (Aufdembrinke, 1982). Only one threshold value is usually obtained.

When this method is used, the variations in response time, i.e. the time needed for a subject to decide whether the stimulus is flickering or not, will cause variations in the degree of flicker exposure. The consequence of this will be variations in temporal adaptation, which cannot be controlled by the investigator (Kranda, 1982b). The chosen starting points also affect the CFFT values obtained.

4. Part II: Test of the Methods of Limits

The study described below was performed using the continuous Method of Limits. The aim of the study was to explore the effect of various individual characteristics and experimental conditions on the CFFT. The equipment used was designed in the department of Non-Ionizing Radiation at the National Institute for Working Life, Umeå, Sweden. The study was performed as a validation of a method of CFFT measurement used as part of a neurophysiological test battery in the department.

4.1 Method

4.1.1 Equipment

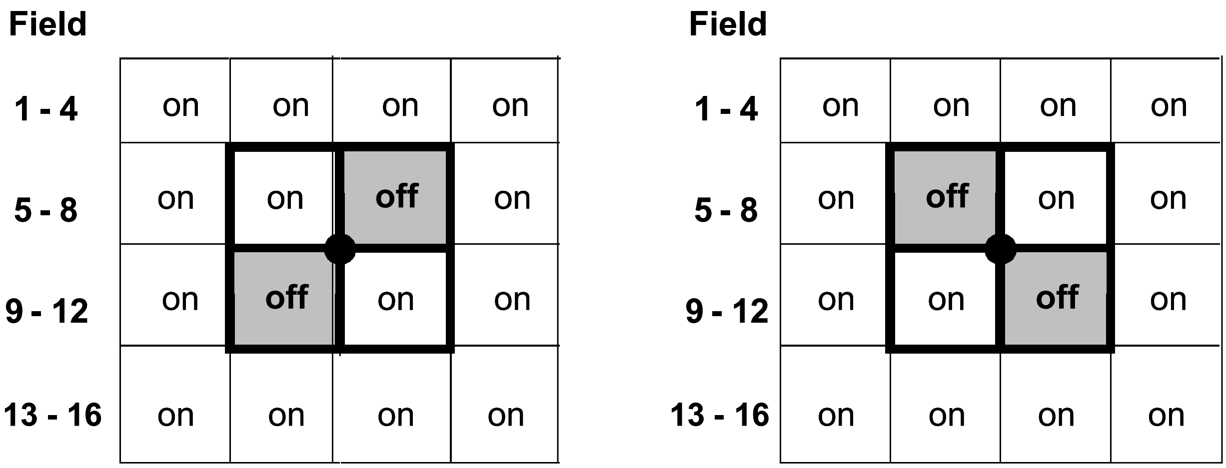
The CFFT measurement equipment consists of two separate units; an LED matrix and a control unit.

The LED matrix consists of 144 light emitting diodes, LEDs. The diodes, Model HLMP-2655, are of size 1*1 cm with a wavelength of 635 nm (color: red). The matrix is divided into 16 quadratic fields. The fields are made up of nine quadratic LED units, consisting of four diodes each. The area of the diode screen is 12*12 cm. The centre of the screen is marked out with a black dot to facilitate focusing of the subject's gaze, and thereby ensure central vision to the greatest possible extent (fig.1). The LED fields may be switched on or off separately, using the control unit. The light can also be modulated with a frequency and character set by an external signal generator. Sinusoidal as well as square pulses may be used. The modulation frequency is electronically controlled by a simple, external control unit to ensure constant and equal speed of change in every run. The frequency is continuously varied between 25 and 70 Hz. The ascending time from 25 to 70 Hz is approximately 20 seconds, and the descending time, from 70 to 25 Hz is approximately 30 seconds.

In standard experiments the 12 outer fields are constantly switched on, while the four central fields are switched on and off in a diagonal, alternating mode. With the LED-fields numbered from 1 to 16, starting in the upper left corner, the different modes are described in fig. 1.

The subject's response (flicker/fusion) is communicated by a hand held switch, connected to the control panel of the experimenter. The frequency change is then interrupted by the investigator, and the actual frequency is read from the display of the signal generator.

In the performed CFFT measurements, a common signal generator (Metrix GX 240) was used. The generated pulse is in this case a square wave with an amplitude of 0.8 mV. The rise time is 0.15 msec. and fall time eight µsec., which is short enough for the pulsed to be considered a pure square wave (Appendix 2; fig. 3, 4).



Field				
1 - 4	on	on	on	on
5 - 8	on	on	off	on
9 - 12	on	off	on	on
13 - 16	on	on	on	on

Field				
1 - 4	on	on	on	on
5 - 8	on	off	on	on
9 - 12	on	on	off	on
13 - 16	on	on	on	on

Figure 1. The LED matrix in the two "flickering" modes. The 4 marked centre fields are activated during the test by either being switched on or off. The black dot marked in the centre is used as a visual focus during the test.

4.1.2 Experimental set-up and performance

The subjects were seated in a semi-reclining chair, placed in a windowless exposure chamber, facing the LED matrix (distance approximately 1.3 m). The matrix was placed with its central point 90 cm above the ground. No head fixation was used (fig. 2). Signal generation and frequency variation were regulated from a control panel outside the exposure chamber. The subjects were adapted to the dark for 5 minutes. At the beginning of the experiment, the subjects were told to focus on the dot in the centre of the LED matrix to ensure the use of central vision during the experiment. The stimulus signal was then turned on, and the frequency of the light ascended and descended until flicker or fusion frequency was reached. This point was indicated by the subject using a hand held switch. Seven runs were carried out in increasing and decreasing direction, respectively. The first two runs were regarded as test runs, and excluded from later processing.

The subjects were tested twice, once in the morning and again in the afternoon (a.m. and p.m.). In all cases except one both tests were performed on the same day. Subjects with visual defects wore their everyday visual correction. After completion of the flicker test, the subjects were asked to fill in a questionnaire regarding age, sex, eye status and color, headaches, VDT-work, experience of the experimental situation etc.

Separate from the main study, a smaller number of subjects were tested for a longer period to investigate the variations of the CFFT over time.

4.1.3 Statistical analysis

The statistical processing of measurement data was performed using SPSS (Statistical Package for the Social Sciences) 11.0 for Windows. The influence on the CFFT of the variables under study was investigated using Univariate Analyses of Variance. Only crude analyses were performed due to the small quantity of data.

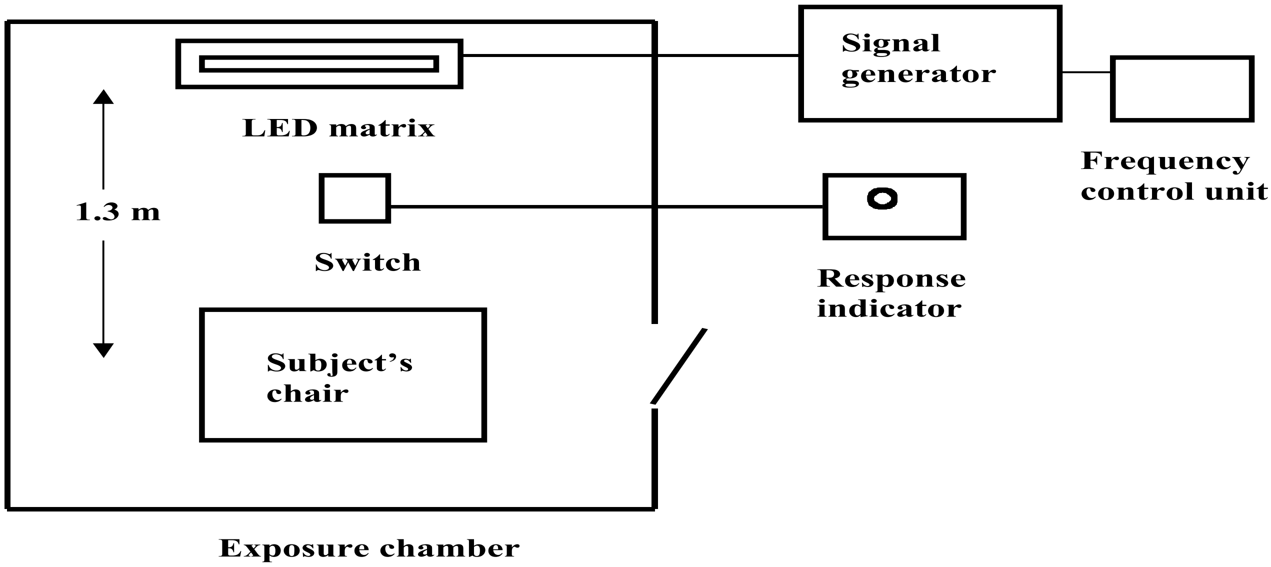


Figure 2. Experimental set-up

4.2 Results

Twenty-five subjects were recruited for the study; 9 men and 16 women, aged from 27 to 60. Prior to the analysis, the subjects were separated into two age groups; aged <40 (9 subjects; 3 male, 6 female) and aged >40 (16 subjects; 6 male, 10 female). The number of subjects with astigmatism was 10 and the number without was 15. All subjects were employed at the National Institute for Working Life, Umeå.

4.2.1 Difference between descending and ascending CFFTs

There is a significant difference between descending and ascending threshold values. DT values are higher than AT values, both for an average of all runs (1.0 Hz; p = 0.009; table 1) and when a.m. and p.m. experiments are separated. However, the difference between a.m. ascending and descending thresholds fails to reach significance (a.m. difference: 1.0 Hz; p= 0.098; p.m. difference 0.9 Hz; p=0.032; table 3). There is a trend toward higher threshold values in the morning compared to the afternoon, although these differences are not statistically significant (DT difference: 0.9 Hz, p= 0.054; AT difference: 0.8 Hz, p= 0.135; table 3). A significant difference between descending and ascending runs is found in the male subject group, but not in the female subject group (males: 1.2 Hz, p= 0.023; females: 0.8, p= 0.085; table 2).

Table 1. Difference between descending and ascending CFFT.

Descending/ascending	No. of runs	No.of subjects	CFF median (Hz)	CFF mean (Hz)	SE	p (crude)
DT	250	25	42.4	41.9	0.2	
AT	250	25	40.9	40.9	0.3	0.009

4.2.2 Sex differences

Male subjects display a higher average CFFT than female subjects. The difference is small, but highly significant (difference: 0.7 Hz; p=0.000; table 2). It is valid for both descending and ascending threshold values (DT difference: 1.3 Hz, p=0.000; AT difference: 1.2 Hz, p=0.035; table 2) and for a.m. and p.m. values, respectively (difference a.m.: 1.9 Hz; p=0.001; difference p.m.: 1.0 Hz, p=0.034; table 3). As mentioned above, male subjects display significantly higher DT than AT values when a comparison is made within the group, while female subjects do not. In the female subject group there is also no significant difference between values from a.m. and p.m. runs. The higher average CFFT for male subjects is significant both in the younger (age: <40) and the older (age: >40) subject group, but is more pronounced among older subjects (difference younger subjects: 1.1 Hz, p=0.042; difference older subjects: 1.8 Hz, p=0.000; table 4). When astigmatic and nonastigmatic subjects are compared, the sex difference remains among astigmatic subjects, but among nonastigmatic subjects the results are reversed, i.e. nonastigmatic females have a higher CFFT average than nonastigmatic males (difference 1.2 Hz, p=0.003; table 5).

Table 2. CFFT and sex

Sex	No. of runs	No. of subjects	CFF median (Hz)	CFF mean (Hz)	SE	p (crude)
Male	90	9	42.3	42.3	0.3	
Female	160	16	41.6	40.9	0.2	0.000
Male; DT	90	9	42.7	42.9	0.3	
Male; AT	90	9	40.6	41.7	0.4	0.023
Female; DT	160	16	41.8	41.3	0.3	
Female; AT	160	16	41.0	40.5	0.4	0.085
Male; DT	90	9	42.7	42.9	0.3	
Female; DT	160	16	41.8	41.3	0.3	0.000
Male; AT	90	9	40.6	41.7	0.4	
Female; AT	160	16	41.0	40.5	0.4	0.035

4.2.3 Differences with time of day

There is at trend towards lower CFFT values in experiments preformed in the morning compared to in the afternoon. The average CFFT is higher for a.m. than for p.m. experiments (difference: 0.8 Hz, p=0.019; table 3). When the CFFT values are separated into DTs and ATs, there is still a significant difference between a.m. and p.m. for descending, but not for ascending, threshold values (difference DT: 0.9 Hz, p=0.054; difference AT: 0.8 Hz, p=0.135; table 3). When subjects are separated on an age basis there is a significant difference between a.m. and p.m. values among older subjects (difference: 1.2 Hz, p=0.010; table 4), but not among younger ones (difference: 0.3 Hz, p=0.613; table 4). Also astigmatic subjects display no significant difference between a.m. and p.m. CFFT, while nonastigmatic subjects do. However, the difference with time of day does not change when astigmatic subjects are sorted out.

Table 3. CFFT and time of day

Time of day	No. of runs	No. of subjects	CFF median (Hz)	CFF mean (Hz)	SE	p (crude)
a.m.	250	25	42.5	41.8	0.3	0.019
p.m.	250	25	41.3	41.0	0.2	
a.m.; DT	125	25	42.8	42.3	0.4	0.098
a.m.; AT	125	25	41.9	41.3	0.5	
p.m.; DT	125	25	42.0	41.4	0.3	0.032
p.m.; AT	125	25	40.5	40.5	0.4	
DT; a.m.	125	25	42.8	42.3	0.4	0.054
DT; p.m.	125	25	42.0	41.4	0.3	
AT; a.m.	125	25	41.9	41.3	0.5	0.135
AT; p.m.	125	25	40.5	40.5	0.4	
Male; a.m.	90	9	43.1	43.0	0.4	0.005
Male; p.m.	90	9	41.5	41.6	0.3	
Female; a.m.	160	16	41.9	41.1	0.4	0.269
Female; p.m.	160	16	41.1	40.6	0.3	
a.m.; Male	90	9	43.1	43.0	0.4	0.001
a.m.; Female	160	16	41.9	41.1	0.4	
p.m.; Male	90	9	41.5	41.6	0.3	0.034
p.m.; Female	160	16	41.1	40.6	0.3	

4.2.4 Age differences

There are pronounced differences between younger (<40) and older (>40) subjects. Younger subjects display a significantly higher average CFFT, both for the whole group (difference 2.3 Hz; p=0.000; table 4) and for male and females, respectively (difference males: 1.9 Hz, p=0.000; difference females: 2.6 Hz; p=0.000; table 4). The difference between the age groups also remains when a.m. and p.m. values are analyzed separately and when subjects are compared with respect to astigmatism. In the older subject group, higher CFFT values are obtained in a.m. compared to p.m. experiments (difference: 1.2 Hz; p=0.010; table 4), but this is not the case in the younger subject group. The same is true for differences between descending and ascending threshold values; i.e. a significant difference is only present among older subjects. Males of both age groups display a higher CFFT, but the sex differences are also more prominent in the older subject group (difference older: 1.8 Hz; p=0.000; difference younger: 1.1 Hz; p=0.042; table 4). The differences between astigmatic and nonastigmatic subjects are also larger among subjects >40 (table 5).

4.2.5 Differences between astigmatic and nonastigmatic subjects

When subjects are compared with respect to astigmatism, astigmatic subjects display a significantly lower average CFFT than nonastigmatic subjects (difference: 1.2 Hz; p=0.000; table 5). This remains true also when females and subjects >40 are compared within groups. For subjects <40 a difference is present, but fails to reach significance. When male subjects are compared, astigmatic subjects have a higher average CFFT than nonastigmatic subjects (difference: 3.3 Hz, p=0.000; table 5).

CFFT values for astigmatic subjects are lower than those for nonastigmatic subjects, both for descending and ascending runs (difference DT: 2.7 Hz; p=0.000; difference AT: 1.5 Hz, p=0.000; table 5). However, there is no significant difference between ascending and descending thresholds within the astigmatic group (difference: 0.2 Hz, p=0.278; table 5). The astigmatic group also displays no difference between CFFT values from a.m. and p.m. experiments, as opposed to the nonastigmatic group (difference: 0.9 Hz, p=0.019; table 5). On the other hand, the higher CFFT of nonastigmatic subjects is highly significant both in a.m. and p.m. experiments (p=0.000; table 5). The difference between astigmatic and nonastigmatic subjects is larger among subjects >40 than among subjects <40 (table 5)

Table 4. CFFT and age.

Age	No. of runs	No. of subjects	CFF median (Hz)	CFF mean (Hz)	SE	p (crude)
<40	180	9	42.9	42.9	0.3	
>40	320	16	40.9	40.6	0.2	0.000
<40; DT	90	9	43.2	42.8	0.3	
<40; AT	90	9	42.6	42.9	0.4	0.898
>40; DT	160	16	41.8	41.3	0.3	
>40; AT	160	16	40.1	39.8	0.4	0.001
<40; a.m.	90	9	43.6	43.0	0.5	
<40; p.m.	90	9	42.6	42.7	0.3	0.613
>40; a.m.	160	16	41.8	41.2	0.4	
>40; p.m.	160	16	40.5	40.0	0.3	0.010
<40; a.m.	90	9	43.6	43.0	0.5	
>40; a.m.	160	16	41.8	41.2	0.4	0.002
<40. p.m.	90	9	42.6	42.7	0.3	
>40. p.m.	160	16	40.5	40.0	0.3	0.000
<40. Male	60	3	44.0	43.6	0.5	
>40. Male	120	6	42.0	41.7	0.3	0.000
<40. Female	120	6	42.7	42.5	0.3	
>40. Female	200	10	40.3	39.9	0.3	0.000
<40; Male	60	3	44.0	43.6	0.5	
<40; Female	120	6	42.7	42.5	0.3	0.042
>40; Male	120	6	42.0	41.7	0.3	
>40; Female	200	10	40.3	39.9	0.3	0.000

Table 5. Difference between astigmatic and nonastigmatic subjects

Astigmatic/nonastigmatic	No. of runs	No. of subjects	CFF median (Hz)	CFF mean (Hz)	SE	p (crude)
Astigm.	200	10	40.5	40.1	0.3	
Nonastigm.	300	20	42.5	42.3	0.2	0.000
DT; Astigm.	100	10	40.5	40.3	0.3	
DT; Nonastigm.	150	15	43.4	43.0	0.3	0.000
AT; Astigm.	100	10	40.8	40.0	0.5	
AT; Nonastigm.	150	15	40.9	41.5	0.3	0.008
Astigm.; DT	100	10	40.5	40.2	0.3	
Astigm.; AT	100	10	40.8	40.0	0.5	0.667
Nonastigm.; DT	150	15	43.4	43.0	0.3	
Nonastigm.; AT	150	15	40.9	41.5	0.3	0.001
Astigm.; a.m.	100	10	40.6	40.5	0.5	
Astigm.; p.m.	100	10	40.5	39.8	0.4	0.278
Nonastigm.; a.m.	150	15	43.4	42.7	0.3	
Nonastigm.; p.m.	150	15	41.9	41.8	0.3	0.019
a.m.; Astigm.	100	10	40.6	40.5	0.5	
a.m.; Nonastigm.	150	15	43.5	42.7	0.3	0.000
p.m.; Astigm.	100	10	40.5	39.8	0.4	
p.m.; Nonastigm.	150	15	41.9	41.8	0.3	0.000
Astigm.; <40	60	3	42.3	42.1	0.6	
Astigm.; >40	140	7	39.2	39.2	0.4	0.000
Nonastigm.; <40	120	6	43.5	43.2	0.3	
Nonastigm.; >40	180	9	41.9	41.6	0.3	0.000
Male; Astigm.	40	2	44.7	44.9	0.5	
Male; Nonastigm.	140	7	41.2	41.6	0.3	0.000
Female; Astigm.	160	8	38.7	39.0	0.3	
Female; Nonastigm.	160	8	43.4	42.8	0.3	0.000
Astigm.; Male	40	2	44.7	44.9	0.5	
Astigm.; Female	160	8	38.7	38.9	0.3	0.000
Nonastigm.; Male	140	7	41.2	41.6	0.3	
Nonastigm.; Female	160	8	43.4	42.8	0.3	0.003

4.2.6 Intraindividual and interindividual differences

The intraindividual differences between runs are small (SE: 0.97-1.5) compared to the differences between individuals (Mean: 35.6-46.4). Among the 25 subjects in the main study, the standard deviation in many cases was smaller in the p.m. than in the a.m. runs.

In figures 2 and 3, the intra- and interindividual differences and their variations over time are illustrated.

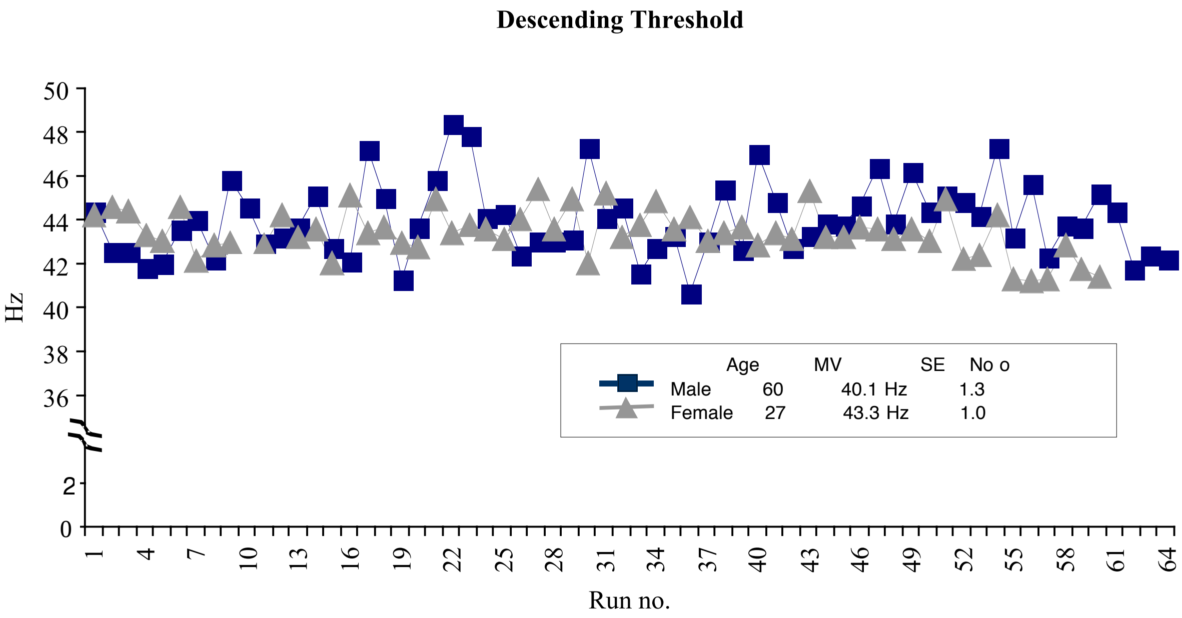

Descending Threshold

Figure 2. Intra- and interindividual differences, descending threshold values

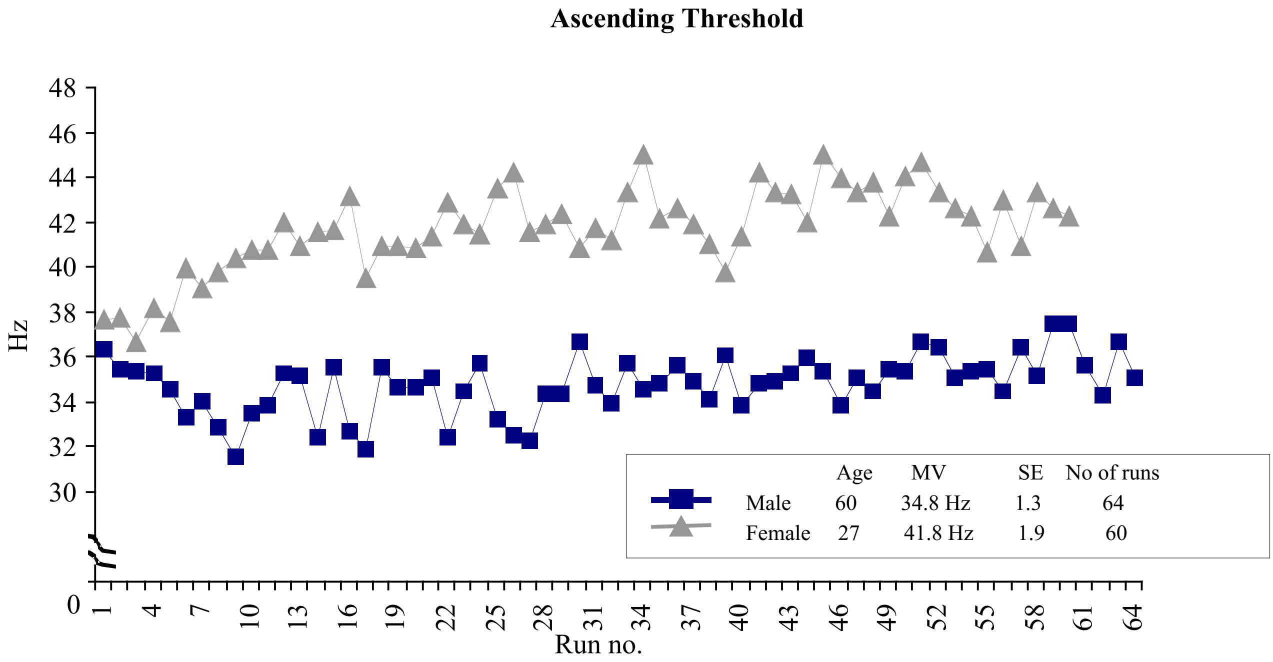

Ascending Threshold

Figure 3. Intra- and interindividal differences, ascending threshold values

4.3 Discussion

The factors with the largest impact on the CFFT were found to be descending or ascending flicker frequency, time of day, age, sex and astigmatism of the subjects. Differences are larger intra- than interindividually, especially over a longer time. This supports the view on the CFFT not as a function of external factors only, but as an individual characteristic, which may be externally modified (Curran & Wattis, 1998; McNemar, 1951; Sandström et al., 2002). There seems to be a slight decrease in intraindividual variation between the first few experiments, but when a greater number of experiments are performed, there is no apparent change in the long run. This might support the idea that threshold values are stable over time, once the subject has become comfortable with the test situation (Simonson & Brozek, 1952).

The difference between descending and ascending thresholds may be caused by the measurement method (continuous Method of Limits), and not by differences in the cerebral processing of flicker input with decreasing or increasing frequency (Aufdembrinke, 1982; Curran & Wattis, 1998; Ott, 1982). During ascending runs, when the stimulus frequency is gradually increased from a low starting frequency, the subject is exposed to clearly visible flicker before responding. Exposure to coarse flicker has been reported to lower the flicker detection limit, as an effect of a summation of afterimages and temporal adaption of neuronal elements. During descending runs, no such effect is present, since the subject in this case is exposed to non-visible flicker only. The greater differences between the DT and the AT in p.m. compared to a.m. runs may be due to an effect of neuronal as well as physical fatigue. This is supported by several subjects reporting difficulties in focusing the LED matrix, as well as in concentrating on the task. The greater difference between the DT and the AT for older than for younger subjects might be explained by fatigue. Older individuals are known to be more susceptible to fatigue, physical as well as visual and neuronal, than younger ones, and this might cause the older subjects to respond stronger to the exposure to visible flicker (Simonson & Brozek, 1952). This lower tolerance of older individuals may also be the factor behind the finding of a greater difference between a.m. and p.m. CFFT among older subjects, when comparing the age groups.

When the results are analyzed with respect to the time of day, a trend toward a CFFT decrease during the day can be observed. The difference is larger between DT than between AT values. If the ascending threshold is actually a product of adaptation, this may have something to do with its smaller variations during the day. The impact of the flicker exposure during ascending runs may be great enough to overcome the effects of possible fatigue, which may be responsible for the observed lowering of the descending threshold. Variations with the time of day are more prominent among older subjects; perhaps due to a decreasing tolerance to fatigue with increasing age (Simonson & Brozek, 1952). However, individual CFFT values apparently do not change considerably over a longer time. The slight decrease observed between the a.m. and p.m. experiments in the main study may be a sign of the subjects being more adapted to the test situation at the second experiment (Simonson & Brozek, 1952). As a consequence of this, it may be reasonable to consider the result from a single experiment representative for the average CFFT of an individual.

Male subjects display a higher average CFFT than female subjects. This has been observed in previous studies (Amir & Ali, 1991; McNemar, 1951; Simonson & Brozek, 1952), but there are also contradictory results and no plausible physiological explanation for a sex dependency of the CFFT has yet been proposed (Ali & Amir, 1988; Amir & Ali, 1991;

McNemar, 1951; Simonson & Brozek, 1952). The sex difference is larger for the DT than for the AT, as well as for a.m. values compared to p.m. values. If the lower ascending values are to be regarded as possible artefacts, this may have something to do with the distribution of the results. On the other hand, if astigmatic and nonastigmatic subjects are separated, the mentioned sex difference remains only in the astigmatic group. In the nonastigmatic group, the female subjects have a higher average CFFT than the male subjects. Considering this, together with the fact that there are more female astigmatic subjects than male ones, the observed higher CFFT among males may merely be a result of the distribution of subjects with astigmatism according to sex.

Subjects of the age <40 generally display higher CFFT values than subjects of the age >40. This difference is present when the subjects are grouped both according to sex and according to astigmatism/nonastigmatism. There are different opinions about the effects of ageing on the CFFT, but threshold values are in general proprosed to decrease with increasing age (Amir & Ali, 1991; Aufdembrinke, 1982; Lachenmayr et al., 1994; Sandström et al., 2002; Simonson & Brozek, 1952). The lowered flicker detection limits are thought to be caused by a decreased transparency of the eye, a slower rate of neuronal processing and loss of neuronal elements. Older individuals are also more susceptible to the effects of fatigue, as mentioned before, and this may increase the influence of the time of day on threshold values (Simonson & Brozek, 1952). In line with this, the present investigation reveals a much smaller difference between the a.m. and p.m. experiments among younger than among older subjects. There is a greater difference between astigmatics and nonastigmatics in the older subject group, for which no explanation can be given. However, the results may be affected by the uneven distribution of the subjects; e.g. there are only two male astigmatics in the group of age <40. This uneven distribution may also be a reason for the greater sex difference in the older subject group (There is a higher percentage of astigmatics in the female than in the male subject group, and within each group there is a higher percentage of astigmatics aged above than below 40).

No explanation can be proposed for the difference between subjects with and without astigmatism. However, it may be suspected to have its origin in the eye. The differences are pronounced in that, upon comparison astigmatics display markedly lower CFFT values than nonastigmatics. The lower average CFFT is not only caused by lower threshold values in general, but also by the fact that astigmatic subjects show no marked difference neither between DT and AT values nor between a.m. and p.m. values. Among nonastigmatic subjects these two differences are present also when the astigmatics have been sorted out. On the other hand, both a.m. and p.m. values are lower for subjects with astigmatism than for subjects without. The same is true for both descending and ascending thresholds. It should be emphasized that all subjects with visual defects wore their normal visual correction when performing the test.

4.4 Conclusion

This pilot study shows that when the continuous Method of Limits is employed, the DT and the AT should be treated separately since the values differ markedly. Furthermore, from the results of this study it may be concluded that age, sex and presence of astigmatism should be considered as individual parameters that might influence the result. When a case-control study is performed, control subjects should be chosen so as to match the cases regarding the factors mentioned, in addition to the factors under study. When matched subject groups are not used, age, sex, and possible astigmatism should still be considered when interpreting the results. The time of the experiments should also be taken into account, and as far as possible all experiments to be compared should be performed at the same time of day.

5. General conclusions

The CFFT is an inherent characteristic, which is modified by the current state of the individual and by various external factors to give a final, measurable value. As such it seems to be of use in investigations of the effects of various factors on the CNS. However, it is of importance that the factors affecting the CFFT at a particular measurement are specified to the greatest possible extent to ensure that any observed effects are in fact caused by the variables under study. The exact CFFT values obtained in an experiment also seem to depend on the experimental method used, and this must be considered both when designing the experiment and in the treatment of data. Since it is difficult to compare results from different studies due to the impact of different experimental conditions, a database of normal values for measurements with the design and equipment in question should be compiled before undertaking a study. However, this should also be done with the various factors affecting the CFFT taken into consideration in order to avoid a skewed distribution of the data, and to be truly useful, such a database would have to include a considerable number of subjects.

Of special interest for further studies is the impact of visual defects, since these are very common in the population, and seem to affect the CFFT even when visual correction is used.

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No.	Investigators	Aim	Test population	Method	Outcome
1	McNemar et al. (1951)	Effects of several factors on the ordering of subjects with respect to the CFFT.	- 72 subjects (46 male, 26 female) - Age: 16-43 (73% < 25)	**1. Stroboscope** Stroboscope with frequency counter; light source: neon lamp in a parabolic reflector. Pulse duration 45 µs; frequency 600-3600 rpm. Test patch with frosted lens; diameter 0.5 in. **2. Episcotister** Light source: 60W-Mazda lamp with two lenses focusing the beam in a single direction. Signal generated by a rotating disc. Test patch with diameter 0.5 in. at eye level. Head fixation with head rest similar to that of a stereoscope. Three ascending and descending runs respectively per test. Background illumination: artificial. The CFFT is computed as an average of all six runs per test.	Different results with different equipment. The ordering of subjects changed markedly with changes in test patch brightness and between different days, but not by changing from monocular to binocular vision, using an artificial pupil or according to the wavelength of the light source. Great intraindividual variations in response error variability.
2	Brundrett et al. (1973)	Flicker sensitivity.	- 19 subjects - Age: ”young”	**1. Subjective visual judgment** Display diameter: 0.5 inches; white light with a luminance of 375 cd/m^2. Sinusoidal modulation of frequency and amplitude; frequencies in the range of 5-50 Hz presented in random order. **2. EEG** Subject lying on a couch with the light source (neon lamp) 15 cm above the eye. Spiky wave with constant amplitude; frequency increased from 30 to 90 Hz in steps of 5 Hz. Longer “presentation time” for higher frequencies. Five ascending and five descending runs.	Great interindividual variations in flicker sensitivity. Decreased sensitivity with increasing age. Lower rate of evoked signal attenuation in subjects reporting regular headaches and/or eyestrain.

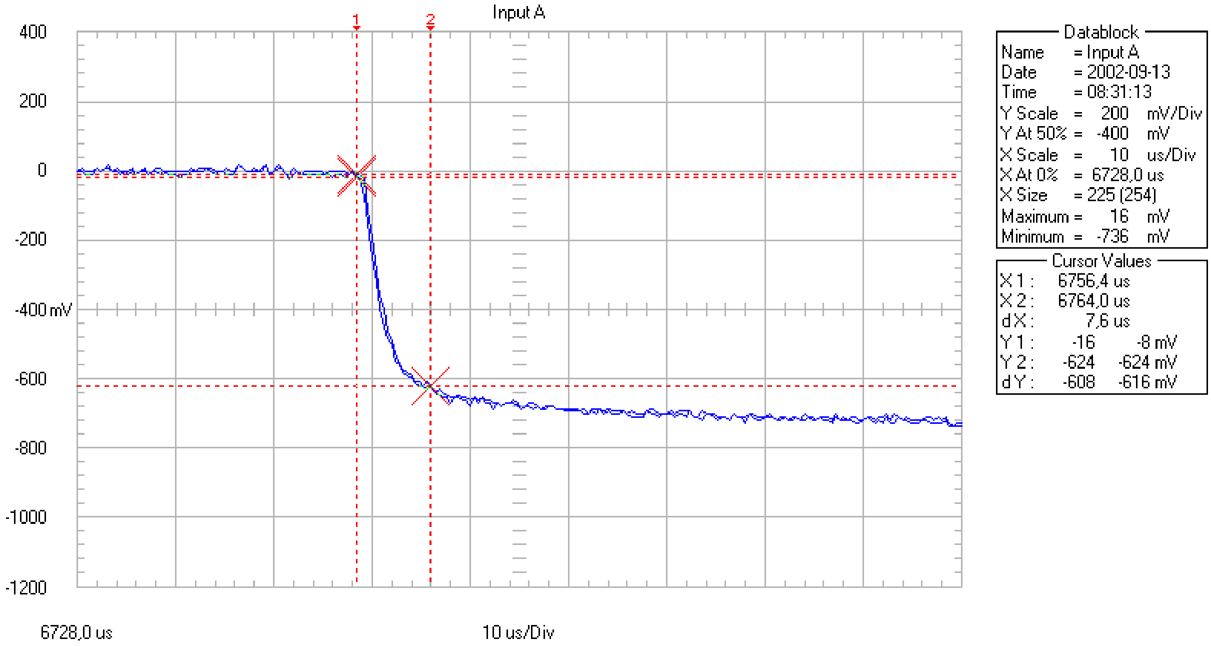
No.	Investigators	Aim	Test population	Method	Outcome
3	Smith, J. M. et al. (1973)	Effects of iris color on the CFFT.	- 56 subjects - Age: 18-25	Monocular CFFT measured with electronic “Flicker Apparatus” from International Applied Science Laboratory (Model FP-104). Light source: glow modulator tube; circular test patch with an area of 12.7 mm. Visual angle 2°; diameter of artificial pupil 2 mm. Square wave pulse with L/D-ratio 50/50; constant intensity. Two alternating ascending and descending runs, respectively; continuous change of frequency in steps of 2 Hz until two consecutive “flicker” or “fusion” responses are obtained. The CFFT is defined as the midpoint between the last positive and the first negative response.	Highest CFFT in subjects with blue eyes, lowest in those with brown eyes, with green-eyed subjects as an intermediate.
4	Moulden, B. et al. (1984)	Adaptation following flicker exposure.	- 4 subjects	A constant and a variable test object, made up of two LEDs each, separated by a septum with the effect that there appears to be only one. Foveal fixation obtained with use of prisms. Visual angle 0.34°; luminance 14.9 cd/m^2; distance to subject 85 cm. Sinusoidal modulation of amplitude and frequency controlled with a potentiometer. Only one LED running at a time. Head of subject fixated with a mask, and the whole set-up covered with black cloth. Six adaptation frequencies presented for 90 sec. each.	Results indicate the existence of different channels for the processing of high- and low-frequency flicker respectively and the involvement of binocular mechanisms in flicker processing.
5	Bruce M. et al. (1986)	Effects of caffeine on the CFFT.	-9 subjects (4 male, 5 female) - Age: 18-40	Monocular Maxwellian view-device, held to the eye by the subject. Light source: red LED, controlled by a computer. Alternating runs, three in ascending and descending mode respectively. No background illumination. The CFFT is computed as an average of both ascending and descending values.	Tendency for the CFFT to increase after administration of caffeine, but effect not significant.

No.	Investigators	Aim	Test population	Method	Outcome
6	Ali, M-R. Amir, T. (1988)	Relation personality/CFFT under various auditory conditions.	- 60 subjects (30 male, 30 female) - Age: 18-26 (mean: 22.4)	The CFFT measured with Lafayette Perception Control with Display Unit, Model No. 58017 plus sinus/square wave generator and tape recorder with headphones. Continuous Method of Limits with frequency varied between 2 and 60 Hz, in steps of 2 Hz. Five runs in each direction under the different auditory conditions (sound pressure 75 dB; frequency 1000 Hz).	Possibly lower CFFT under noisy conditions, but no significant effect. Significant connection between low scores on social nonconformity scale and a high CFFT.
7	Ali, M-R., Amir, T. (1989)	Relation between personality, sex and CFFT.	- 40 subjects (20 male, 20 female; 10 with social problems an 10 without for each sex group) - Age: 13-16	CFFT measurements using a Lafayette Visual Perception Control with Display Unit, Model No. 58017. The subjects head fixated with a chin rest 50 cm away from the test object; signal source at eye level. The continuous Method of Limits employed; frequency varied from 2 to 60 Hz. Five alternating runs in each direction.	The CFFT of boys significantly lower than that of girls. The CFFT of children defined as “problem children” in psychometric tests significantly lower than that of normal children.
8	Curran, S. et al (1990)	CFFT in a normal, elderly population.	- 644 subjects (229 male, 415 female)	“Leeds Psychomotor Tester” with light source: Four LEDs. Distance to the eye 1 m; foveal fixation. The continuous Method of Limits employed; Frequency varied between 12 and 50 Hz in steps of 1 Hz/sec. Frequency variation stopped by the subject when flicker starts/stops. Background illumination: artificial. Three ascending and descending runs respectively, with half of the subjects starting in the ascending, half in the descending mode. One min. rest between runs. The CFFT is computed as average of ascending and descending runs respectively.	Normal distribution of CFFT scores. Reduced difference between the AT and the DT with increasing age, primarily caused by reduction of DT values.

No.	Investigators	Aim	Test population	Method	Outcome
9	Ali, M-R., Amir, T. (1991)	Differences between monocular and binocular CFFT.	- 40 subjects (20 male, 20 female) - Age: 18-20 (mean: 19)	The CFFT measured with Lafayette Perception Control with Display Unit, Model No. 58017. Light source: red LEDs with an intensity of 0.05 mW/cm^2. Distance between subject and signal source 50 cm. Ten ascending and descending runs respectively; half of the subjects beginning in monocular mode, and half in binocular mode. Two min. rest between tests. Background illumination: 40W-bulb. The CFFT is computed as an average of all monocular and binocular runs respectively.	The CFFT is significantly lower under monocular than under binocular conditions. The CFFT of men is higher than that of women.
10	Stockman, A. et al. (1993)	Flicker registration of blue cones.	- 2 subjects (male)	Five channelled Maxwellian view-system,. Light source: 900W Xenon lamp; different wavelengths obtained with use of filters. Sinusoidal modulation using LCD light shutters with a carrier wave of 400 Hz. Rise time < 50μsec. Head of subject fixated with dental rest. Signals of three different wavelengths projected directly onto the retina (artificial pupil, diameter 2 mm). Frequency variation by the Method of Adjustment; subject adjusts the flicker frequency to the smallest possible. Four runs.	Flicker detected by blue cones fuses at lower frequencies than flicker detected by red or green cones.
11	Lachenmayr et al. (1994)	Effects on aging on CFFT.	- 130 subjects -Age: 9-86 (mean: 43)	Automatic Flicker Perimeter developed by the research group. Light source: yellow (wavelength 590 nm) LEDs with a diameter of 1 cm and luminance 50 cd/m^2. Square wave modulation with Gaussian onset/offset (to avoid edge effects). Response measured at defined points on the retina up to a visual angle of 40° from the fovea; exposure, recordings and computations are computer generated.	A gradual decrease of the CFFT with increasing age.

No.	Investigators	Aim	Test population	Method	Outcome
12	Küller, R., Laike, T. (1998)	Effects of flicker on well-being and performance.	- 37 subjects (19 male, 18 female) - Age: 21-50 (mean: 29.9)	Light source: 4*5W lamps with a luminance of 4.5 cd/m^2, enclosed in a box, 26*26 cm with a round window (test patch) with a diameter of 2.5 cm. Flicker generating by a rotating disc in front of the window. Visual angle 3°. Method of minimal changes employed. Frequency varied between 30 and 80 pps. Twenty consecutive runs with alternating ascending and descending frequency. Surroundings arranged to simulate an office environment; background illumination ordinary and HF fluorescent lighting. The CFFT computed as the average value of all runs.	Subjects with high CFFTs responding with pronounced attenuation of EEG waves and impaired performance when exposed to flickering light.
13	Curran et al. (2000)	The CFFT of patients with Alzheimers Dementia (AD).	- 26 subjects (male) -Age: 67-89 (mean: 81.7)	Leeds Psychomotor tester. Procedure not specified; probably similar to that of studies 8, 15 and 16.	Significantly lower CFFT and DT in patients with AD compared with controls.
14	Curran et al. (2000)	Reliability of CFFT values from studies on patients with Alzheimer's Dementia.	Not specified; probably those of study 13.	Split-half and test-retest-reliability tests	High reliability of CFFT, AT and DT in AD patients.
15	Curran et al. (2000)	Validity of CFFT values from studies on patients with Alzheimer's dementia.	- 26 subjects (3 male, 23 female) - Age: 67-89 (mean: 81.7)	The CFFT measured using Leeds Psychomotor Tester. Various measures of intellectual status and capacity obtained from established tests.	The CFFT, AT and DT significantly correlated with several established neurophysiological and psychometric measures, but not with all of them.
16	Curran et al. (2000)	Inter-rater reliability of CFFT tests.	- 8 subjects - Age: 77-89 (mean: 78.8)	The CFFT measured using Leeds Psychomotor tester, with the test population split in two groups with different investigators. Analysis of the differences between groups with respect to the investigator.	High inter-rater reliability of the CFFT, AT and DT.
17	Lyskov, E. et al. (2001)	The CFFT of patients with 'electrical hypersensitivity'.	- 20 subjects (9 male, 11 female) - Age: 42-53 (mean: 47)	Light source: LED-matrix made up of 144 red LED:s (size 10*10 mm), divided in a central, flickering field (pattern reversal mode) and a constant, surrounding field. Frequency change manually controlled.	Significantly higher CFFT in EHS patients than in controls.

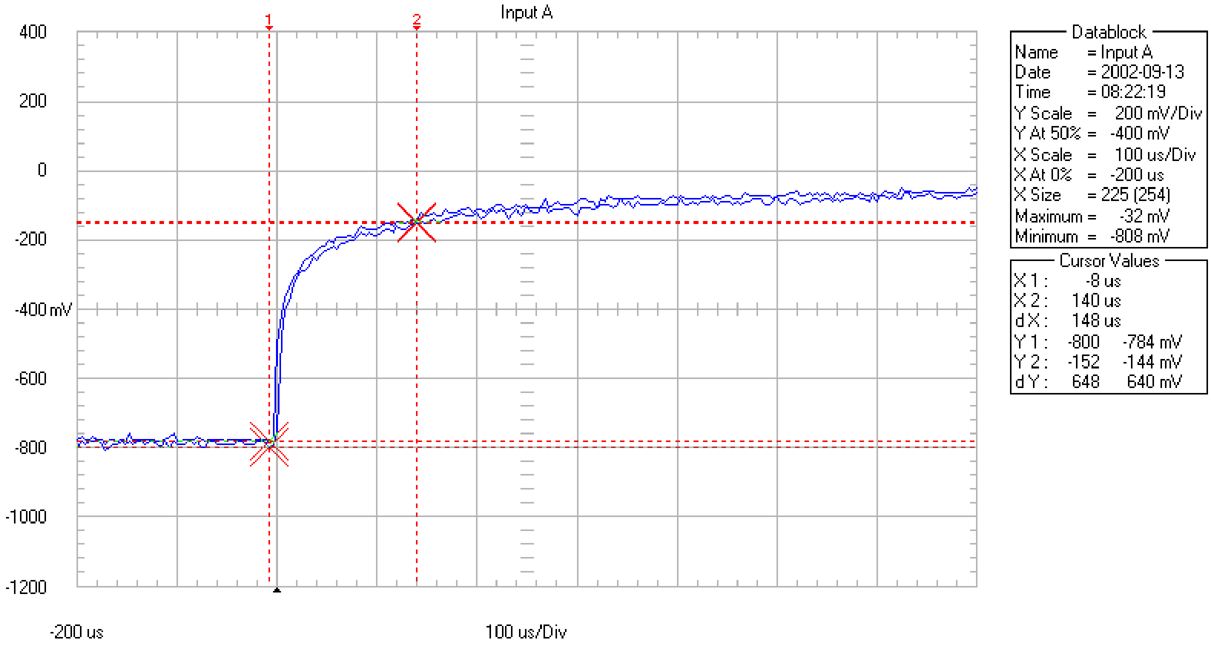
No.	Investigators	Aim	Test population	Method	Outcome
18	Lyskov E. et al. (2001)	Effects of electromagnetic provocation on the CFFT of EHS patients.	- 20 subjects (5 male, 11 female) - Age: 31-60 (mean: 45.8)	Light source: LED matrix made up of 144 red LEDs (size 10*10 mm), divided into a central, flickering field (pattern reversal mode) and a constant, surrounding field. Frequency manually controlled. Subjects instructed to fix their gaze on a central point of the matrix, to assure central vision. three ascending and three descending runs. The CFFT computed as the average of all six runs.	Significantly higher CFFT in EHS patients than in controls. No effects of electromagnetic provocation.
19	Takahashi K. et al. (2001)	Effects of different environmental working conditions in VDT-related work.	- 6 subjects (male) - Age: 21-23	Portable “fatigue meter” (Hosokawa et al. 1997).	Significant increase in the CFFT in a noisy, high luminance condition.



Datablock
Name = Input A
Date = 2002-09-13
Time = 08:31:13
Y Scale = 200 mV/Div
Y At 50% = -400 mV
X Scale = 10 us/Div
X At 0% = 6728,0 us
X Size = 225 (254)
Maximum = 16 mV
Minimum = -736 mV

Cursor Values
X 1 : 6756,4 us
X 2 : 6764,0 us
d X : 7,6 us
Y 1 : -16 -8 mV
Y 2 : -624 -624 mV
d Y : -608 -616 mV

Figure 3. Fall time of stimulus signal



Datablock
Name = Input A
Date = 2002-09-13
Time = 08:22:19
Y Scale = 200 mV/Div
Y At 50% = -400 mV
X Scale = 100 us/Div
X At 0% = -200 us
X Size = 225 (254)
Maximum = -32 mV
Minimum = -808 mV

Cursor Values
X 1 : -8 us
X 2 : 140 us
d X : 148 us
Y 1 : -800 -784 mV
Y 2 : -152 -144 mV
d Y : 648 640 mV

Figure 4. Rise time of stimulus signal