11-8-2018 10:30 AM

Magnetic Field Frequency-Response for Human Magnetophosphene Perception and Associated EEG Modulations

Cadence M. Baker
The University of Western Ontario

Supervisor
Legros, Alexandre
The University of Western Ontario

Graduate Program in Kinesiology
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

Abstract

Background: Magnetophosphenes are among the most reliably reported effects resulting from magnetic induction. The frequency dependence of the perception threshold is crucial, as guideline agencies use this information to set exposure limits whose purpose is to protect public and workers.

Objective: Establish the magnetophosphene perception thresholds throughout the extremely low frequency range (0-300 Hz) and evaluate the use of EEG as a biomarker.

Hypothesis: Perception thresholds will be lowest at ~30 Hz. EEG occipital alpha power will decrease upon perception.

Methods: 60 participants were exposed to homogenous magnetic fields up to 300 Hz, and 70 mT. EEG alpha power was calculated during each exposure.

Results: Magnetophosphene thresholds were found to be lowest (16.92 mT_{rms}) at 35 Hz. Thresholds established at powerline frequencies. Magnetophosphene perception was not accompanied by a change in EEG activity.

Conclusions: Magnetophosphenes frequency dependence is consistent with previous studies involving magnetic stimuli. Occipital EEG alpha power is not an appropriate biomarker of magnetophosphene perception.

Keywords

Magnetic Field, Magnetic Induction, Biophysical Mechanisms, Perception Threshold, Neurophysiology, Electroencephalography

Co-Authorship Statement

Cadence Baker: Performed all manuscript writing, data acquisition, data and statistical analysis.

Dr. Alexandre Legros: Supervisor, managed the project through initiating experimental design, provided funding and supervised manuscript preparation and revisions.

Dr. Sebastien Villard: Assisted with manuscript revisions, computer programming, data acquisition, and statistical analysis.

Michael Corbacio: Assisted with experimental design, computer programming, and data collection.

Dr. Julien Modolo: Advisory committee member.

Dr. Lindsay Nagamatsu: Advisory committee member.

Dr. Jim Dickey: Advisory committee member.

Acknowledgments

I would like to thank the following individuals for their support throughout my Masters degree and this research project:

To start, this project wouldn't have been possible without the support from my supervisor, Dr. Alexandre Legros. I am so grateful for the learning opportunities provided over the last two years, as well as the many international opportunities to present my research.

I appreciate the support, guidance and expertise my labmates have given me throughout my time in the Human Threshold Research Group. Thank you to Dr. Sebastien Villard, Nicolas Bouisset, Michael Corbacio, and Lynn Keenliside. Not only did they support my research, they have supported my personal development throughout this journey as a graduate student.

I would also like to acknowledge my advisory committee members: Dr. Julien Modolo, Dr. Lindsay Nagamatsu, and Dr. Jim Dickey. Thank you for your expertise!

Of course, this project wouldn't be possible without the support of Industry Sponsors and Research Support Funding: MITACS Accelerate Funding, Lawson Internal Research Fund, Western Graduate Research Scholarship, Hyrdo-Quebec, Électricité de France (EDF), Réseau de Transport d'Électricité (RTE) and Electric Power Research Institute (EPRI).

Thank you to the many friends that have helped me along the way!

I forever appreciate the support my family has given me. Thank you, Mom, Dad, Skyla, Grammie, Grandpa, Grandma and Bompy.

Last but not least, thank you Steven and Koda for being the best support team I could ever need!

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AC – Alternating Current

B – Magnetic Field Flux Density (mT)

CNS – Central Nervous System

E - Electric Field

EEG – Electroencephalography

ELF – Extremely Low Frequency

FSQ – Field Status Questionnaire

ICNIRP – International Commission on Non-Ionizing Radiation Protection

IEEE-ICES – International Committee on Electromagnetic Safety of the Institute of Electrical and Electronics Engineers

MF(s) – Magnetic Field(s)

MRI – Magnetic Resonance Imaging

tACS – transcranial Alternating Current Stimulation

V1 – Primary Visual Cortex

Units:	A – Ampere	m – Meter	T - Tesla
	cm – Centimeter	MHz – Megahertz	V - Volt
	GHz – Gigahertz	mT – milliTesla	Ω – Ohm
	Hz – Hertz	mV – Millivolt	μT – microTesla
	Lux – Illumination	s – Second	

List of Appendices

Chapter 1

1 General Introduction

Magnetic fields (MFs) are present throughout our daily lives. Most are familiar with the Earth's MF, however, MFs are also produced by powerlines and household electrical appliances. Throughout the following sections we will explore the human visual system, through evaluating a phenomenon called magnetophosphene perception. Magnetophosphenes consists of a visual experience of flickering lights upon exposure to a sufficiently strong MF; they occur in the absence of a visual stimulus. An overview of previous magnetophosphene research will be presented, as well as an overview of the visual system.

1.1 Magnetic Fields

We are exposed to manmade and natural MFs every day. The Earth's MF is generated as a consequence of electric currents within the Earth's molten core. This very slowly changing (essentially static) MF is rather weak at the earth's surface but can be detected with a compass. A static MF refers to the fact that the field does not vary over time. A common household fridge magnet is, for example, also produces a static MF. Magnetic resonance imaging (MRI) scanners produce the strongest common static MFs.

The concept of time-varying MFs refer to MFs having their intensity changing over time (as opposed to static MFs). They are most commonly produced by alternating currents, which are oscillating over time (i.e. they reverse their direction at a regular interval). MFs produced through use of our everyday household appliances and electrical wires are alternating. Alternating current flowing through a wire produces an alternating MF around it (Figure 1). Alternating MFs are classified into the following categories: extremely low frequency (ELF, 0-300 Hz), low frequency (300 Hz – 3 MHz), and high frequency (3 MHz – 300 GHz). The remainder of this research study will focus on ELF MFs, such as those we encounter in our daily lives. In Canada and the US, powerlines operate at 60 Hz, whereas in Europe, powerlines operate at 50 Hz. Both 50 and 60 Hz are within the ELF range, therefore, we are exposed to ELF MFs daily.

The intensity, H, of a MF is measured in amperes per meter (A/m), however, it is most often reported in terms of its MF flux density, B, measured in Tesla (T), or milliTesla (mT). The intensity and flux density of a MF are related by the equation:

$$B = \mu H \tag{1}$$

where μ is the permeability of the space. The MF flux density decreases with increasing distance from the source and is proportional to the current intensity (I) and distance from the source (r), such that for an isolated straight conductor carrying current:

$$B = \frac{(\mu . I)}{2\pi r} \tag{2}$$

Time-varying MFs such as those resulting from a current flowing through a wire induce electric fields in a conductive object, such as the human body (Figure 1). This means that the MFs we interact with in our everyday lives are inducing electric fields in our body. Depending on magnitude, frequency and waveshape, induced electric fields may affect biological processes.

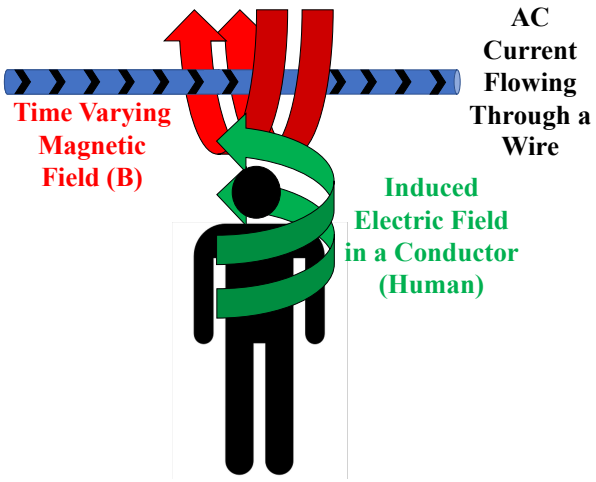


Figure 1: Alternating current creates a time-varying MF, which ultimately creates an induced electric field in a nearby conductor, such as the human body.

1.2 MF Interactions with the Human Body

Time-varying MF interactions with human biology and the central nervous system (CNS) has been studied for many years. Numerous research topics have been explored, with respect to ELF MF exposure including, but not limited to: cardiovascular function (McNamee et al., 2009; Sastre, Cook, & Graham, 1998), postural control (Allen et al., 2016; Glover, Cavin, Qian, Bowtell, & Gowland, 2007; Legros et al., 2012; Prato, Thomas, & Cook, 2001; Thomas, Drost, & Prato, 2001; Van Nierop, Slottje, Kingma, & Kromhout, 2013), reproduction (Al-Akhras, 2008), cognitive function (Corbacio et al., 2011; Crasson & Legros, 2005; Delhez, Legros, & Crasson, 2004; Nevelsteen, Legros, & Crasson, 2007; Preece, Wesnes, & Iwi, 1998), EEG (Cook, Saucier, Thomas, & Prato, 2009; Cook, Thomas, Keenliside, & Prato, 2005; Cook, Thomas, & Prato, 2002; Heusser, Tellschaft, & Thoss, 1997; Legros et al., 2012; Lyskov et al., 1993) and visual perception (Barlow, Kohn, & Walsh, 1947; D'Arsonval, 1896; Legros et al., 2016; Lövsund, Öberg, & Nilsson, 1980a, 1980b). All the related scientific literature has been reviewed by the WHO (World Health Organization, 2007) and the two main international guideline agencies (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002; International Commission on Non-Ionizing Radiation Protection, 2010), and it was concluded that the most reliable and relevant biological effect, resulting from low levels of ELF MF exposure, relevant to serve as a basis for setting exposure limits in the ELF range was phosphene perception. International guideline agencies aim to protect the general public and workers from adverse effects of exposure, which they define to be: "an effect detrimental to the health of an individual" (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002; International Commission on Non-Ionizing Radiation Protection, 2010). In addition to establishing a reliable threshold of ELF MF effects, it is important to understand the possible mechanisms of action involved in ELF MF interactions with biological processes to confidently state if it is adverse or not, ultimately impacting exposure guidelines. These guidelines (explained in further detail in section 1.3) are based on the most reliably reported effect of ELF MF exposure, magnetophosphene perception.

1.3 Magnetophosphenes and Safety Guidelines

Appliances such as a hairdryer or electric shaver can produce ELF MF exposures of 2 mT in their immediate proximity, however typical daily exposures usually remain below 1 μT (Gandhi, Kang, Wu, & Lazzi, 2001; Zaffanella & Kalton, 1998). The "Thousand Person Study" was designed to assess ELF MF exposures in Americans throughout a normal day. Out of all 1 000 volunteers, the top 1% experienced exposures up to 1 μT (Zaffanella & Kalton, 1998). Occupational powerline workers are often exposed to ELF MF flux densities of 1 mT (World Health Organization, 2007).

To protect the public and workers from adverse effects resulting from MF exposures, international agencies set exposure guidelines and recommendations. The two major guideline organizations, the International Committee on Electromagnetic Safety of the Institute for Electrical and Electronic Engineers (IEEE-ICES) and the International Commission on Non-Ionizing Radiation Protection (ICNIRP), publish guidelines for the entire non-ionizing frequency range, however, this section focuses on ELF guidelines, encompassing the powerline frequencies (50 and 60 Hz) (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002; International Commission on Non-Ionizing Radiation Protection, 2010). ELF exposures do not contain enough energy to damage cells, that is, why they are referred to as non-ionizing, but as described previously (Section 1.1), ELF MF exposures have the ability to induce electric fields and currents in a conductor (i.e. the human body) and therefore to possibly affect cells and tissues, including those in the CNS (Attwell, 2003).

The current guidelines are based in part on a reliably reported effect of ELF MF exposure, magnetophosphene perception (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002; International Commission on Non-Ionizing Radiation Protection, 2010). Magnetophosphene perception is a consequence of magnetic induction, upon exposure to a sufficiently strong MF. At power frequencies and their lower harmonics, guidelines are currently based on experimental work that assessed thresholds from 10-45 Hz, and not powerline frequencies (Lövsund et al., 1980a, 1980b). This is an important limitation to note in the guidelines, since magnetophosphene perception is reported to be frequency dependent (Legros et al., 2016; Lövsund et al., 1980b, 1980a; Silny, 1984). Both the IEEE-

ICES and ICNIRP guidelines which encompass the ELF range are presented in Table 1, at 20 Hz (the most sensitive frequency, reported by Lövsund), 50 Hz (European powerline frequency) and 60 Hz (North American powerline frequency).

The current IEEE-ICES recommendations were developed with respect to short term effects associated with electrostimulation. Exposure limits are designed to protect against short term reactions, including: painful stimulation of sensory or motor neurons, muscle excitation, alteration of synaptic activity in the brain, cardiac excitation, or adverse effects associated with induced potentials (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002). The restrictions for exposure of the head and torso, in terms of MF flux density are frequency dependent and are separated into two categories: general public and controlled environment. Below 0.153 Hz, the general public restriction is 118 mT_{rms}, whereas the controlled environment restriction is 353 mT_{rms} (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002). As frequency increases, the maximum permissible exposure values decrease, such that above 20 Hz, the general public restriction is 0.904 mT_{rms} and the controlled environment restriction is 2.71 mT_{rms} (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002). Based on the work of Lövsund in 1980, magnetophosphene thresholds were reported to be lowest at 20 Hz, and increase until 45 Hz (Lövsund et al., 1980b). Electrophosphene thresholds have been assessed up to 75 Hz and have a similar frequency-response to magnetophosphenes. However, it is assumed that magnetophosphene thresholds follow the frequency-proportional law above 20 Hz, up to at least 760 Hz, above which PNS is the defining effect (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002). Experimental data are limited below 45 Hz, however, IEEE-ICES uses extrapolation to generate ELF MF exposure recommendations.

ICNIRP ELF MF guidelines are also based on magnetophosphene perception, and state that “avoiding retinal phosphenes should protect against any possible effects on brain function”. ICNIRP notes that phosphene thresholds are a minimum around 20 Hz and rise rapidly at higher and lower frequencies (International Commission on Non-Ionizing Radiation Protection, 2010; Lövsund et al., 1980b). Magnetophosphenes thresholds are thought to occur at an induced electric field of approximately 50-100 mV/m at 20 Hz in the retina (Saunders & Jefferys, 2007). Therefore, the occupational restriction is 50 mV/m,

and the general public restriction is 10 mV/m, at 20 Hz. With respect to MF flux density, the occupational and general public restrictions are 1.25 mT_{rms} and 0.25 mT_{rms}, respectively, at 20 Hz (International Commission on Non-Ionizing Radiation Protection, 2010). Extrapolating to powerline frequencies, the occupational restrictions are 1 mT_{rms} at 50 and 60 Hz, or the general public restrictions are 0.2 mT_{rms} at 50 and 60 Hz (International Commission on Non-Ionizing Radiation Protection, 2010).

Magnetophosphenes are the most robustly reported effect of electric and magnetic stimulation below the threshold for direct muscle activation or CNS neurostimulation (i.e. triggering of an action potential). Although guidelines are based in part on magnetophosphenes, they are recognized to be the best existing model for CNS exposures until more is known (International Commission on Non-Ionizing Radiation Protection, 2010).

Table 1: ICNIRP and IEEE-ICES ICES reference levels for ELF MF exposures at 20 Hz, 50 Hz and 60 Hz.

	ICNIRP Guidelines (mT_{rms})			IEEE-ICES Guidelines (mT_{rms})
	20 Hz	50 Hz	60 Hz	20 – 759 Hz
Occupational/Controlled Environment Guidelines	1.25	1	1	2.71
General Public Guidelines	0.25	0.2	0.2	0.904

Guidelines use magnetophosphene perception as a model for evaluating the interactions between an ELF MF and the CNS. Magnetophosphenes are experienced as a visual phenomenon believed to be transduced in the retinal photoreceptors, however, the exact location of origin remains uncertain. To better understand the possible origins of magnetophosphene perception, the following section provides an outline of the visual system.

1.4 The Visual System

The human visual system is a component of the CNS. Light entering the eye passes through the cornea and then the pupil. The amount of light passing through the pupil is controlled through constriction and dilation of the iris. The lens refracts the light, projecting an inverted image onto the retina. The retina is illustrated in Figure 2.

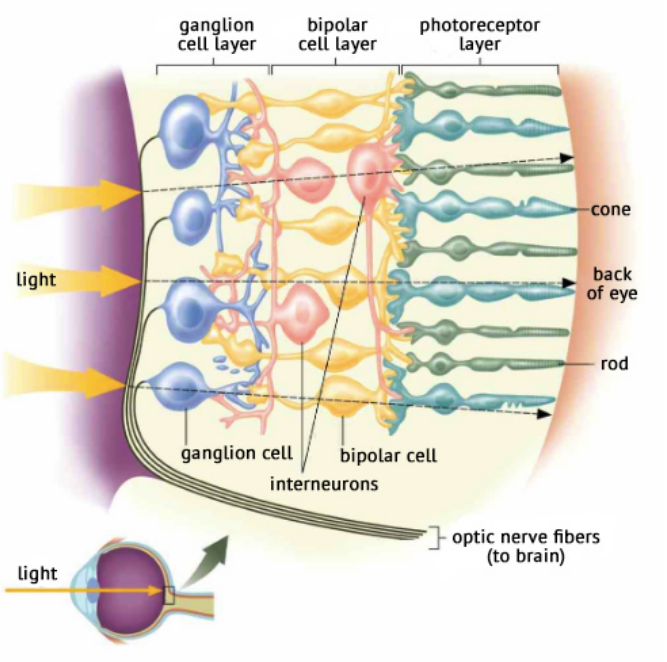


Figure 2: Representation of the retina. As light hits the eye it travels to the back of the retina, where the photoreceptors begin the process of phototransduction. Image acquired, and permission granted from Philpot Education.

The photoreceptors are the site of phototransduction of the visual signal. The photoreceptors are at the back of the retina, meaning that light must travel through the other retinal layers before arriving at the photoreceptors. To protect the quality of the light stimulus, the neuron layers in front of the photoreceptors are unmyelinated, so that these layers of neurons are relatively transparent. Movement of the eye also allows light to be projected onto the fovea: a region of the retina where the neural axons are pushed to the side, allowing photoreceptors to receive the least distorted light (Kandel, Schwartz, & Jessell, 2000).

Information received by the photoreceptor cells is sent to retinal bipolar cells. Rods and cones respond to light with graded changes in membrane potentials. Horizontal and amacrine cells combine signals from several photoreceptors while maintaining the temporal patterns of the stimulus. Using graded membrane potentials, the bipolar cells then synapse with ganglion cells. For the first time in the visual pathway, the ganglion cells then transmit stimuli information using action potentials. The axons of the retinal ganglion cells converge into a bundle that comprises the optic nerve, which transmits visual signals for processing in the brain.

Rods and cones are the retinal photoreceptor cells, which differ structurally and functionally. Rods are achromatic and are distributed throughout the retina, including the periphery. Cones are trichromatic and are found in the center of the retina. Rods are larger and much more sensitive to a visual stimulus than cones. In fact, rods are so sensitive that they can detect and perceive a single photon of light (Tinsley et al., 2016). Several rods converge onto a single bipolar cell, ultimately amplifying the signal, whereas cones are connected in a one-to-one manner with bipolar cells. Photoreceptors detect a flickering visual stimulus, however, it depends on both the flicker frequency and the intensity of the light stimulus. The critical flicker frequency, the highest frequency of flickering perceived, has been reported up to 80 Hz (Perz, 2010). Rods and cones have different frequency sensitivities, that depend on the light level. Light adapted rods can detect a flickering light up to 28 Hz (Conner & MacLeod, 1977). Differences between rods are cones are outlined in Table 2.

Table 2: Differences between rod and cone photoreceptors.

Rods	Cones
Very sensitive, high amplification	Less sensitive, low amplification
Specialized for night vision	Specialized for day vision
Low acuity	High acuity
Achromatic	Chromatic
Periphery of retina	Central retina

As one of the twelve cranial nerves, the optic nerve is a part of the CNS and carries visual information to the brain. The optic nerve travels to the optic chiasm where the visual information from both eyes is crossed. Most optic nerve fibers terminate in the lateral geniculate nucleus; however, the remaining fibers terminate in the pretectal nucleus or the suprachiasmatic nucleus. From the lateral geniculate nucleus, visual information is sent to the occipital cortex, specifically, the primary visual cortex (V1). Visual information treated by V1 will modulate EEG signals collected from the occipital electrodes (O1, O2, and Oz – further EEG specifics to be found in Section 1.7). The visual centers of the brain contain a retinotopic map, or a neural map of the retina, such that spatial relationships from the retina are maintained throughout visual processing.

After visual information is sent to V1, it is processed in one of two distinct pathways (Figure 3). The dorsal pathway runs from V1 through the middle temporal area to the posterior parietal cortex (Kandel et al., 2000). The dorsal stream is known as the "where" or "how" pathway and is involved in spatial awareness and guidance of actions. The ventral stream runs from V1 to the inferior temporal cortex (Kandel et al., 2000). The ventral stream is also known as the "what" stream and is responsible for object recognition.

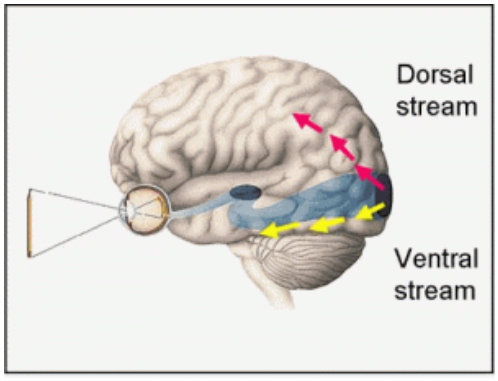


Figure 3: Outline of the dorsal and ventral streams of visual processing. Image is open access from (visionhelp.wordpress.com).

Guideline agencies use the retina as a model for the CNS for a few reasons. First, the retina is part of the CNS. Second, the retina functions to amplify small signals, and perceptually detect a stimulus, in this case the stimulus being the effects of ELF MF exposures (Attwell, 2003). Although a good model, the retina also differs from the CNS, making this a conservative model. Retinal photoreceptor cells detect very weak stimuli because of the

amplification process involved in perception. These cells are graded potential neurons that are fairly unique to the retina, and not found throughout the entirety of the CNS. Although graded potential cells are not found in all areas on the CNS, they are also found in the hair cells of the vestibular system. Although the retina differs from the CNS, magnetophosphene perception remains the most reliable measure of ELF MF exposure below peripheral nerve stimulation.

1.5 Origin of Phosphene Perception

Phosphenes are a visual perception occurring without a visible stimulus (Lövsund et al., 1980a). They are described as a flickering light perceived in the periphery of one's visual field and can be a result from mechanical pressure, chemical agents, electric currents and MFs (Lövsund et al., 1980b). Phosphenes perceived as a result of MFs are referred to as magnetophosphenes and were first explored in the late 1800s. In 1896 d'Arsonval concluded that phosphenes were perceived upon exposure to a MF at 42 Hz (D'Arsonval, 1896; Geddes, 2008).

Later on, an experiment conducted by Thompson (1910) revealed a faint visual perception when his head was in close proximity to an alternating electromagnet. Notably, this visual effect was brighter in the periphery of the visual field (Thompson, 1910). Following Thompson's experiment, Magnusson and Stevens (1911) looked to confirm this visual phenomenon caused by exposure to a MF. Unlike previous studies, their experimental design allowed for vertical movement of the coils generating the MF (Magnusson & Stevens, 1911). The maximum effect was obtained when the participants head was centred in the coil such that the middle of the coil passed through the upper edge of the eyes. By raising and lowering the coils, relative to the position of the participants head, the visual effect diminished. Magnusson and Stevens also found that phosphene perception was frequency dependent, noting that the effect of MF exposure was greatest between 20 and 30 Hz, and that perception was strongest in the periphery of the visual field.

Similar to magnetophosphenes, electrophosphenes are a flickering perception occurring as a result of electric stimulation. Barlow et al. (1947) were the first to compare perceptual responses between electrophosphenes and magnetophosphenes. Phosphene perception was

investigated up to 90 Hz and similarities were noted between electro- and magnetophosphenes. Both electro- and magnetophosphenes were found to be strongest in the periphery of the visual field. They appeared colourless, were abolished by pressure on the eyeball and perception was prolonged by eye movements. This lead to the hypothesis that electro- and magnetophosphenes are a product of the same neural pathway, and suggested to be a result of retinal activity (Barlow et al., 1947). In this experiment, phosphene perception was evaluated with different positions of the MF exposure device; magnetophosphenes were perceived when the exposure device was placed near the participants temples, but not perceived when placed near the occipital cortex (Barlow et al., 1947). This suggests retinal involvement, as opposed to occipital cortex involvement in phosphene perception.

Based on the thought that phosphene perception is a result of retinal activity, Abe (1951) quantitatively measured electrophosphene perception thresholds up to 120 Hz under different experimental conditions, differentiating between rod and cone photoreceptor characteristics. The results showed two different frequency-response curves; one curve representing electrophosphene perception for a light-adapted retina, and a second curve for a dark-adapted retina. Light-adapted thresholds were measured after 90 seconds of pre-illumination at 24 000 lux. Light-adapted eyes have the lowest electrophosphene threshold at 20 Hz (Abe, 1951). After 30 minutes of dark adaptation, 7 Hz and 37 Hz were the most sensitive frequencies, eliciting the lowest electrophosphene thresholds. Different frequency-response curves between light and dark adaptation highlight the unique characteristics of the retinal cells, such as the photoreceptors.

To further establish the differences in rod and cone photoreceptors, phosphene thresholds were analyzed in various regions of the visual field. Thresholds were dependent on the location within the visual field in which phosphenes were perceived (Gebhard, 1952). A lower threshold in the periphery than in the centre of the visual field provides support towards rod involvement in phosphene perception (Attwell, 2003). Although the threshold was found to be lowest using a 20 Hz exposure in both the central visual field and the periphery, the thresholds were higher in the centre (Gebhard, 1952).

Lövsund compared electrophosphenes to magnetophosphenes under varying background lighting conditions to further understand the mechanisms involved. Confirming that both types of phosphenes are a result of activation of the same pathways in the visual system, it was found that both electro- and magnetophosphenes require the lowest stimulus to elicit perception at 20 Hz. Both electric and magnetic stimulations follow a similar frequency-response curve when frequency is considered (Lövsund et al., 1980a). Following the previous experiments (Abe, 1951; Gebhard, 1952) showing that phosphene generation is a result of retinal stimulation, Lövsund et al. (1980) further explored the frequency-response of magnetophosphenes under several conditions designed to target different retinal characteristics. Magnetophosphene frequency-response curves were established in darkness after 10 minutes of adaptation, as well as three different background lighting conditions. In darkness, the perception threshold was lowest at 30 Hz, whereas in the other three lighting conditions the lowest threshold was found from 20-25 Hz (Lövsund et al., 1980b). This study was the first to document the frequency-response of magnetophosphenes, however, it is limited between 10 and 45 Hz, and only involved 11 participants. Lövsund also evaluated magnetophosphene thresholds as a function of time spent in the dark, to assess the involvement of retinal adaptation in phosphene perception. This experiment tested eight volunteers at 20, 30 and 35 Hz, however, the results are an average of threshold values across all three frequencies. Lövsund found the magnetophosphene threshold to change as a function of time spent in the dark, which he reports to follow a similar dynamic to photic stimuli thresholds during dark-adaptation (Lövsund et al., 1980b).

In an improvement from Lövsund's (1980) experimental set up, Silny (1984) established magnetophosphene thresholds using a Helmholtz coil, generating a homogenous MF around the participants' head. The physiological response to magnetophosphene perception appeared to have a hysteresis effect when using the classical psychophysics method of limits to determine threshold (Silny, 1984). In an attempt to objectively measure magnetophosphene thresholds and the effect of a MF on humans, the visually evoked potential was measured in the occipital region. This study found no change in occipital activity, although it began the search for an objective biomarker of perception in the visual cortex (Silny, 1986).

Furthering the search for an objective measurement of phosphene perception, Morimoto et al. (2006) attempted to supplement electrophosphene subjective results by evaluating the electrically evoked pupillary response, since the pupillary response is more than a subjective yes/no participant report. Three types of thresholds were found in this experiment for both healthy patients and those with retinal disease: initial phosphene thresholds (peripheral threhsolds), central vision phosphene thresholds as well as the threshold for a relative pupillary constriction (Morimoto et al., 2006). Transcorneal electrical stimulation was given to participants at 20 Hz, while current intensity was increased to determine the perception threshold. Pupillary responses were measured using an infrared pupillometer and thresholds were considered to be the electrical current necessary to increase the pupillary response by 3%. All thresholds were found to be higher for healthy patients. Electrically evoked pupillary response thresholds were twice that of the peripheral thresholds and were successfully measured objectively. This is the first indication of finding an objective measurement associated with electric stimulation, and potentially translated to MF stimulation (Morimoto et al., 2006). A second experiment took place evaluating the frequency-response of electrophosphene perception, where phosphenes were strongest at 20 Hz, as well as the electrically evoked pupillary responses (Fujikado et al., 2007). These experiments were completed with the hope that electric stimulation and associated electrophosphene thresholds would provide insight into the qualification for retinal prosthesis.

Opposing the popular retinal hypothesis of phosphene generation, Kanai et al. (2008) elicited phosphenes in a light and dark environment using electrical stimulation on the scalp by the occipital cortex (Kanai et al., 2008). Phosphene perception was reported using a subjective rating, as opposed to a yes/no response. Supporting the frequency dependency of phosphene perception, phosphenes were found to be strongest in the light from 14-20 Hz, whereas phosphenes in the dark were reported to be the strongest from 10-12 Hz (Kanai et al., 2008). Overall, phosphenes were stronger in the dark condition than the light condition. Using only four participants, the electrophosphene threshold was lowest at 20 Hz in the light, while it was 10 Hz in darkness (Kanai et al., 2008). It was hypothesized that the occipital stimulation interacts with the ongoing cortical activity of the brain. However, the results that are attributing to the occipital cortex are the cause of retinal

activation, where computational modelling further interprets these results and indicates that a significant portion of the occipital stimulation current goes through the eye, ultimately stimulating the retina (Laakso & Hirata, 2013).

To experimentally dispute the occipital origin hypothesis of the previously mentioned study (Kanai et al., 2008), Kar and Krekelberg established electrophosphene thresholds using three different electrode placements. Thresholds were found to be lowest when the electrodes were placed closest to the retina and furthest from the occipital lobe, thus providing support to the retinal origin of phosphene generation (Kar & Krekelberg, 2012).

Lastly, in our group, we started tackling the question of magnetophosphene perception thresholds as a function of frequency. Participants were exposed to 20/50/60/100 Hz MFs, using three different experimental set-ups: retinal exposure, occipital exposure, and homogenous global whole head exposure, up to 50 mT_{rms} (Legros et al., 2016). Phosphene perception reported using the retinal and global exposure, the results of this experiment indicate that phosphene perception is frequency dependent, as the proportion of exposures eliciting magnetophosphene perception increased with an increasing dB/dt (proportional to the induced electric field in the retina) (Legros et al., 2016). The occipital exposure device failed to elicit phosphene perception. Although still subjective, this evaluation confirms the retinal origin of magnetophosphenes.

1.6 Perceptual Thresholds

Guidelines are based on a sensory threshold termed the magnetophosphene perception threshold. A sensory threshold is considered to be the lowest stimulus strength one can detect (Kandel et al., 2000). Based on Gustav Fechner's (1860) classical psychophysics methods, there are three ways to determine a threshold: method of constant stimuli, method of limits, and the method of self-adjustment.

The method of constant stimuli uses the same set of stimuli throughout an experiment, presented randomly, and requires each stimulus to be presented many times. A participant self-reports perception after each stimulus trial. The overall threshold is typically considered the stimulus intensity that elicits a perception 50% of the time (Gescheider,

1997). The method of constant stimuli is effective in determining a threshold, however, it poses a few problems experimentally. First, each intensity of stimuli must be repeated many times, making the experiment very long and perhaps causing a participant to fatigue. In fact, it has been recommended that each stimulus is presented over 100 times (Gescheider, 1997). Legros et al. (2016) used the method of constant stimuli to determine magnetophosphene thresholds, however, only four frequency conditions were tested. Each participant was assigned to one of four frequency groups (20, 50, 60 or 100 Hz), and MF flux densities were randomly presented from 0 to 50 mT_{rms}, each repeated 5 times (Legros et al., 2016). From this, it was confirmed that magnetophosphene thresholds are frequency dependent, but with only four frequency conditions examined, a precise frequency-response is unknown. Magnetophosphene thresholds were determined successfully for four frequencies but using the method of constant stimuli creates a major challenge in testing a wide range of frequencies and flux densities, all within a reasonable experimental timeframe.

An efficient alternative to the method of constant stimuli is the method of limits. Although the method of limits is not as reliable as the method of constant stimuli, it is much less time consuming. When using the method of limits to determine a threshold, a stimulus is presented below the threshold and increased until perception occurs. Then, the stimulus is presented above the threshold and decreased until no longer perceived. The average between the increasing and decreasing thresholds is considered the overall threshold. This procedure is often repeated multiple times, both increasing and decreasing (Gescheider, 1997). Limitations exist in determining thresholds using the method of limits, since participants may begin to anticipate perception. This leads to higher than normal thresholds in descending trials, and lower than normal thresholds in ascending trials. However, by averaging thresholds from both ascending and descending experiments may minimize the effects of anticipation and habituation (Haggard, 2010).

The method of limits has been used in many electro- and magnetophosphene experiments (Ambrosini et al., 2015; Aurora, Welch, & Al-Sayed, 2003; Elkin-Frankston, Fried, Pascual-Leone, Rushmore, & Valero-Cabr, 2010; Morimoto et al., 2006; Mulleners, Chronicle, Palmer, Koehler, & Vredeveld, 2001), and was used in the experiments from

1980 (Lövsund et al., 1980a, 1980b). As described previously (Section 1.5), MF exposures were presented from 10-45 Hz, in steps of 5 Hz. The magnetic flux density was increased until magnetophosphene perception occurred and then decreased until perception disappeared, averaging these two values to establish an overall threshold for that frequency condition. Using method of limits enabled data collection from a wide range of frequencies, however the accuracy is questionable. Frequencies were presented in a consecutive manner, which allows for habituation and expectation, and using the method of limits accentuates these problems. Randomizing the MF frequency conditions would have at least addressed a portion of this issue; however, the method of limits still proves to enable habituation and anticipation.

Upon adapting the method of limits, the staircase method of determining thresholds arose. The level of stimulus is changed on a trial-by-trial bases, in response to the participants ability to perceive stimuli. The stimulus is lowered each time perception occurs, until the stimulus is no longer noticed. Then, the stimulus is increased trial-by-trial until perception returns. This process is repeated consecutively until the researcher is able to specify where the threshold occurs. Although this staircase adapted method of limits is more accurate and addresses the problem of habituation, it is very time consuming, and can elicit participant fatigue during a long experimental session (Gescheider, 1997). The staircase method was found to be useful and accurate; it was also faster than the method of constant stimuli, but more time consuming than the traditional method of limits (Abrahamyan et al., 2011).

The method of self-adjustment is the third and final classical psychophysics method to determine a sensory threshold. For this type of experiment, a participant is asked to self-control the magnitude of a stimulus until the point where perception is noticed. It is assumed that the initial stimulus is presented far (above or below) from the expected threshold. To date, no magnetophosphene threshold studies have used the method of self-adjustment, however, the first experiment of its kind has been completed in this research study.

1.7 Electroencephalography (EEG)

Discovered in the 1920s, Electroencephalography (EEG) is a non-invasive measurement of brain electrical activity (Berger, 1929). Action potentials and post-synaptic potentials occurring in the brain elicit a current flow, which is in turn picked up through EEG electrodes. Electrical activity is measured on the scalp surface of the head, therefore making it non-invasive and suitable for all populations.

EEG assesses neuronal electrical activity by measuring current flow during synaptic activation of the cerebral cortex. Current flow is generated through sodium, potassium, calcium, and chlorine ions being pumped through membrane channels, changing the membrane potential of neurons. To detect the current flow and alternating electrical activity at the scalp it must first travel through several layers, including the skull and skin. Once electrical signals are detected, they are largely amplified for interpretation.

Brain activity are reflected in fluctuating patterns within defined frequency bands and are measured in terms of peak to peak spectral power. The frequency associated with the sinusoidal brain activity is analyzed and can be separated into four main frequency bands (beta, alpha, theta and delta). Using a frequency spectrum analysis, the extent of each frequency band is be determined. The alpha band (8-12 Hz) is the most robustly studied frequency band. Awake with the eyes closed, regular oscillations in the occipital cortex are classified as “alpha waves”. Alpha activity decreases upon eye opening, or other alerting stimuli. While alpha activity decreases upon visual perception, beta activity (>13 Hz) increases. Alpha activity decreases upon falling asleep; theta (4-8 Hz) and delta (<4 Hz) activity increase (Teplan, 2002).

There are many applications of EEG use to date, including but certainly not limited to: evaluating effectiveness of drugs (Saletu, Anderer, & Saletu-Zyhlarz, 2006), diagnosing neurological abnormalities (Smith, 2005) and consciousness (Gajraj, Doi, Mantzaridis, & Kenny, 1998). Due to the non-invasive nature of EEG, it is suitable for patients, healthy individuals, infants and all other demographic groups.

The method of limits and the method of constant stimuli have both been used for documenting magnetophosphene thresholds within a narrow range of frequencies. In order to establish magnetophosphene thresholds across a wide range of frequencies, the method of self-adjustment is suitable.

1.8 Conclusion

In conclusion, MFs are known to interact with the human body in several ways, however, the visual system and magnetophosphene perception appears to be a reliable outcome of ELF MF exposure. Magnetophosphenes, the associated frequency response and the variance in threhsolds will help guideline organizations protect the public and workers from adverse effects of ELF MF exposure. The current ELF MF exposure guidelines are limited in data, do not span the entire ELF range, and are entirely subjective. EEG is a potential tool for assessing ELF MF exposures and evaluating the effect on the CNS.

1.9 References:

Abe, Z. (1951). Influence of Adaptation on the Strength-Frequency Curve of Human Eyes, as Determined with Electrically Produced Flickering Prosphenes. *The Tohoku Journal of Experimental Medicine*, *54*(1).

Abrahamyan, A., Clifford, C. W. G., Ruzzoli, M., Phillips, D., Arabzadeh, E., & Harris, J. A. (2011). Accurate and rapid estimation of phosphene thresholds (REPT). *PLoS ONE*, *6*(7). https://doi.org/10.1371/journal.pone.0022342

Adrian, D. J. (1977). Auditory and visual sensations stimulated by low-frequency electric currents. *Radio Science Supplement*, *12*(6), 243–250.

Al-Akhras, M. A. (2008). Influence of 50 Hz magnetic field on sex hormones and body, uterine, and ovarian weights of adult female rats. *Electromagnetic Biology and Medicine*, *27*(2), 155–163. https://doi.org/10.1080/15368370802072125

Allen, A., Villard, S., Corbacio, M., Goulet, D., Plante, M., Souques, M., … Legros, A. (2016). Impact of electromagnetic fields on human vestibular system and standing balance: Pilot results and future developments. *IOP Conference Series: Materials Science and Engineering*, *120*(1). https://doi.org/10.1088/1757-899X/120/1/012018

Ambrosini, A., Iezzi, E., Perrotta, A., Kisialiou, A., Nardella, A., Berardelli, A., … Schoenen, J. (2015). Correlation between habituation of visual-evoked potentials and magnetophosphene thresholds in migraine: A case-control study. *Cephalalgia : An International Journal of Headache*, *36*(3), 0333102415590241-. https://doi.org/10.1177/0333102415590241

Attwell, D. (2003). Interaction of low frequency electric fields with the nervous system: the retina as a model system. *Radiation Protection Dosimetry*, *106*(4), 341–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14690277

Aurora, S. K., Welch, K. M. A., & Al-Sayed, F. (2003). The threshold for phosphenes is lower in migraine. *Cephalalgia*, *23*(4), 258–263. https://doi.org/10.1046/j.1468-2982.2003.00471.x

Barlow, H. B., Kohn, H. I., & Walsh, E. G. (1947). Visual sensations aroused by magnetic fields. *The American Journal of Physiology*, *148*(2), 372–275.

Berger, H. (1930). Uber das Elektrenkephalogramm des Menschen. Zweite Mitteilung. *J. Psycho. Neurol.*, *40*(1875), 160–179. https://doi.org/10.1055/s-0028-1130334

Conner, J. D., & MacLeod, D. I. . (1977). Rod Photoreceptors Detect Rapid Flicker. *Science*, *195*(4279), 698–699.

Cook, C. M., Saucier, D. M., Thomas, A. W., & Prato, F. S. (2009). Changes in human EEG alpha activity following exposure to two different pulsed magnetic field sequences. *Bioelectromagnetics*, *30*(1), 9–20. https://doi.org/10.1002/bem.20434

Cook, C. M., Thomas, A. W., Keenliside, L., & Prato, F. S. (2005). Resting EEG effects during exposure to a pulsed ELF magnetic field. *Bioelectromagnetics*, *26*(5), 367–376. https://doi.org/10.1002/bem.20113

Cook, C. M., Thomas, A. W., & Prato, F. S. (2002). Human Electrophysiological and Cognitive Effects of Exposure to ELF Magnetic and ELF Modulated RF and Microwave Fields: A Review of Recent Studies. *Bioelectromagnetics*, *23*(2), 144–157. https://doi.org/10.1002/bem.107

Cook, M. R., Graham, C., Cohen, H. D., & Gerkovich, M. M. (1992). A replication study of human exposure to 60Hz fields: Effects on neurobehavioral measures. *Bioelectromagnetics*, *13*(4), 261–285. https://doi.org/10.1002/bem.2250130403

Corbacio, M., Brown, S., Dubois, S., Goulet, D., Prato, F. S., Thomas, A. W., & Legros, A. (2011). Human cognitive performance in a 3 mT power-line frequency magnetic field. *Bioelectromagnetics*, *32*(8), 620–633. https://doi.org/10.1002/bem.20676

Crasson, M., & Legros, J. J. (2005). Absence of daytime 50 Hz, 100 μTrms magnetic field or bright light exposure effect on human performance and psychophysiological parameters. *Bioelectromagnetics*, *26*(3), 225–233. https://doi.org/10.1002/bem.20070

D'Arsonval, A. (1896). Dispostifis pour la mesure des courants alternatifs de toutes frequences. *Comput. Rendus. Soc. Biol.*, 450–451.

Delhez, M., Legros, J. J., & Crasson, M. (2004). No influence of 20 and 400 mu T 50 Hz magnetic field exposure on cognitive function in humans. *Bioelectromagnetics*, *25*(8), 592–598. https://doi.org/10.1002/bem.20040

Elkin-Frankston, S., Fried, P. J., Pascual-Leone, A., Rushmore, R. J., & Valero-Cabr, A. (2010). A novel approach for documenting phosphenes induced by transcranial magnetic stimulation. *Journal of Visualized Experiments : JoVE*, (38), 1–4. https://doi.org/10.3791/1762

Fujikado, T., Morimoto, T., Kanda, H., Kusaka, S., Nakauchi, K., Ozawa, M., … Tano, Y. (2007). Evaluation of phosphenes elicited by extraocular stimulation in normals and by suprachoroidal-transretinal stimulation in patients with retinitis pigmentosa. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *245*(10), 1411–1419. https://doi.org/10.1007/s00417-007-0563-z

Gajraj, R. J., Doi, M., Mantzaridis, H., & Kenny, G. N. C. (1998). Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness. *British Journal of Anaesthesia*, *80*(1), 46–52. https://doi.org/10.1093/bja/80.1.46

Gandhi, O. P., Kang, G., Wu, D., & Lazzi, G. (2001). Currents induced in anatomic models of the human for uniform and nonuniform power frequency magnetic fields. *Bioelectromagnetics*, *22*(2), 112–21. https://doi.org/10.1002/1521-186X(200102)22:2<112::AID-BEM1014>3.0.CO;2-0

Gebhard, J. W. (1952). Thresholds of the human eye for electric stimulation by different wave forms.

Geddes, L. A. (2008). The history of magnetophosphenes, 101–102.

Gescheider, G. A. (1997). *Psychophysics, The Fundamentals* (3rd ed.). Mahwah, NJ, NJ: Lawrence Erlbaum Associates.

Glover, P. M., Cavin, I., Qian, W., Bowtell, R., & Gowland, P. A. (2007). Magnetic-field-induced vertigo: A theoretical and experimental investigation. *Bioelectromagnetics*, *28*(5), 349–361. https://doi.org/10.1002/bem.20316

Haggard, M. (2010). *Hearing: An Introduction to Psychological and Physiological Acoustics*. *Journal of neurology, neurosurgery, and psychiatry* (5th ed., Vol. 45). Colchester: Informa Healthcare. https://doi.org/10.1136/jnnp.45.12.1175-b

Heusser, K., Tellschaft, D., & Thoss, F. (1997). Influence of an alternating 3 Hz magnetic field with an induction of 0.1 millitesla on chosen parameters of the human occipital EEG. *Neuroscience Letters*, *239*(2–3), 57–60. https://doi.org/10.1016/S0304-3940(97)00881-1

Institute of Electrical and Electronics Engineers Inc., & IEEE. (2002). *IEEE Standards for Safety Levels with Respect to Human Exposure to Electromagnetic Fields, 0-3 kHz*. *IEEE Standard C95.6*. New York. https://doi.org/10.1109/IEEESTD.2002.94130

International Commission on Non-Ionizing Radiation Protection. (2010). *Guidelines for Limiting Exposure to Time-Varying Electric and Magnetic Fields (1 Hz to 100 kHz)*. https://doi.org/10.1097/HP.0b013e3181f06c86

Jazi, S. D., Modolo, J., Baker, C., Villard, S., & Legros, A. (2017). Effects of a 60 Hz magnetic field of up to 50 millitesla on human tremor and EEG: A pilot study. *International Journal of Environmental Research and Public Health*, *14*(12). https://doi.org/10.3390/ijerph14121446

Kanai, R., Chaieb, L., Antal, A., Walsh, V., & Paulus, W. (2008). Frequency-Dependent Electrical Stimulation of the Visual Cortex. *Current Biology*, *18*(23), 1839–1843. https://doi.org/10.1016/j.cub.2008.10.027

Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (2000). *Principles Of Neural Science* (4th ed.). New York: McGraw-Hill. https://doi.org/10.1007/s13398-014-0173-7.2

Kar, K., & Krekelberg, B. (2012). Transcranial electrical stimulation over visual cortex

evokes phosphenes with a retinal origin. *Journal of Neurophysiology*, *108*(8), 2173–8. https://doi.org/10.1152/jn.00505.2012

Laakso, I., & Hirata, A. (2013). Computational analysis shows why transcranial alternating current stimulation induces retinal phosphenes. *Journal of Neural Engineering*, *10*(4). https://doi.org/10.1088/1741-2560/10/4/046009

Legros, A., Corbacio, M., Beuter, A., Modolo, J., Goulet, D., Prato, F. S., & Thomas, A. W. (2012). Neurophysiological and behavioral effects of a 60 Hz, 1,800 lT magnetic field in humans. *European Journal of Applied Physiology*, *112*(5), 1751–1762. https://doi.org/10.1007/s00421-011-2130-x

Legros, A., Modolo, J., Goulet, D., Plante, M., Souques, M., Deschamps, F., … Thomas, A. W. (2016). Magnetophosphenes perception threshold and EEG response in humans exposed to 20, 50, 60 and 100 Hz MF up to 50,000 μT. *5th International Conference on Electromagnetic Fields, Health and Environment - EHE2014, Porto, Portugal, April 24th - 26th 2014.*, *2*(July 2016), 6–7. https://doi.org/https://doi.org/10.1016/j.brs.2015.01.365

Logothetis, N. K., Kayser, C., & Oeltermann, A. (2007). In Vivo Measurement of Cortical Impedance Spectrum in Monkeys: Implications for Signal Propagation. *Neuron*, *55*(5), 809–823. https://doi.org/10.1016/j.neuron.2007.07.027

Lövsund, P., Öberg, P. Å., & Nilsson, S. E. G. (1980a). Magneto- and electrophosphenes: A comparative study. *Medical & Biological Engineering & Computing*, *18*(6), 758–764. https://doi.org/10.1007/BF02441902

Lövsund, P., Öberg, P. Å., & Nilsson, S. E. G. (1980b). Magnetophosphenes: a quantitative analysis of thresholds. *Medical & Biological Engineering & Computing*, *18*(3), 326–334. https://doi.org/10.1007/BF02443387

Lyskov, E. B., Juutilainen, J., Jousmaki, V., Partanen, J., Medvedev, S., & Hanninen, O. (1993). Effects of 45-Hz magnetic fields on the functional state of the human brain. *Bioelectromagnetics*, *14*(2), 87–95.

Magnusson, C. E., & Stevens, H. C. (1911). Visual sensations caused by changes in the strength of a magnetic field.

McNamee, D. A., Legros, A. G., Krewski, D. R., Wisenberg, G., Prato, F. S., & Thomas, A. W. (2009). A literature review: the cardiovascular effects of exposure to extremely low frequency electromagnetic fields. *International Archives of Occupational and Environmental Health*, *82*(8), 919–933. https://doi.org/10.1007/s00420-009-0404-y

Min, B. K., Jung, Y. C., Kim, E., & Park, J. Y. (2013). Bright illumination reduces parietal EEG alpha activity during a sustained attention task. *Brain Research*, *1538*, 83–92. https://doi.org/10.1016/j.brainres.2013.09.031

Modolo, J., Hassan, M., & Legros, A. (2018). Reconstruction of brain networks involved in magnetophosphene perception using dense electroencephalography. *BioEM 2918 Conference Proceedings*, 1–6.

Morimoto, T., Fukui, T., Matsushita, K., Okawa, Y., Shimojyo, H., Kusaka, S., … Fujikado, T. (2006). Evaluation of residual retinal function by pupillary constrictions and phosphenes using transcorneal electrical stimulation in patients with retinal degeneration. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *244*(10), 1283–1292. https://doi.org/10.1007/s00417-006-0260-3

Mulleners, W. M., Chronicle, E. P., Palmer, J. E., Koehler, P. J., & Vredeveld, J.-W. (2001). Visual Cortex Excitability in Migraine With and Without Aura. *Headache: The Journal of Head and Face Pain*, *41*, 565–572. https://doi.org/10.1046/j.1526-4610.2001.041006565.x

Nevelsteen, S., Legros, J.-J., & Crasson, M. (2007). Effects of information and 50 Hz magnetic fields on cognitive performance and reported symptoms. *Bioelectromagnetics*, *28*(1), 53–63. https://doi.org/10.1002/bem.20265

Perz, M. (2010). Flicker Perception in the Periphery.

Prato, F. S., Thomas, A. W., & Cook, C. M. (2001). Human standing balance is affected

by exposure to pulsed ELF magnetic fields: light intensity-dependent effects. *Neuroreport*, *12*(7), 1501–1506. https://doi.org/10.1097/00001756-200105250-00040

Preece, A. W., Wesnes, K. A., & Iwi, G. R. (1998). The effect of a 50 Hz magnetic field on cognitive function in humans. *Int J Radiat Biol*, *74*(4), 463–470.

Saletu, B., Anderer, P., & Saletu-Zyhlarz, G. M. (2006). EEG Topography and Tomography (LORETA) in the Classification and Evaluation of the Pharmacodynamics of Psychotropic Drugs. *Clinical EEG and Neuroscience*, *37*(2), 66–80. https://doi.org/10.1177/155005940603700205

Sastre, A., Cook, M. R., & Graham, C. (1998). Nocturnal exposure to intermittent 60 Hz magnetic fields alters human cardiac rhythm. *Bioelectromagnetics*, *19*(2), 98–106. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9492166

Saunders, R. D., & Jefferys, J. G. R. (2007). A neurobiological basis for ELF guidelines. *Health Physics*, *92*(6), 596–603. https://doi.org/10.1097/01.HP.0000257856.83294.3e

Silny, J. (1984). Changes in VEP caused by strong magnetic fields. *Second International Evoked Potential Symposium*.

Silny, J. (1986). The Influence of the Time-Varying Magnetic Field in the Human Organism. *Biological Effects of Static and Extremely Low Frequency Magnetic Fields*.

Smith, S. J. M. (2005). EEG in neurological conditions other than epilepsy: When does it help, what does it add? *Neurology in Practice*, *76*(2), 8–12. https://doi.org/10.1136/jnnp.2005.068486

Teplan, M. (2002). FUNDAMENTALS OF EEG MEASUREMENT. *Measurement Science Review*, *2*(2), 1–11.

Thomas, A. W., Drost, D. J., & Prato, F. S. (2001). Human subjects exposed to a specific

pulsed (200 μT) magnetic field: Effects on normal standing balance. *Neuroscience Letters*, *297*(2), 121–124. https://doi.org/10.1016/S0304-3940(00)01688-8

Thompson, S. P. (1910). A Physiological Effect of an Alternating Magnetic Field. *Proceedings of the Royal Society B: Biological Sciences*, *82*(557), 396–398. https://doi.org/10.1098/rspb.1910.0032

Tinsley, J. N., Molodtsov, M. I., Prevedel, R., Wartmann, D., Espigulé-Pons, J., Lauwers, M., & Vaziri, A. (2016). Direct detection of a single photon by humans. *Nature Communications*, *7*. https://doi.org/10.1038/ncomms12172

Van Nierop, L. E., Slottje, P., Kingma, H., & Kromhout, H. (2013). MRI-related static magnetic stray fields and postural body sway: A double-blind randomized crossover study. *Magnetic Resonance in Medicine*, *70*(1), 232–240. https://doi.org/10.1002/mrm.24454

World Health Organization. (2007). *Extremely Low Frequency Fields. Environmental Health Criteria*. *World Health Organization*. Geneva. Retrieved from http://www.scopus.com/inward/record.url?eid=2-s2.0-77955459021&partnerID=40&md5=298ffb383a138d66c0d2c27528febac8

Zaffanella, L. E., & Kalton, G. W. (1998). *Survery of Personal Magnetic Field Exposure. Phase II: 1000-Person Survey*.

Chapter 2

2 Research Article

2.1 Introduction

Everything on Earth is continually exposed to both natural and manmade Magnetic Fields (MFs). These exposures can result from the natural Earth's geomagnetic field or the static MF from magnetic resonance imaging (MRI) devices. They are also generated by the alternating current flowing through everyday household appliances and electrical wires and in these cases, they are called time-varying or alternating MFs. In North America, alternating MF exposures in daily life are generally under 1 μT (Zaffanella & Kalton, 1998). However, these exposures can exceed 1 mT in close proximately to appliances or powerlines (World Health Organization, 2007). An interesting feature of time-varying MFs is that they have the ability to interact with biological tissues through magnetic induction (Attwell, 2003), i.e. they induce electric fields and current within exposed tissues. Since MFs have the potential to interact with biological processes, it is important to make sure that humans are not exposed to harmful levels. Hence, in order to avoid exposures leading to possible adverse biological interactions, exposure guidelines set by international agencies, are established to protect the public and workers (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002; International Commission on Non-Ionizing Radiation Protection, 2010). The guidelines for Extremely Low Frequency (ELF, < 300 Hz) MFs, are mostly based on the most reliably reported acute effect of low levels of ELF MF exposure: magnetophosphene perception. Magnetophosphenes are described as white flickering lights, perceived with the eyes closed in the dark upon exposure to a sufficiently strong ELF MF. Magnetophosphenes are thought to be a consequence of magnetic induction in the retina (refer to Section 1.5), where the induced electric fields affect signaling in the chain of cells between the photoreceptors and the retinal ganglion cells, by which the visual signals are transmitted in graded potentials (rather than action potentials) via ribbon synapses to the ganglion cells (Attwell, 2003).

Magnetophosphene phenomena were first reported by D'Arsonval in 1896. Since then laboratory studies with human subjects have reported magnetophosphene perception for

more than a century (Barlow et al., 1947; D'Arsonval, 1896; Legros et al., 2016; Lövsund et al., 1980a, 1980b; Magnusson & Stevens, 1911; Silny, 1984). The magnetophosphene threshold corresponds to the lowest stimulus intensity that elicits visual perception and is used as the basis to specify exposure guidelines to protect the general public and workers against adverse effects. (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002; International Commission on Non-Ionizing Radiation Protection, 2010).

To understand the mechanism of magnetophosphene perception, electro- and magnetophosphene threshold curves were compared. Barlow et al. (1947) were the first to compare perceptual responses. With a 60 Hz stimulation, the duration of perception was assessed while varying the stimulus strength. Both electro- and magnetophosphene perception duration were increased with stimulus strength, leading to the hypothesis that they are a product of the same neural pathway (Barlow et al., 1947). Furthering the comparison, Lövsund established frequency response curves for both magneto- and electrophosphenes. Establishing magneto- and electrophosphene thresholds identified that both stimulations were most sensitive at 20 Hz. Yet, the frequency response curves for Electro- and magnetophosphene thresholds followed similar trends only between 17 and 25 Hz. Based on the law of induction, that is, induced current density is directly proportional to the frequency and intensity of the MF, theoretical thresholds were calculated in order to accurately compare magneto- and electrophosphene thresholds (Lövsund et al., 1980a). The theoretical threshold curve fits the magnetophosphene threshold curve, indicating that the pathway involved in phosphene perception is sensitive to not only the magnetic flux density but more accurately to the induced electric field (Lövsund et al., 1980a). Therefore, in addition to reporting magetnophosphene threshold values in terms of flux density, it is important to report threshold values in dB/dt (T/s), which is linearly proportional to the induced electric field.

Yet the mechanism of magnetophosphene perception remains unclear since many discrepancies can be identify. Magnetophosphene perception thresholds were reported to be lowest (~10 mT_{rms}) from 20-30 Hz (Lövsund et al., 1980a, 1980b), but the exact frequency eliciting the lowest perception has not been confirmed and conditions such lighting, source of phosphene generation (electric or magnetic) or duration spent in the

darkness are known to modulate the perception threshold. For instance, in complete darkness, the lowest magnetophosphene threshold was reported at 30 Hz, but the lowest threshold was found to be between 20 and 25 Hz when the lights were on (Lövsund et al., 1980b). Similarly, electrophosphenes (phosphenes perceived as a result of electric stimulation) are frequency dependent as well, and have been reported to be lowest for a wide range of frequencies ranging from 7-37 Hz (Abe, 1951; Adrian, 1977; Kanai et al., 2008; Lövsund et al., 1980a). Using transcranial alternating current stimulation (tACS), phosphenes were strongest from 10-12 Hz (Kanai et al., 2008). Moreover, phosphenes have overwhelmingly been described as white flickering lights; however, using electrical stimulation, coloured phosphenes have been reported in one study, and were the most prominent at 30 Hz, however requiring ~20 times more stimulus (Adrian, 1977). Magnetophosphene threshold studies require an improved understanding of the mechanisms involved and replications of Lovsund's (1980) previous experiments. Furthermore, previous magnetophosphene threshold reports were also limited to very few participants, and a larger sample size would strengthen and improve precision of the overall findings.

Although a larger sample size will increase the precision of magnetophosphene thresholds, results remain entirely based on subjective reports of perception. An objective measurement of neuronal activity would greatly improve the investigation of magnetophosphene thresholds. In that regard, electroencephalography (EEG) appears as a relevant option. EEG is a non-invasive objective measurement of brain electrical activity resulting from action potentials in the cerebral cortex. Brain activity patterns can be broken into various frequency bands. The alpha frequency band (8-12 Hz) has been recognized as the most prominent component of occipital brain oscillations while awake with the eyes closed. Known as the "Berger effect", alpha power decreases upon visual perception (Berger, 1930; Teplan, 2002). An increase in ambient lighting decreases alpha activity (Min, Jung, Kim, & Park, 2013). Occipital alpha activity preceding phosphene perception has been used as a predictor of perception. This suggests that EEG alpha activity has the potential of being an objective biomarker of ELF MF exposure and magnetophosphene perception. Determining an effective objective biomarker has the potential to address the

inconsistencies between frequency response experiments, both electric and magnetic, as it overcomes the subjective component in threshold analysis.

Finally, significant knowledge gaps still remain, since only frequencies in the range of 10-45 Hz were studied, and as such, powerline frequencies (50 and 60 Hz) were not experimentally evaluated in humans (Lövsund et al., 1980a, 1980b). Currently, ELF MF exposure guidelines extrapolate previous findings acquired at lower frequencies when establishing guidelines to protect the general public and powerline workers at power frequencies (50 and 60 Hz). Therefore, an experimental study considering an expanded frequency range throughout the entire ELF range is needed.

The primary objective of this study is to generate the frequency-response curve in the ELF range (<300 Hz) for magnetophosphene perception in humans, and specifically the first experimental threshold values at powerline frequencies (50 and 60 Hz). The secondary objective is to determine if magnetophosphene perception can be captured using EEG as an objective biomarker.

Based on the work from Lövsund, the threshold for magnetophosphene perception in darkness is expected to be the lowest at 30 Hz (Lövsund et al., 1980b). Additionally, if treated like a visual stimulus, magnetophosphene perception should be associated with a decreased EEG power in the alpha frequency band in occipital electrodes. These threshold values and their variance will allow guidelines to evaluate the probability of perception for a given population.

2.2 Materials and Methods

2.2.1 Participants

Sixty healthy participants (mean age: 24.31 ± 3.69) were tested in this experiment. All testing took place in the Human Threshold Research Facility at Lawson Health Research Institute (St. Joseph's Hospital, London, Ontario, Canada). Participants were between the ages of 18 and 33 years old. Exclusion criteria for the experiment include participants who are claustrophobic, have limited movement, who have experienced an epileptic seizure, those who suffer from chronic illness (e.g. diabetes, cardiovascular problems, psychiatric

problems, etc.), and those who have an implanted electrical device. Participants were instructed to refrain from exercise, caffeine, alcohol and nicotine intake for 12 hours prior to the study. Volunteers had the opportunity to ask questions regarding the experimental procedure before providing written consent to participate. The volunteers did not have pathological visual dysfunctions. This protocol was approved by the Western University Health Sciences Research Ethics Board (HSREB #108934).

2.2.2 Materials

A custom global head exposure system was used throughout this experiment. This device was designed and built at the Lawson Health Research Institute (St. Joseph's Hospital, London, Ontario, Canada). The global exposure system consists of two 99-turn coils, 11 turns of 9 layers, made with square copper wire, and cooled with circulating water (Figure 4). Enclosed in PVC plastic, the coils have a 356 mm inner diameter and a 501 mm outer diameter and are arranged in a Helmholtz-like manner, enabling the generation of a homogenous MF over the participant's head. Each of the two coils is independently driven by an MTS MRI gradient amplifier (MTS Automation 0105870, Horsham, PA, USA). The amplifiers were driven by a command by of a customized LabVIEW script and a 16-bit National Instruments A/D Card (National Instrument, Austin, Texas). The coil system generates a homogenous MF (± 5%) around the head of the participant (Figure 5). MF flux density (mT_{rms}) was confirmed using a single axis MF Hall transducer probe (± 200 mT_{rms} range with 0.1% accuracy, SenisTM 0YA05F-C.2T2K5J; Senis, Baar, Switzerland). A motorized non-magnetic lift enabled vertical movement of the coil system such that it could raise and lower centering the participants eyes between the coils.

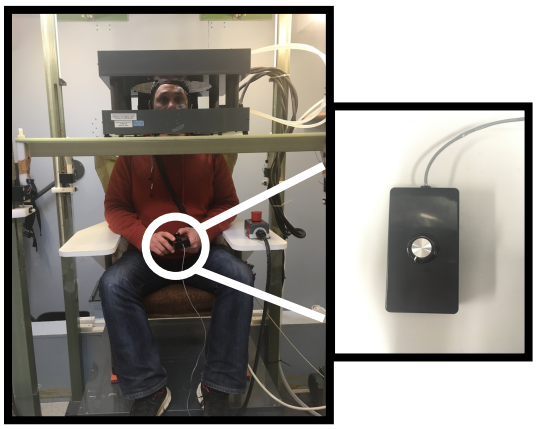


Figure 4: Depiction of the global exposure device. A participant is shown sitting in the global MF exposure device, holding a handheld potentiometer used to control the MF flux density (left). Handheld potentiometer (right).

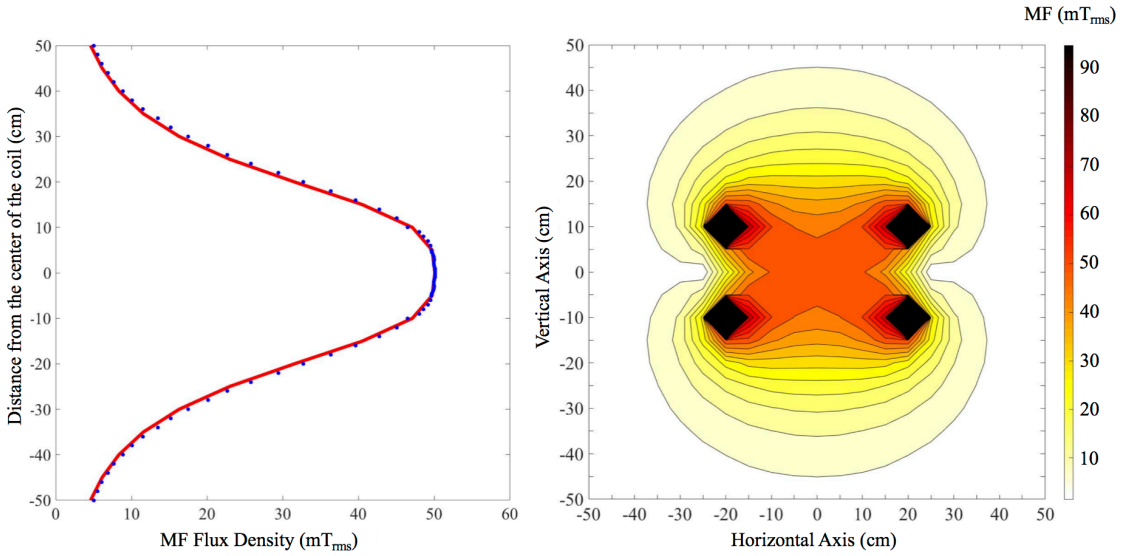


Figure 5: Left: MF flux density calculated (red) and measured (blue) along the vertical axis in the center of the coils. The flux density decreases with distance from the center of the exposure device. Right: Magnetic field produced by our exposure system calculated using the Biot–Savart law. The MF flux density is homogenous about the head of the participant (5% variation). This diagram depicts the flux density when the participant is exposed to a 50 mT$_{rms}$ MF. The central orange region is the homogenous region, where the participants head is positioned (frontal view depicted). Contour lines represent a 5 mT$_{rms}$ change in MF flux density.

EEG was measured throughout this experiment using a 64-channel MRI compatible EEG cap and a SynAmps2 amplifier (Compumedics Neuroscan Inc., Charlotte, NC, USA). Data collected through a cap of EEG electrodes, placed according to the 10/20 system, and referenced to a point half-way between the Cz electrode and the CPz electrode. The ground electrode was placed half-way between the Fz and FPz electrodes. A conductive gel was used to improve conductance (Compumedics Quik-Gel™; Compumedics Neuroscan Inc., Charlotte, NC, USA) and electrode impedances were kept below 10 kΩ. Based on the brain region of interest O1, O2 and Oz electrodes were analyzed, as they correspond with the occipital lobe and V1.

Highpass and lowpass filters (3-17 Hz) were used to isolate the EEG activity from the ELF MF after a Hanning window was applied to 5 seconds of stationary MF exposure. The Hanning window was applied to prevent edge effects when filtering, while maintaining the integrity of the signal frequency. The frequency spectrum analysis, using the Welch's power spectral density estimate over 2.5 s Hamming windows with 1.5 s overlaps. MATLAB function, was performed on the filtered signal to quantify the alpha activity (Figure 6).

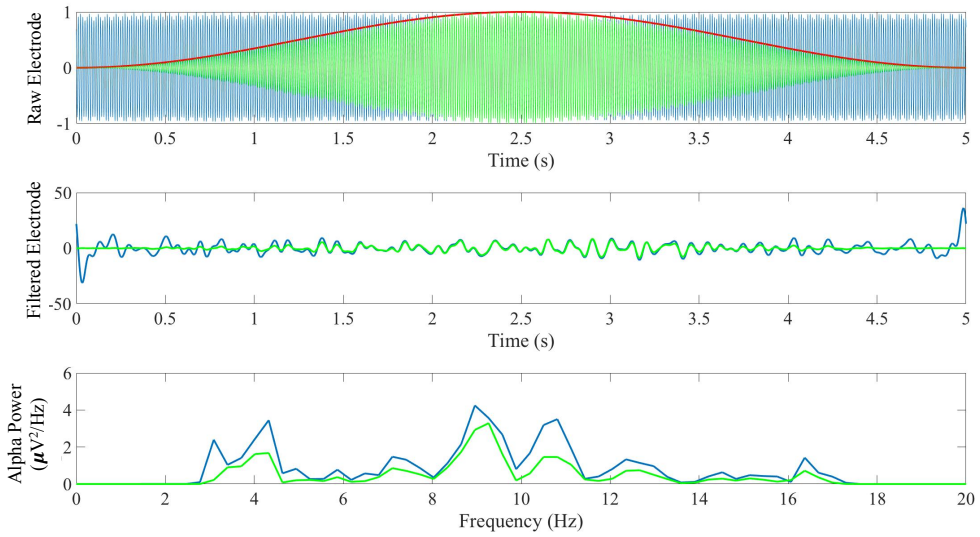


Figure 6: Example of EEG activity during ELF MF exposure. Top: Raw data collected from an electrode (blue), hanning window (red) and windowed data (green). Middle: Filtered signal with (green) and without (blue) the hanning

window. Bottom: Frequency spectrum analysis on filtered signal, with (green) and without (blue) the use of the hanning window.

Previously, a phantom (watermelon) was used to confirm the post-processing signals were successful in removing possible MF-induced artifacts from EEG data. There was no detectible difference in the EEG spectral power between MF exposure and sham exposure (Davarpanah Jazi, Modolo, Baker, Villard, & Legros, 2017).

2.2.3 Experimental Procedure

This experiment consisted of a single session lasting about 2 hours. The initial 15 minutes was allotted to explaining the experiment to the participant and gaining written consent. The following 30 minutes was devoted to attaching the EEG apparatus to the subject's head. After setting the participant up, 15 minutes were spent familiarizing the participant with the experiment while they were set up inside the exposure system, allowing them to practice the required tasks before data collection began. To familiarize, participants were exposed to a 5 second MF exposure at 20 Hz, 50 mT_{rms}, and asked to confirm magnetophosphene perception. They were then instructed to practice the required task of selecting the magnetophosphene threshold. Instructions were as follows: "When you hear 'begin' please use the dial to increase the MF until you clearly perceive a visual phenomenon. Slowly decrease the MF until the visual perception has disappeared, and then slowly move in a step-wise manner to find the point where you just barely perceive something. There will be 25 seconds to adjust the MF until the point where you just barely perceive something. You will hear a beep, indicating that you have 5 seconds left to find your threshold. You will hear the word "End" when the trial is over. If there is a condition when you turn the dial to its' maximum and still don't see anything, please leave the dial at max and tell me over the intercom – at this point I will turn the MF off from my control". Once trained on the experiment, data collection began and lasted 50 minutes. After completion of the experiment, participants responded to a standardized Field Status Questionnaire (Cook, Graham, Cohen, & Gerkovich, 1992).

The experiment consisted of 25 frequency conditions between 0 and 300 Hz were tested: every 5 Hz from 0 (sham) to 100 Hz (5 Hz, 10 Hz, 15 Hz, etc.), and then every 50 Hz from

100 to 300 Hz (150 Hz, 200 Hz, 250 Hz, 300 Hz). MF frequency conditions were randomly given in a blinded counterbalanced order via a LabVIEW program delivering exposure conditions. Each frequency condition was presented twice, making a total of 50 exposures. Thresholds were averaged between the two trials at each frequency. Ten participants were also exposed to six additional trials at 20 Hz, totaling 8 exposures at 20 Hz, to determine the test-retest reliability of the threshold estimation method.

Each exposure was presented immediately after the lights were extinguished and lasted 30 seconds. During this time, the participant was required to self-adjust the MF flux density using a handheld potentiometer, as explained in the practice trials. Turning a dial on the potentiometer controlled the flux density of the MF, such that the maximum position of the dial corresponded to the maximum flux density of that frequency condition. Due to hardware limitation, from 5 to 60 Hz the maximum flux density was 70 mT_{rms}, from 65 to 90 Hz the maximum flux density was 60 mT_{rms}. Above 90 Hz, the dB/dt value equivalent to the maximum possible at 90 Hz was maintained and converted to flux density for each frequency condition (Figure 7). The initial 25 seconds of each exposure allowed participants to self-determine their magnetophosphene threshold. The last 5 seconds of each exposure was a constant MF flux density, given at the self-determined magnetophosphene threshold (Figure 8). Upon completion of the trial, a 30 second rest period occurred, with the lights on to avoid adaptation to the darkness.

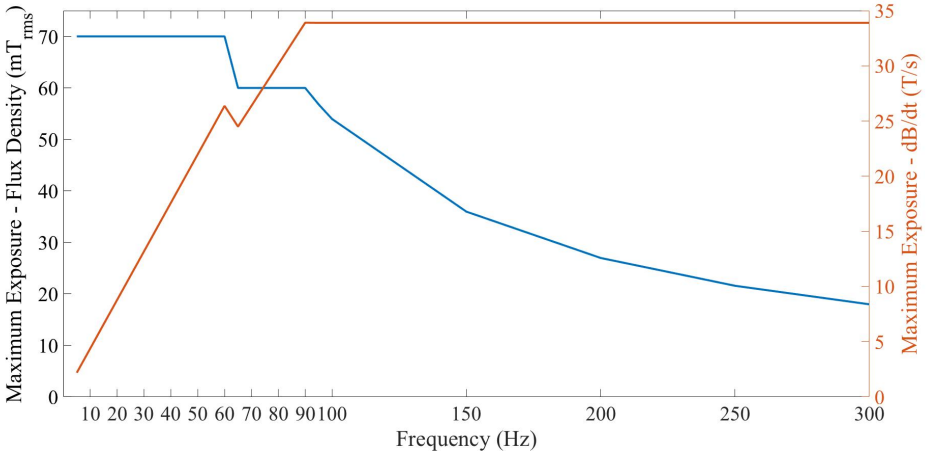


Figure 7: Maximum exposure in all frequency conditions expressed in terms of flux density (blue) and dB/dt (red). The maximum flux density was 70mT$_{rms}$ from 5 to 60 Hz, 60 mT$_{rms}$ from 65 to 90 Hz, and decreased above 90 Hz (blue). The maximum flux density above 90 Hz decreased such that maximum dB/dt remained consistent (orange).

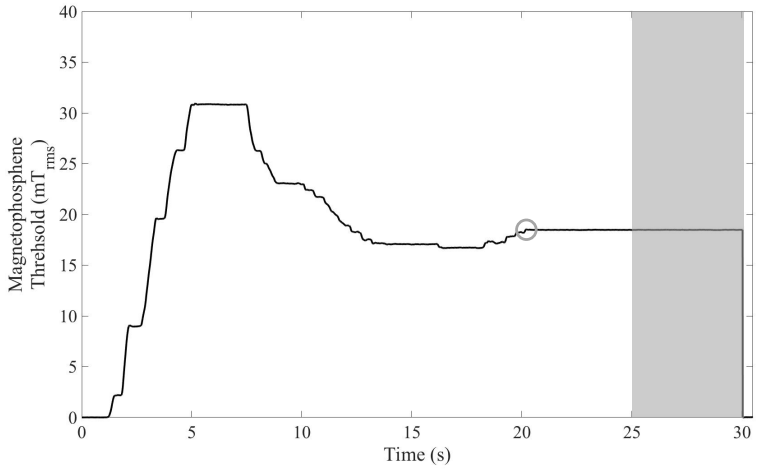


Figure 8: Schematic depiction of the timeline of events. The dark line starting at 0 represent the rms field flux density as a function of time while it is self-driven by the participant using the potentiometer. Initial 25 seconds are allocated to determining the magnetophosphene threshold. Participants receive warning via an audible "beep" that 20 seconds have passed, and that threshold determination must be completed within the remaining 5 seconds. A second audible "beep", at 25 seconds, indicates that the self-adjustment period is complete. The final 5 seconds are

constant MF flux density at the self-reported magnetophosphene threshold (shaded grey). The instant that the participant identified the magnetophosphene threshold is indicated by a grey circle.

2.3 Results

2.3.1 Percentage of Participants Perceiving Phosphenes

It is important to notice that participants did not perceive magnetophosphenes at every frequency. Indeed, while the participants reported phosphene perceptions 95 to 100% of the time for frequencies between 10 and 70 Hz, their perception rate was lower at 5 Hz and at/above 75 Hz (Figure 9). Interestingly, above 75 Hz the perception rate decreased as the frequency increased, until stabilizing below 10% from 150-300 Hz. Since it appeared from participants' subjective reports that these higher frequencies involved a higher sound made by the coils, biasing the threshold data, further statistics were run on frequencies eliciting over a 50% perception rate. This will limit biased artificial data in the statistical analysis. The sound produced by the coils may have been a confounding factor in establishing the threshold and in order to avoid conducting statistical analyzes based on a small number of subjects, the threshold analysis was limited to the frequency range between 5 and 8h Hz.

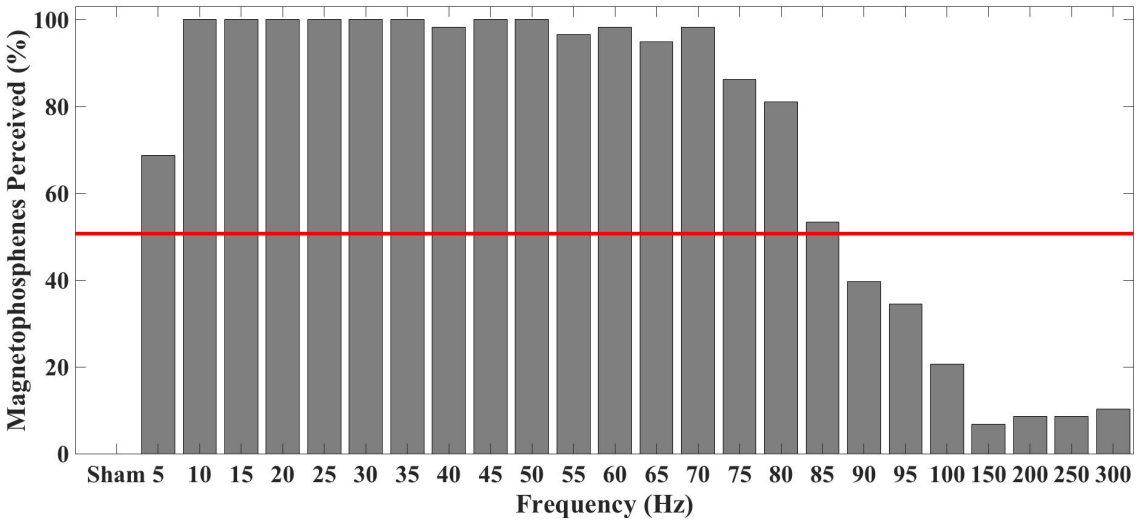


Figure 9: Percentage of participants perceiving magnetophosphenes through the entire ELF range (n=60). The 50% cutoff region is indicated by a red line.

2.3.2 Threshold Determination Repeatability

In order to evaluate the test/re-test reliability of the threshold detection method selected for this experiment, four repetitions of the same frequency condition (20 Hz – each given twice) were given to a set of ten participants. A one-way ANOVA for repeated measures (4 conditions – 20 Hz repeated 4 times) was conducted to test our test-retest reliability (Figure 10 (left)). This analysis showed no significant main effect ($F(3,27)=0.917$, $p>0.05$). The method of self-adjustment is valid for determining magnetophosphene thresholds, as participants were able to reliably and repeatedly select the same threshold at a given (20 Hz) frequency.

2.3.3 Frequency-Response

Thresholds were found to change as a function of frequency (Figure 10). A one-way ANOVA with repeated measures (17 conditions –from 5 to 85 Hz) showed a main effect in mean thresholds as a function of frequency ($F(16,813)=53.12$, $p<0.0001$, $\eta^2=0.51$, power= 1). Post hoc comparisons (Tukey adjusted for multiple comparisons) showed that the magnetophosphene threshold is lowest at 35 Hz (16.92 mT_{rms} ± 6.87 mT_{rms}; Figure 10 (top)), while the threshold increases both above and below this frequency. Although the threshold decreases above 85 Hz, these frequencies were omitted from analysis, due to the low percentage of perception. All significant differences in mean thresholds from 5 to 85 Hz are reported in Table 3. Magnetophosphene thresholds are also reported in dB/dt (Figure 10 (bottom)), as this is proportional to both the intensity and the frequency of the MF, and a direct relationship to the induced electric field seen in the retina. When increasing the frequency, the induced electric field at the retina increases. By representing the frequency-response in terms of dB/dt, the true frequency-response is evaluated, since it is a direct correlate of the induced electric field (Figure 11). Different correlation strategies were explored in order to evaluate the best fit to describe the dynamics of the data. The linear relationship ($p<0.001$, $R^2 = 0.94$) is explained by the equation:

$$y = 0.203x - 1.8671 \qquad 5 \leq x \leq 85 \tag{3}$$

where $\boldsymbol{y}$ represents the threshold value in terms of mT_{rms} and $\boldsymbol{x}$ represents the stimulation frequency in Hz.

Upon further analysis of the magnetophosphene threshold data, with respect to dB/dt, was more accurately explained ($p < 0.001$, $R^2 = 0.99$) by a polynomial function:

$$y = 0.0022x^2 + 0.002x + 1.3082 \qquad 5 \leq x \leq 85 \tag{4}$$

where $\boldsymbol{y}$ represents the threshold value in terms of mT_{rms} and $\boldsymbol{x}$ represents the stimulation frequency in Hz.

Or explained by two linear equations, with a breaking point at 40 Hz ($p < 0.001$, $R^2 = 0.98$ and $p < 0.001$, $R^2 = 0.99$):

$$y = 0.0897x + 0.6928 \qquad 5 \leq x \leq 40 \tag{5}$$

$$y = 0.20212x - 6.9362 \qquad 40 \leq x \leq 85 \tag{6}$$

where $\boldsymbol{y}$ represents the threshold value in terms of mT_{rms} and $\boldsymbol{x}$ represents the stimulation frequency in Hz.

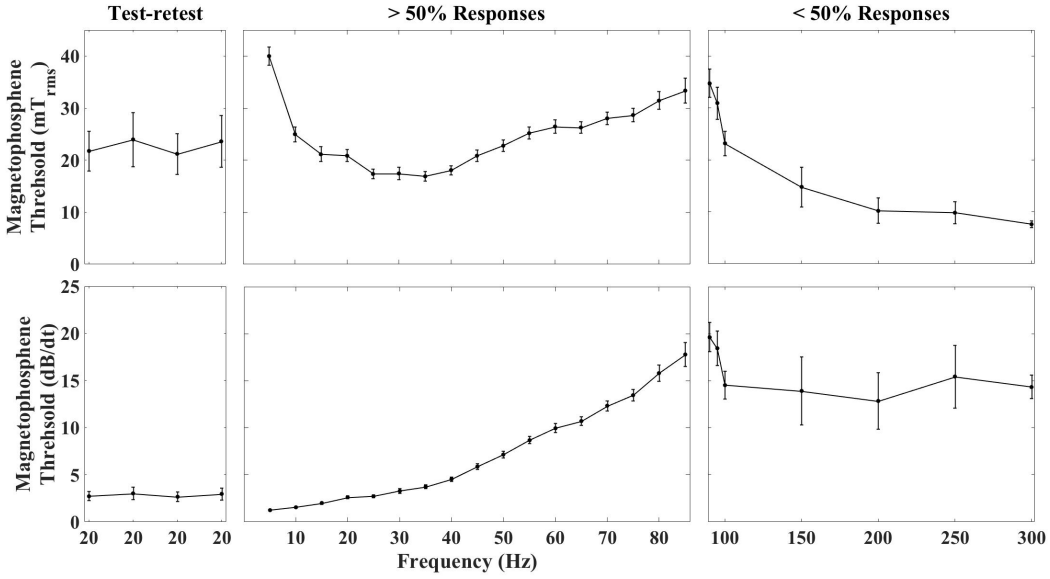


Figure 10: Left: Test-retest reliability at 20 Hz in mT_{rms} (top) and dB/dt (bottom). Middle: Frequency-response reported in mT_{rms} (top) and dB/dt (bottom) from 0-85

Hz. Right: Frequency-response reported in mT_{rms} (top) and dB/dt (bottom) from 90-300 Hz. Error bars represent the standard error of the mean (n=60).

Table 3: Post hoc (Tukey) comparisons from 5-85 Hz establish many differences in threshold values (mT). Significant differences in mean threshold values across frequencies (5-85 Hz). Representing significance, p<0.05 is *, p<0.01 is **, and p<0.001 is *.**

Frequency (Hz)																		
Frequency (Hz)		5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85
	5		***	***	***	***	***	***	***	***	***	***	***	***	***	***	***	***
	10				**	***	***	***	***	**							***	***
	15					**	*	**					*	**	***	***	***	***
	20							*				**	***	***	***	***	***	***
	25										***	***	***	***	***	***	***	***
	30										***	***	***	***	***	***	***	***
	35									*	***	***	***	***	***	***	***	***
	40										**	***	***	***	***	***	***	***
	45											**	***	***	***	***	***	***
	50														*	***	***	***
	55															*	***	***
	60																***	***
	65																**	***
	70																	***
	75																	*
	80																	
	85																	

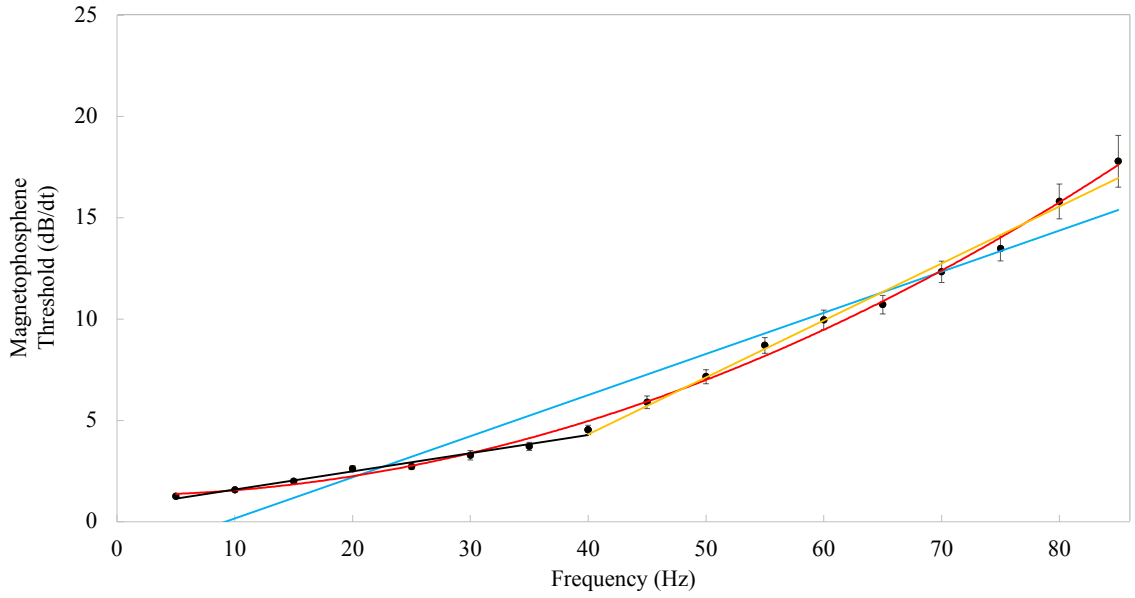


Figure 11: Magnetophosphene thresholds and frequency-response in dB/dt (T/s) explained by various regressions. Data is explained by a single linear equation (blue;

$p < 0.001$, $R^2=0.94$), two linear equations (black from 5-40 Hz and yellow from 40 to 85 Hz; respectively, $p < 0.001$, $R^2=0.98$ and $p < 0.001$, $R^2=0.99$), and a polynomial equation (red; $p < 0.001$, $R^2=0.99$).

2.3.4 EEG Alpha Power

To evaluate the use of EEG as an objective biomarker, alpha power from occipital electrodes was calculated during each 5 second stationary MF exposure. Comparing the alpha power between conditions eliciting and conditions not eliciting magnetophosphene perception allows us to evaluate the use of occipital EEG alpha power as an objective biomarker of magnetophosphene perception (Figure 12). A paired t-test was used to compare alpha power throughout the ELF range in Oz for trials with (mean: 6.68×10^{-5} $\mu V^2/Hz$) and without (mean: 7.14×10^{-5} $\mu V^2/Hz$) magnetophosphene perception; O1 in trials with (mean: 1.95×10^{-10} $\mu V^2/Hz$) and without (mean: 1.86×10^{-10} $\mu V^2/Hz$) magnetophosphene perception; and O2 in trials with (mean: 2.54×10^{-10} $\mu V^2/Hz$) and without (mean: 2.23×10^{-10} $\mu V^2/Hz$) magnetophosphene perception. Alpha power was not different upon perception for Oz, ($t(928) = 0.63$, $p = 0.53$), O1 ($t(1221) = 0.56$, $p = 0.58$) or O2 ($t(1757) = 1.44$, $p = 0.15$).

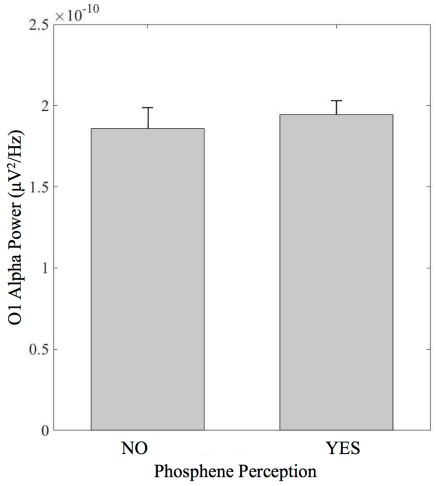


Figure 12: Occipital EEG alpha activity with and without magnetophosphene perception. This figure is a depiction of the O1 electrode (representative of the 3 occipital electrodes). Error bars represent standard error of the mean.

Additionally, a one-way ANOVA with repeated measures (15 conditions – 0, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85 Hz) showed no main effect in mean alpha power as a function of frequency in Oz ($F(21,819) = 1.15$, $p>0.05$), O1 ($F(21,819) = 0.94$, $p>0.05$) or O2 ($F(21, 819) = 0.93$, $p>0.05$) during magnetophosphene perception (Figure 13). EEG signals from three frequencies (5, 10 and 15 Hz) could not be analyzed due to bandpass filtering near the alpha range.

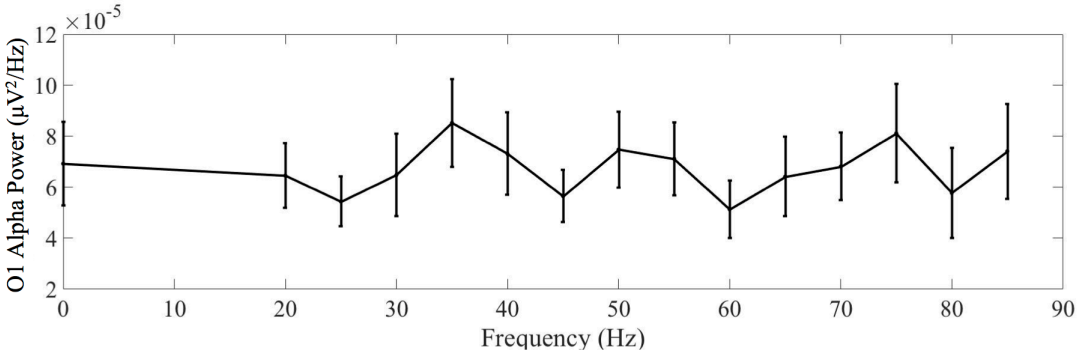


Figure 13: Alpha power calculated from occipital electrode (Oz) during magnetophosphene perception. Error bars represent the standard error of the mean.

2.3.5 Field Status Questionnaire (FSQ)

Using a standardized FSQ, all participants reported the presence of the MF during testing. The mean certainty score of the MF presence was 4.70 ± 0.57 (scored out of 5). This confirms the extent to which participants were able to determine when the MF exposure was happening. Most participants based their certainty of MF presence on magnetophosphene perception (often reported as “flickering lights”) or sound from the exposure device. There were 56 trials with reported discomfort, such as: tooth pain, pressure, or annoying sound. On a continuum between stressful (1) and relaxing (10), the mean stress rating of the experiment was 6.62 ± 1.92. Similarly, the mean comfort rating (comfortable = 1, uncomfortable =10) was 4.35 ± 2.24.

2.4 Discussion

This study tested the highest number of participants over the widest range of frequencies using the highest available maximum flux density, and it first confirms that magnetophosphene perception changes as a function of frequency. Nearly all participants (>95%) perceived magnetophosphenes from 10 Hz to 70 Hz. No perception was reported during the sham exposure. A decreased percentage of perception occurred at 5 Hz, and above 70 Hz. Given that less than 50% of participants perceived magnetophosphenes above 85 Hz, statistical analysis was restricted from 5 to 85 Hz. A potential bias was identified in the threshold reports above 85 Hz since participants self-reported that the exposure device was loud, an audible high frequency noise could be heard, and reported vibrations from the exposure device. Yet, no over-reporting of magnetophosphene perception seem to have been caused over 85 Hz.

The use of the standardized FSQ proved that participants were successfully able to determine when the MF exposure occurred, regardless of whether or not phosphene perception occurred. All participants self-reported that they could detect the presence of the MF and on average stated that they were 94% confident in their answer. Most based their answer on the presence of magnetophosphenes or alternatively on the noise and vibrations generated by the exposure device. To address this limitation, modifications to the exposure device would be required. In contrast, experiments using lower flux densities reported that participants were unable to judge whether exposure occurred (M. R. Cook et al., 1992; Legros et al., 2012). For example, an experiment with exposures up to 1.8 mT_{rms} reported that participants were unable to detect the presence of a MF, as they indicated incorrectly on the FSQ in 76% of trials (Legros et al., 2012).

With respect to the MF flux density, from 5 to 85 Hz, the lowest threshold was found at 17 mT_{rms} at 35 Hz. This compares to the study of Lövsund, who found the threshold (~10 mT_{rms}) to be lowest at 30 Hz, in darkness (Lövsund et al., 1980b). Magnetophosphene perception is known to evolve as a function of time spent in the dark, such that the threshold increases over time and stabilizes after approximately 16 minutes (Lövsund et al., 1980b). Lövsunds' experiment involved a 30-minute dark adaptation period before determining thresholds, therefore allowing sufficient time for the retina to adapt to the darkness.

Exposures in the present study were presented immediately after extinguishing the room lighting, therefore, by turning the lights on between each frequency condition, adaptation to the darkness was avoided (Lövsund et al., 1980b). A direct comparison therefore cannot be made between the threshold values of Lövsund's experiment and the present study, due to the different adapted state of the retina, however a dark adaptation period preceding threshold determination should result in higher thresholds.

However, the lowest thresholds reported in the current study are ~7 mT_{rms} higher than the lowest threshold previously reported in darkness (Lövsund et al., 1980b). This difference likely results from methodological differences. For example, the MF used in this study is homogenous in the head region, whereas it was heterogeneous in Lövsund's study (Lövsund et al., 1980b). Lövsund et al. (Lövsund et al., 1980b) presented the magnetophosphene threshold values according to the approximate position of the center of the eye, however within the eye region there was a 20% difference in MF flux density. Therefore, the heterogeneous MF was such that the medial aspect of the eye was exposed to a MF 10% lower than the center of the eye, and that the lateral aspect of the eye was exposed to a MF 10% higher than the center of the eye, perhaps underestimating the maximum exposure and the perception thresholds. For example, in complete darkness at 30 Hz, a 10 mT_{rms} magnetophosphene threshold is reported at the center of the eye, meaning that the lateral aspect of the eye is exposed to a flux density of 11 mT_{rms}, and the medial aspect of the eye is exposed to a flux density of 9 mT_{rms}. Also, the perception threshold in Lövsund's study was evaluated using the psychophysics method of limits, as opposed to the method of self-adjustment, creating variability. A differing method of threshold determination has the potential to account for differing results, thus requiring the test-retest reliability protocol of the current experiment.

To confirm that the method of self-adjustment is viable in determining magnetophosphene thresholds, ten participants completed a test-retest protocol. Four thresholds at 20 Hz were compared and found to be not significantly different, confirming the reliability of our threshold estimation method. The 20 Hz exposures were randomized amongst all other exposures, ensuring that participants were blinded to this component of the experiment. The means of all four thresholds at 20 Hz were found to be not significantly different;

participants are able to repeatedly select the same threshold for a given frequency condition. Since the same threshold could be repeatedly selected, the method of self-adjustment appears to be valid, accurate and reliable when selecting magnetophosphene thresholds. Determining a reliable method to determine thresholds is important, as other studies vary in the method to determine threshold (Legros et al., 2016; Lövsund et al., 1980a, 1980b). An alternative to the method of self-adjustment is the method of constant stimuli, which is regarded to be reliable but is very time consuming. The method of constant stimuli is effective when evaluating only a few frequency conditions, however, establishing a frequency response throughout the entire ELF range would require a long duration experiment, and potential participant fatigue. By using the method of self-adjustment this study was able to explore the entire ELF range, while maintaining accuracy and a reasonable experiment duration. However, the method of self-adjustment required the threshold to be considered as the lowest intensity eliciting perception, as opposed to an average of an increasing and decreasing threshold used in the method of limits (Lövsund et al., 1980a, 1980b), or a 50% perception rate in the method of constant stimuli (Legros et al., 2016). Additionally, frequencies were randomized in this experiment; an improvement from previous work where frequencies were presented in consecutive order (Lövsund et al., 1980a, 1980b).

Magnetophosphene thresholds are also represented in dB/dt. This is a direct correlate of the induced electric field sensed by the retina and is proportional to both the intensity and the frequency of the MF (Chapter 1.1). Since magnetophosphene perception is a result of magnetic induction, it implies that the retina is sensitive to the induced electric field, and not simply the flux density of the MF. From previous comparison of electro- and magnetophosphene threshold reports, it is not enough to simply represent magnetophosphene thresholds in terms of the flux density, but should rather be represented in dB/dt (Lövsund et al., 1980a). By representing the perception thresholds in terms of dB/dt, it shows that perception requires an increase in induced electric field as frequency increases. The extent of the increase in induced electric field with respect to increasing frequency is still debated, as the contributions of retinal cells is unknown. An exploratory attempt is made in this study to characterize the dynamics of the frequency response reported in dB/dt. The objective is to evaluate if different mechanisms of action might be

involved (i.e. possible recruitment of different retinal cell populations) depending on the frequency. Interestingly, the linear regression did not show the best fit to the magnetophosphene frequency-response and the threshold reports where best described using 2 different linear regressions with a breaking point at 40 Hz, suggesting that perception may not be limited to a single mechanism but that slightly different mechanisms were involved below and above this frequency. Note that this is a speculative and empirical observation at this point, but it deserves to be further explored. Interestingly, a two-order polynomial is also an excellent model of the perception reports, which suggests a possible combination of sources explaining the dynamics. Hence, the mechanism may not be linked to a single aspect of the visual system (see Section 1.4) and could in fact involve multiple components of the retina (i.e. Photoreceptors, bipolar cells, amacrine cells, or horizontal cells). To establish the contribution of various cells involved in magnetophosphene perception, we first must know the frequency sensitivities of these cells.

The threshold values presented in dB/dt differ from previous electro- and magnetophosphene studies. Lövsund reports magnetophosphene thresholds in terms of flux density; converting those values into dB/dt, we notice a similar increasing trend to the results of the current study. However, consistent with the flux density, it is apparent that the current study reports higher thresholds in dB/dt. In comparison to electrophosphene thresholds, studies report a non-linear trend in electrophosphene thresholds, such that the lowest threshold has been reported at ~10 Hz, increasing above and below 10 Hz (Kanai et al., 2008; Kar & Krekelberg, 2012). Magnetophosphenes are thought to arise from the same mechanism eliciting electrophosphene perception, however frequency-response dynamics are different. This difference is potentially accounted for when considering that an electric stimulation must travel through several layers of tissue (i.e. skin, skull) before arriving at the retina and modulating the visual signals (Logothetis, Kayser, & Oeltermann, 2007). Travelling through each of these tissue layers adds resistance to the signal and, which we speculate to modulate the properties of the electrical signal reaching the retina. Computational models indicate that current density originating from occipital electrode stimulation travel through the cortical layers of the brain, ultimately eliciting retinal phosphene perception (Laakso & Hirata, 2013). Contrary to this, the MF penetrates through these layers, meaning that the induced electric field at the retina is unaltered.

Although the MF was detected through conscious perception, and threshold determination was apparently accurate and reproducible, the results are entirely limited to participant subjectivity. These findings would be best supported by an objective measurement. Occipital EEG alpha activity showed no effect when comparing trials with and without perception of magnetophosphenes. Perception of magnetophosphenes was expected to create a visual stimulus that would be comparable to visual perception known to modulate EEG alpha power (Berger, 1929). Based on the "Berger effect" alpha power was expected to decrease upon magnetophosphene perception (Berger, 1929). Since the present study evaluated EEG alpha power at phosphene thresholds, future studies should evaluate EEG alpha activity during exposures significantly above threshold values to determine if the strength of visual perception affects the alpha activity. Additionally, other EEG analyses techniques such as source reconstruction could turn out to be more appropriate for discriminating magnetophosphene perception. Source reconstruction is different from alpha activity, since it evaluates temporal relationships in neural activity at a millisecond scale. Evaluation of source reconstruction has shown preliminary success in determining an objective biomarker for ELF MF exposure, as magnetophosphene perception was regarded to modulate the ventral pathway of visual processing (See section 1.5.1 for additional information regarding the ventral pathway) (Modolo, Hassan, & Legros, 2018). Although the present study showed no main effect in occipital alpha power, the use of EEG in determining an objective biomarker of ELF MF exposure remains promising.

Determining a method of EEG analysis that proves to be an effective biomarker of ELF MF exposure is necessary as the retina (and magnetophosphene perception) is merely a conservative model of CNS function (Attwell, 2003). Retinal photoreceptors are unique cells that are very sensitive and respond to stimuli with graded changes in membrane potential, unlike the CNS. Rod photoreceptor cells are 100 times more sensitive than cones and respond to the summation of stimuli. Several rods are connected to a single bipolar cell, ultimately amplifying the signal and enabling the detection of very weak stimuli (Conner & MacLeod, 1977; Kandel et al., 2000).

Magnetophosphene perception is the current basis for defining ELF MF exposure guidelines to protect the public and occupational workers from adverse effects of ELF MF

exposure. We report for the first time perception thresholds resulting from MF exposures at powerline frequencies (23 mT_{rms} at 50 Hz and 26 mT_{rms} at 60 Hz), that could be applied to further document the existing guidelines and recommendations (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002; International Commission on Non-Ionizing Radiation Protection, 2010). We have also improved the precision of magnetophosphene thresholds, as the current study involved 60 participants, whereas the previous magnetophosphene reports by Lovsund were limited to the involvement of only 11 participants. Currently, IEEE-ICES recommends that exposure in controlled environments from 20-759 Hz (encompassing powerline frequencies of 50 and 60 Hz) is limited below 2.71 mT_{rms} general public and the below 0.904 mT_{rms} (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002). ICNIRP recommends that occupational exposure at 50 and 60 Hz is below 1 mT_{rms}, and the general public exposure is below 0.2 mT_{rms} (International Commission on Non-Ionizing Radiation Protection, 2010). The magnetophosphene thresholdsat powerline frequencies reported in this study are more than 20 times higher than ICNIRP occupational guidelines, and 8 times higher than IEEE-ICES MPEs in controlled environments, thereby protecting the general public and workers from adverse effects of ELF MF exposure.

In conclusion, the present research study has documented the frequency-response of magnetophosphene perception across a significant portion of the ELF range. Perception thresholds measured in terms of flux density, which is the metric used in the guidelines as reference levels (ICNIRP 2010), were lowest at 35 Hz and increased at higher and lower frequencies. This study also documents perception thresholds at power frequencies (where most ELF exposure occurs) which aim to prevent *adverse* effects. Adverse effects are defined as “an effect detrimental to the health of an individual” (Institute of Electrical and Electronics Engineers Inc. & IEEE, 2002; International Commission on Non-Ionizing Radiation Protection, 2010). ELF MF was not associated with any change in the alpha power of EEG occipital electrodes even when magnetophosphenes were perceived. Alternative methods of EEG analysis should be considered as we further the need for an objective biomarker.

2.5 References

Abe, Z. (1951). Influence of Adaptation on the Strength-Frequency Curve of Human Eyes, as Determined with Electrically Produced Flickering Prosphenes. *The Tohoku Journal of Experimental Medicine*, *54*(1).

Abrahamyan, A., Clifford, C. W. G., Ruzzoli, M., Phillips, D., Arabzadeh, E., & Harris, J. A. (2011). Accurate and rapid estimation of phosphene thresholds (REPT). *PLoS ONE*, *6*(7). https://doi.org/10.1371/journal.pone.0022342

Adrian, D. J. (1977). Auditory and visual sensations stimulated by low-frequency electric currents. *Radio Science Supplement*, *12*(6), 243–250.

Al-Akhras, M. A. (2008). Influence of 50 Hz magnetic field on sex hormones and body, uterine, and ovarian weights of adult female rats. *Electromagnetic Biology and Medicine*, *27*(2), 155–163. https://doi.org/10.1080/15368370802072125

Allen, A., Villard, S., Corbacio, M., Goulet, D., Plante, M., Souques, M., … Legros, A. (2016). Impact of electromagnetic fields on human vestibular system and standing balance: Pilot results and future developments. *IOP Conference Series: Materials Science and Engineering*, *120*(1). https://doi.org/10.1088/1757-899X/120/1/012018

Ambrosini, A., Iezzi, E., Perrotta, A., Kisialiou, A., Nardella, A., Berardelli, A., … Schoenen, J. (2015). Correlation between habituation of visual-evoked potentials and magnetophosphene thresholds in migraine: A case-control study. *Cephalalgia : An International Journal of Headache*, *36*(3), 0333102415590241-. https://doi.org/10.1177/0333102415590241

Attwell, D. (2003). Interaction of low frequency electric fields with the nervous system: the retina as a model system. *Radiation Protection Dosimetry*, *106*(4), 341–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14690277

Aurora, S. K., Welch, K. M. A., & Al-Sayed, F. (2003). The threshold for phosphenes is lower in migraine. *Cephalalgia*, *23*(4), 258–263. https://doi.org/10.1046/j.1468-2982.2003.00471.x

Barlow, H. B., Kohn, H. I., & Walsh, E. G. (1947). Visual sensations aroused by magnetic fields. *The American Journal of Physiology*, *148*(2), 372–275.

Berger, H. (1930). Uber das Elektrenkephalogramm des Menschen. Zweite Mitteilung. *J. Psycho. Neurol.*, *40*(1875), 160–179. https://doi.org/10.1055/s-0028-1130334

Conner, J. D., & MacLeod, D. I. . (1977). Rod Photoreceptors Detect Rapid Flicker. *Science*, *195*(4279), 698–699.

Cook, C. M., Saucier, D. M., Thomas, A. W., & Prato, F. S. (2009). Changes in human EEG alpha activity following exposure to two different pulsed magnetic field sequences. *Bioelectromagnetics*, *30*(1), 9–20. https://doi.org/10.1002/bem.20434

Cook, C. M., Thomas, A. W., Keenliside, L., & Prato, F. S. (2005). Resting EEG effects during exposure to a pulsed ELF magnetic field. *Bioelectromagnetics*, *26*(5), 367–376. https://doi.org/10.1002/bem.20113

Cook, C. M., Thomas, A. W., & Prato, F. S. (2002). Human Electrophysiological and Cognitive Effects of Exposure to ELF Magnetic and ELF Modulated RF and Microwave Fields: A Review of Recent Studies. *Bioelectromagnetics*, *23*(2), 144–157. https://doi.org/10.1002/bem.107

Cook, M. R., Graham, C., Cohen, H. D., & Gerkovich, M. M. (1992). A replication study of human exposure to 60Hz fields: Effects on neurobehavioral measures. *Bioelectromagnetics*, *13*(4), 261–285. https://doi.org/10.1002/bem.2250130403

Corbacio, M., Brown, S., Dubois, S., Goulet, D., Prato, F. S., Thomas, A. W., & Legros, A. (2011). Human cognitive performance in a 3 mT power-line frequency magnetic field. *Bioelectromagnetics*, *32*(8), 620–633. https://doi.org/10.1002/bem.20676

Crasson, M., & Legros, J. J. (2005). Absence of daytime 50 Hz, 100 μTrms magnetic field or bright light exposure effect on human performance and psychophysiological parameters. *Bioelectromagnetics*, *26*(3), 225–233. https://doi.org/10.1002/bem.20070

D'Arsonval, A. (1896). Dispostifis pour la mesure des courants alternatifs de toutes frequences. *Comput. Rendus. Soc. Biol.*, 450–451.

Davarpanah Jazi, S. D., Modolo, J., Baker, C., Villard, S., & Legros, A. (2017). Effects of a 60 Hz magnetic field of up to 50 millitesla on human tremor and EEG: A pilot study. *International Journal of Environmental Research and Public Health*, *14*(12). https://doi.org/10.3390/ijerph14121446

Delhez, M., Legros, J. J., & Crasson, M. (2004). No influence of 20 and 400 mu T 50 Hz magnetic field exposure on cognitive function in humans. *Bioelectromagnetics*, *25*(8), 592–598. https://doi.org/10.1002/bem.20040

Elkin-Frankston, S., Fried, P. J., Pascual-Leone, A., Rushmore, R. J., & Valero-Cabr, A. (2010). A novel approach for documenting phosphenes induced by transcranial magnetic stimulation. *Journal of Visualized Experiments : JoVE*, (38), 1–4. https://doi.org/10.3791/1762

Fujikado, T., Morimoto, T., Kanda, H., Kusaka, S., Nakauchi, K., Ozawa, M., … Tano, Y. (2007). Evaluation of phosphenes elicited by extraocular stimulation in normals and by suprachoroidal-transretinal stimulation in patients with retinitis pigmentosa. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *245*(10), 1411–1419. https://doi.org/10.1007/s00417-007-0563-z

Gajraj, R. J., Doi, M., Mantzaridis, H., & Kenny, G. N. C. (1998). Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness. *British Journal of Anaesthesia*, *80*(1), 46–52. https://doi.org/10.1093/bja/80.1.46

Gandhi, O. P., Kang, G., Wu, D., & Lazzi, G. (2001). Currents induced in anatomic models of the human for uniform and nonuniform power frequency magnetic fields. *Bioelectromagnetics*, *22*(2), 112–21. https://doi.org/10.1002/1521-186X(200102)22:2<112::AID-BEM1014>3.0.CO;2-0

Gebhard, J. W. (1952). Thresholds of the human eye for electric stimulation by different

wave forms.

Geddes, L. A. (2008). The history of magnetophosphenes, 101–102.

Gescheider, G. A. (1997). *Psychophysics, The Fundamentals* (3rd ed.). Mahwah, NJ, NJ: Lawrence Erlbaum Associates.

Glover, P. M., Cavin, I., Qian, W., Bowtell, R., & Gowland, P. A. (2007). Magnetic-field-induced vertigo: A theoretical and experimental investigation. *Bioelectromagnetics*, *28*(5), 349–361. https://doi.org/10.1002/bem.20316

Haggard, M. (2010). *Hearing: An Introduction to Psychological and Physiological Acoustics*. *Journal of neurology, neurosurgery, and psychiatry* (5th ed., Vol. 45). Colchester: Informa Healthcare. https://doi.org/10.1136/jnnp.45.12.1175-b

Heusser, K., Tellschaft, D., & Thoss, F. (1997). Influence of an alternating 3 Hz magnetic field with an induction of 0.1 millitesla on chosen parameters of the human occipital EEG. *Neuroscience Letters*, *239*(2–3), 57–60. https://doi.org/10.1016/S0304-3940(97)00881-1

Institute of Electrical and Electronics Engineers Inc., & IEEE. (2002). *IEEE Standards for Safety Levels with Respect to Human Exposure to Electromagnetic Fields, 0-3 kHz*. *IEEE Standard C95.6*. New York. https://doi.org/10.1109/IEEESTD.2002.94130

International Commission on Non-Ionizing Radiation Protection. (2010). *Guidelines for Limiting Exposure to Time-Varying Electric and Magnetic Fields (1 Hz to 100 kHz)*. https://doi.org/10.1097/HP.0b013e3181f06c86

Kanai, R., Chaieb, L., Antal, A., Walsh, V., & Paulus, W. (2008). Frequency-Dependent Electrical Stimulation of the Visual Cortex. *Current Biology*, *18*(23), 1839–1843. https://doi.org/10.1016/j.cub.2008.10.027

Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (2000). *Principles Of Neural Science* (4th ed.). New York: McGraw-Hill. https://doi.org/10.1007/s13398-014-0173-7.2

Kar, K., & Krekelberg, B. (2012). Transcranial electrical stimulation over visual cortex evokes phosphenes with a retinal origin. *Journal of Neurophysiology*, *108*(8), 2173–8. https://doi.org/10.1152/jn.00505.2012

Laakso, I., & Hirata, A. (2013). Computational analysis shows why transcranial alternating current stimulation induces retinal phosphenes. *Journal of Neural Engineering*, *10*(4). https://doi.org/10.1088/1741-2560/10/4/046009

Legros, A., Corbacio, M., Beuter, A., Modolo, J., Goulet, D., Prato, F. S., & Thomas, A. W. (2012). Neurophysiological and behavioral effects of a 60 Hz, 1,800 lT magnetic field in humans. *European Journal of Applied Physiology*, *112*(5), 1751–1762. https://doi.org/10.1007/s00421-011-2130-x

Legros, A., Modolo, J., Goulet, D., Plante, M., Souques, M., Deschamps, F., … Thomas, A. W. (2016). Magnetophosphenes perception threshold and EEG response in humans exposed to 20, 50, 60 and 100 Hz MF up to 50,000 μT. *5th International Conference on Electromagnetic Fields, Health and Environment - EHE2014, Porto, Portugal, April 24th - 26th 2014.*, *2*(July 2016), 6–7. https://doi.org/https://doi.org/10.1016/j.brs.2015.01.365

Logothetis, N. K., Kayser, C., & Oeltermann, A. (2007). In Vivo Measurement of Cortical Impedance Spectrum in Monkeys: Implications for Signal Propagation. *Neuron*, *55*(5), 809–823. https://doi.org/10.1016/j.neuron.2007.07.027

Lövsund, P., Öberg, P. Å., & Nilsson, S. E. G. (1980a). Magneto- and electrophosphenes: A comparative study. *Medical & Biological Engineering & Computing*, *18*(6), 758–764. https://doi.org/10.1007/BF02441902

Lövsund, P., Öberg, P. Å., & Nilsson, S. E. G. (1980b). Magnetophosphenes: a quantitative analysis of thresholds. *Medical & Biological Engineering & Computing*, *18*(3), 326–334. https://doi.org/10.1007/BF02443387

Lyskov, E. B., Juutilainen, J., Jousmaki, V., Partanen, J., Medvedev, S., & Hanninen, O. (1993). Effects of 45-Hz magnetic fields on the functional state of the human brain.

Bioelectromagnetics, *14*(2), 87–95.

Magnusson, C. E., & Stevens, H. C. (1911). Visual sensations caused by changes in the strength of a magnetic field.

McNamee, D. A., Legros, A. G., Krewski, D. R., Wisenberg, G., Prato, F. S., & Thomas, A. W. (2009). A literature review: the cardiovascular effects of exposure to extremely low frequency electromagnetic fields. *International Archives of Occupational and Environmental Health*, *82*(8), 919–933. https://doi.org/10.1007/s00420-009-0404-y

Min, B. K., Jung, Y. C., Kim, E., & Park, J. Y. (2013). Bright illumination reduces parietal EEG alpha activity during a sustained attention task. *Brain Research*, *1538*, 83–92. https://doi.org/10.1016/j.brainres.2013.09.031

Modolo, J., Hassan, M., & Legros, A. (2018). Reconstruction of brain networks involved in magnetophosphene perception using dense electroencephalography. *BioEM 2918 Conference Proceedings*, 1–6.

Morimoto, T., Fukui, T., Matsushita, K., Okawa, Y., Shimojyo, H., Kusaka, S., … Fujikado, T. (2006). Evaluation of residual retinal function by pupillary constrictions and phosphenes using transcorneal electrical stimulation in patients with retinal degeneration. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *244*(10), 1283–1292. https://doi.org/10.1007/s00417-006-0260-3

Mulleners, W. M., Chronicle, E. P., Palmer, J. E., Koehler, P. J., & Vredeveld, J.-W. (2001). Visual Cortex Excitability in Migraine With and Without Aura. *Headache: The Journal of Head and Face Pain*, *41*, 565–572. https://doi.org/10.1046/j.1526-4610.2001.041006565.x

Nevelsteen, S., Legros, J.-J., & Crasson, M. (2007). Effects of information and 50 Hz magnetic fields on cognitive performance and reported symptoms. *Bioelectromagnetics*, *28*(1), 53–63. https://doi.org/10.1002/bem.20265

Perz, M. (2010). Flicker Perception in the Periphery.

Prato, F. S., Thomas, A. W., & Cook, C. M. (2001). Human standing balance is affected by exposure to pulsed ELF magnetic fields: light intensity-dependent effects. *Neuroreport*, *12*(7), 1501–1506. https://doi.org/10.1097/00001756-200105250-00040

Preece, A. W., Wesnes, K. A., & Iwi, G. R. (1998). The effect of a 50 Hz magnetic field on cognitive function in humans. *Int J Radiat Biol*, *74*(4), 463–470.

Saletu, B., Anderer, P., & Saletu-Zyhlarz, G. M. (2006). EEG Topography and Tomography (LORETA) in the Classification and Evaluation of the Pharmacodynamics of Psychotropic Drugs. *Clinical EEG and Neuroscience*, *37*(2), 66–80. https://doi.org/10.1177/155005940603700205

Sastre, A., Cook, M. R., & Graham, C. (1998). Nocturnal exposure to intermittent 60 Hz magnetic fields alters human cardiac rhythm. *Bioelectromagnetics*, *19*(2), 98–106. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9492166

Saunders, R. D., & Jefferys, J. G. R. (2007). A neurobiological basis for ELF guidelines. *Health Physics*, *92*(6), 596–603. https://doi.org/10.1097/01.HP.0000257856.83294.3e

Silny, J. (1984). Changes in VEP caused by strong magnetic fields. *Second International Evoked Potential Symposium*.

Silny, J. (1986). The Influence of the Time-Varying Magnetic Field in the Human Organism. *Biological Effects of Static and Extremely Low Frequency Magnetic Fields*.

Smith, S. J. M. (2005). EEG in neurological conditions other than epilepsy: When does it help, what does it add? *Neurology in Practice*, *76*(2), 8–12. https://doi.org/10.1136/jnnp.2005.068486

Teplan, M. (2002). FUNDAMENTALS OF EEG MEASUREMENT. *Measurement Science Review*, *2*(2), 1–11.

Thomas, A. W., Drost, D. J., & Prato, F. S. (2001). Human subjects exposed to a specific pulsed (200 μT) magnetic field: Effects on normal standing balance. *Neuroscience Letters*, *297*(2), 121–124. https://doi.org/10.1016/S0304-3940(00)01688-8

Thompson, S. P. (1910). A Physiological Effect of an Alternating Magnetic Field. *Proceedings of the Royal Society B: Biological Sciences*, *82*(557), 396–398. https://doi.org/10.1098/rspb.1910.0032

Tinsley, J. N., Molodtsov, M. I., Prevedel, R., Wartmann, D., Espigulé-Pons, J., Lauwers, M., & Vaziri, A. (2016). Direct detection of a single photon by humans. *Nature Communications*, *7*. https://doi.org/10.1038/ncomms12172

Van Nierop, L. E., Slottje, P., Kingma, H., & Kromhout, H. (2013). MRI-related static magnetic stray fields and postural body sway: A double-blind randomized crossover study. *Magnetic Resonance in Medicine*, *70*(1), 232–240. https://doi.org/10.1002/mrm.24454

World Health Organization. (2007). *Extremely Low Frequency Fields. Environmental Health Criteria*. *World Health Organization*. Geneva. Retrieved from http://www.scopus.com/inward/record.url?eid=2-s2.0-77955459021&partnerID=40&md5=298ffb383a138d66c0d2c27528febac8

Zaffanella, L. E., & Kalton, G. W. (1998). *Survery of Personal Magnetic Field Exposure. Phase II: 1000-Person Survey*.

3 General Conclusion

This research project evaluated magnetophosphene thresholds across the ELF range in a large sample of subjects. This study is the first follow up study of experimental work conducted in the early 1980's. However, several improvements have since been made, including: improvements to the exposure device, additional frequencies tested, and a large sample size. The exposure device used in the present experiment created a homogenous MF, enabling a precise measurement of the magnetophosphene thresholds. This is the first study to quantify magnetophosphene thresholds throughout the entire ELF range, including power frequencies of 50 and 60 Hz. Additionally, the current research project enrolled 60 volunteers; a large sample size further supports the findings of this study.

Although it is relying on a reliable psychophysics evaluation, magnetophosphene thresholds remain limited to subjective reports of perception, therefore this study aimed to determine a quantitative biomarker of ELF MF exposures through the use of EEG. Although this study showed no main effect in EEG alpha activity during ELF MF exposure, alternative analysis techniques such as EEG source reconstruction are possible, and EEG persists as a potential tool for determining an objective biomarker. Another biomarker with a potential promising outcome is related to the quantification of pupil dilation associated with phosphene perception.

3.1 Future Developments

While the search for an objective biomarker continues, other experiments are planned to further evaluate the mechanisms involved in magnetophosphene perception. To discriminate between photoreceptor involvement, magnetophosphene thresholds will be determined throughout time spent in complete darkness. Rods and cones vary in their response to time spent in the dark and each have a unique adaption to the darkness trend. Assessing thresholds throughout time in the dark will contribute to show the extent of each photoreceptor's involvement in magnetophosphene perception.

Another method of evaluating photoreceptor involvement would be to test a patient population with various retinal diseases. Evaluating patients with abnormalities in their rod

and/or cone function will assist to determine the exact mechanism of action involved in phosphene perception. Current phosphenes are reported to be achromatic, pointing towards rod modulation in perception. Evaluating thresholds in patients with rod dysfunction will highlight the extent of which rods are involved.

Phosphenes have been previously proposed as a clinical tool, as clinicians want to use phosphene thresholds as a means to assess the electrical excitability of the eye. Furthering this, clinicians hope to discriminate between those who are suitable for a visual prosthesis and those who are not. This research was previously evaluated with electrophosphenes, but the findings in the current research study have produced reliable magnetophosphene threshold data, which could also be used to assess visual prosthetic candidates.

3.2 Limitations

One limitation in this study is the capabilities in the exposure device. Although we state that the exposure device was an improvement from that used in the 1980's, it still has limitations in the maximum exposures generated. Below 85 Hz, magnetophosphene thresholds were well within the operational range of the exposure device, however the decreasing percentage of participants perceiving phosphenes at higher frequencies may be the consequence of the exposure device limitation, and the possibility of perceiving phosphenes at frequencies above 85 Hz could only be properly tested with higher stimulation capabilities. Addressing this limitation has the potential to improve the validity of threshold reports above 85 Hz. Also, an exposure device capable of creating an increased maximum flux density could potentially elicit coloured phosphenes. Phosphenes are hypothesized to be a result of rod stimulation. However, increasing the flux density substantially may enable coloured perception and cone mediated phosphenes, which would provide a strong validation of the rods' hypothesis.

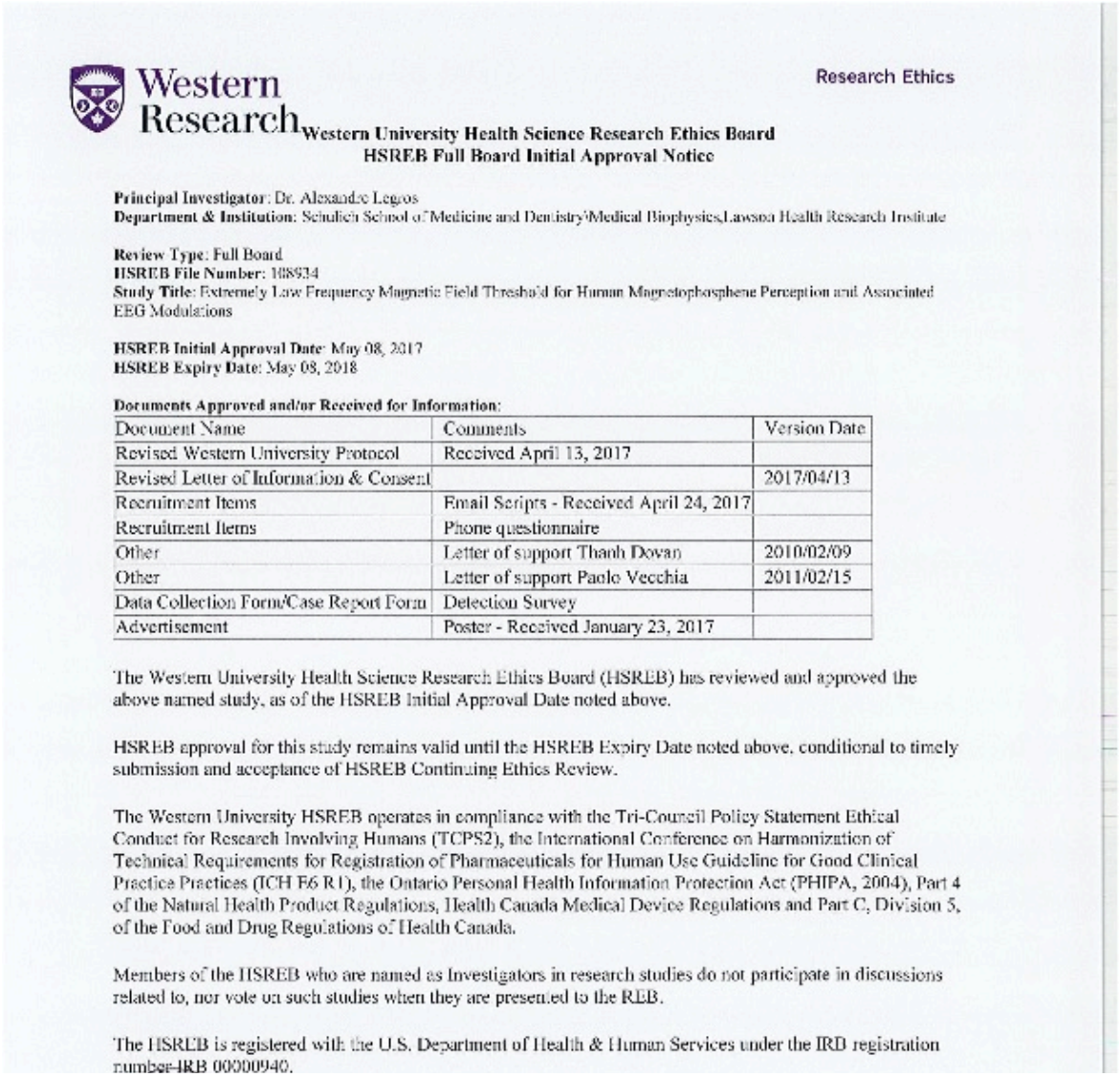
3.3 Conclusion

Overall, this study reported magnetophosphene thresholds and the frequency-response throughout the ELF range. This experiment provides important and relevant input to the guideline/standard-setting process. The guidelines are designed to protect against

potentially *adverse* effects of exposure to ELF MFs, including excitation of central or peripheral neurons or modulation of brain synaptic activity. Magnetophosphene perception originates with photoreceptor responses where visual stimuli are also received, suggesting that the phosphene response as a biological response is *perhaps not truly adverse*. Nonetheless, with regard to guideline/standard-setting, the magnetophosphene has been adopted as a surrogate for potentially adverse synaptic excitation in the CNS g. Until such time as an effect that better represents a potential adverse CNS interaction with magnetic fields is known, it remains important to understand the exposure-response characteristics of magnetophosphenes. The research in this report will also help advance our fundamental understanding of signal transmission from the outer to inner retina and into the brain.

Appendices

Appendix A: Health Science Research Ethics Board Approval



Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice

Principal Investigator: Dr. Alexandre Legros
Department & Institution: Schulich School of Medicine and Dentistry\Medical Biophysics,Lawson Health Research Institute

Review Type: Full Board
HSREB File Number: 108934
Study Title: Extremely Low Frequency Magnetic Field Threshold for Human Magnetophosphene Perception and Associated EEG Modulations

HSREB Initial Approval Date: May 08, 2017
HSREB Expiry Date: May 08, 2018

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Received April 13, 2017	
Revised Letter of Information & Consent		2017/04/13
Recruitment Items	Email Scripts - Received April 24, 2017	
Recruitment Items	Phone questionnaire	
Other	Letter of support Thanh Dovan	2010/02/09
Other	Letter of support Paolo Vecchia	2011/02/15
Data Collection Form/Case Report Form	Detection Survey	
Advertisement	Poster - Received January 23, 2017	

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Western Research

Date: 4 May 2018

To: Dr. Alexandre Legros

Project ID: 108934

Study Title: Extremely Low Frequency Magnetic Field Threshold for Human Magnetophosphene Perception and Associated EEG Modulations

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: May 15, 2018

Date Approval Issued: 04/May/2018

REB Approval Expiry Date: 08/May/2018

Dear Dr. Alexandre Legros ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date
108934 - Magnetophosphenes - Letter of info and consent - April 2018 - Clean	Consent Form	03/May/2018
108934_April24_2018_Clean	Protocol	Received May 3, 2018

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Karen Gopaul, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix B: Participant Characteristics.

Participant	Age	Sex
1	19	Female
2	25	Male
3	27	Female
4	26	Female
5	24	Male
6	24	Female
7	28	Male
8	30	Female
9	25	Male
10	21	Male
11	25	Male
12	22	Female
13	23	Female
14	25	Female
15	21	Female
16	33	Male
17	33	Female
18	28	Male
19	18	Female
20	21	Male
21	33	Male
22	19	Female
23	29	Female
24	26	Male
25	18	Female
26	23	Female
27	27	Female
28	28	Male
29	20	Female
30	24	Female
31	24	Male
32	27	Female
33	25	Male
34	26	Male
35	21	Male
36	25	Female
37	21	Male
38	20	Male
39	22	Female
40	26	Female
41	20	Female
42	23	Male
43	22	Female
44	22	Female
45	27	Male
46	22	Female
47	20	Male
48	22	Male
49	26	Female
50	22	Female
51	29	Female
52	25	Female
53	30	Male
54	27	Female
55	25	Male
56	27	Female
57	20	Male
58	21	Female
59	23	Female
60	24	Female
n = 60	**24.31 ± 3.62**	**F = 35**
		M = 25

Appendix C: Magnetophosphene Letter of Information and Consent Form

LAWSON
HEALTH RESEARCH INSTITUTE

St. Joseph's Hospital
268 Grosvenor Street
London, Ontario N6A 4V2
CANADA

[redacted]

LETTER OF INFORMATION
Version date: May 3 2018

Investigators: Dr. Alexandre Legros, Imaging, Lawson Health Research Institute

Place of Research: [redacted]
Lawson Health Research Institute
St. Joseph's Health Centre
268 Grosvenor Street
London, Ontario

Extremely Low Frequency Magnetic Field Threshold for Magnetophosphene Perception and Associated EEG Modulations

Study Rationale

Electrical currents like those circulating in power-lines and domestic electrical appliances produce magnetic fields in their surroundings. These domestic magnetic fields oscillate, or change direction, from positive to negative values 60 times in a second in North America and 50 times in Europe: they are said to have a frequency of 60 or 50 Hertz (60 Hz – 50 Hz), and are often referred to as power-line frequency magnetic fields. The intensity of a magnetic field is measured in milliTesla (mT). For example, the intensity of the magnetic field emitted by a clinical MRI is usually 1,500 or 3,000 mT, but research MRI systems can go up to 11,000 mT.

Oscillating magnetic fields (magnetic fields with intensity changing over time) have the ability to make electrical micro-currents in the human body. Stronger magnetic fields make stronger electrical micro-currents. Everyone is exposed to power-line frequency magnetic fields on a daily basis. This is the reason why potential effects of magnetic fields on humans should be studied. This current study is aiming to use magnetic fields from 5-300 Hz up to 100 mT. The strength of the exposure will be lower than what you would experience in a Magnetic Resonance Imaging (MRI) scanner.

Initials: _____

Purpose of the Study

You are invited to participate in a study looking at the possible effects of magnetic field exposure on a flickering visual perception called magnetophosphenes and on very weak electrical brain activity. This study will eventually test 80 volunteers.

Procedures

If you agree to participate in this study, you will take part in one experimental session after signing the consent form. You will be asked on the consent form whether or not you wish to be contacted about future research studies. This session will last approximately 2 hours and will involve magnetic field exposure. During this session, the first 30 minutes will be designated to collecting your participant information, and informing you about the study. You will then be given the opportunity to have all your questions about the study answered. After you have signed the consent form, formally agreeing to take part in the study, we will set you up with an electroencephalography (EEG) cap, in order to measure the electrical activity of your brain. The cap will cover your entire scalp and contains 64 electrodes (see the picture on page 3).

You will then sit in a confortable armchair in which you will stay for the entire experiment (it will last about 1 hour). The experiment will be conducted in a dark room (lights off) and you will be asked to keep your eyes closed. You will sit in a whole head MF exposure device, wearing a EEG cap. MF exposure will involve frequencies from 0-300 Hz, for a total of 25 conditions each repeated twice. You will be instructed to self-adjust the strength of the MF (between 0 and 70 mT over a 25 s period).

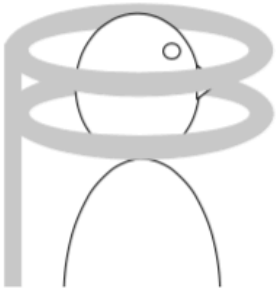


Figure 2: Diagram of the position of the set of coils around your head.

Initials: _____

During this experiment, you will be given short periods during which a magnetic field may or may not be delivered. When delivered, the magnetic field may or may not be strong enough to produce visual perceptions while you have your eyes closed. The beginning and the end of each short exposure period will be indicated by a "beep", but neither you nor the researcher will be aware if the magnetic field is actually generated or how strong it could be. Your only action while sitting on the armchair will be to adjust the level of the MF using a handheld dial to a point where you are perceiving a noticeable change in what you "see" (while you have your eyes closed) during the short exposure periods. After this experiment, you will be asked to complete a magnetic field detection survey.

During this session your EEG (electroencephalogram, i.e. the electrical activity of your brain) will be recorded continuously.

When you will have completed this experiment, you will have been exposed to a magnetic field for a total duration of 25 minutes. Then the staff will remove the EEG cap.

Figure 3: Illustration of an EEG cap similar to the one that will be fitted to your head.

Reimbursement

Reimbursement for travelling and parking will be provided for this study. You will receive a reimbursement of $50 for the experimental session. Even if you cannot complete a session for any reason, you will receive a reimbursement for your participation as a proportion of the time you spent toward the session.

Inclusion criteria

You must be healthy and be between 18 and 55 years old.

Initials: _____

Exclusion criteria

You should not take part if you are claustrophobic; have a limitation of movement; if you have ever experienced epileptic seizure; if you suffer from chronic illness (e.g., diabetes, a psychiatric condition or severe cardiovascular problems, including susceptibility to arrhythmias) or neurological diseases; if you use illicit drugs regularly; if you have a history of head or eye injury involving metal fragments; if you have ever worked in a metal shop or been a soldier; if you have some type of implanted electrical device (such as a cardiac or cerebral pacemaker, a cochlear implant, an insulin pump etc.); if you have an aneurysm clip; if you are wearing a hearing aid system; if you are wearing metal braces on your teeth; if you have permanent piercing, if you could be pregnant; or if you have an intrauterine device. Moreover, you will be asked to not smoke or have caffeinated or alcoholic beverages in the 12 hours preceding your participation to the study.

Risks

Participant Frustration: This study requires you to be connected to various recording devices. Although we are always improving our connection procedure, it still takes time. You will also be required to keep calm, quiet and as immobile as possible. If you experience difficulties to fulfil these criteria, you may withdraw from the study.

Electroencephalogram (EEG): There are no risks associated with EEG use, however, you may find the cap slightly uncomfortable.

Power-line frequency magnetic fields: Although there are no known risks of exposure to power-line frequency magnetic fields at the level and duration you will be exposed in this study (up to 100 mT), there could be unknown risks as magnetic field exposure of 5 to 300 Hz MF above 5 and up to 100 mT have not yet been systematically investigated in humans. However, both the International Commission on Non Ionizing Radiation Protection (ICNIRP, 2010) and the World Health Organization (WHO, 2007) have conducted exhaustive review of the scientific literature on the topic and concluded the absence of health effects to power-line frequency magnetic field exposure at those levels.

Participation in this study requires that you refrain from alcohol, caffeine or nicotine consumption 12 hours prior to the experiment, and until the end of the experiment. If you usually drink coffee on a regular basis, then this abstinence may eventually induce headaches. Furthermore, if you are a regular or occasional smoker, you may experience, anxiety, depressive feelings or impulsive behaviour caused by nicotine deprivation during 12 hours.

Initials: _____

Benefits

You will receive no direct benefits as a result of your participation in this study.

Withdrawal

Participation in this study is completely voluntary. You may refuse to participate, refuse to answer questions or withdraw from the study at any time with no affect on your employment or academic status. You may withdraw from the study at any point including after the study is complete, and data will be deleted.

Confidentiality

The information collected from you will include your name, date of birth and phone number, this enables us to validate your age and contact you. All information will be kept strictly confidential. You will be given a code number so that no names will be used in recorded data. The consent form with the name and the code number will be kept in a locked file cabinet. All results from the study will be kept confidential and any publication of this research study will be in grouped form with no reference to individual names. Storage of the EEG data will be performed electronically. This electronic folder will be stored on a computer with updated antivirus and firewalls of [redacted] a locking door) at Lawson Health Research Institute. Only staff have the key to the door and only members of the research team have the password for the computer. Representatives of The University of Western Ontario Health Sciences Research Ethics Board or Lawson's Quality Assurance Education Program (QAEP) may contact you or require access to your study-related records to monitor the conduct of this research.

Further Information

You will be given a copy of this "Letter of Information" to keep for your records.

You do not waive any legal rights by signing the consent form.

If you have any questions or you would like to further discuss any aspect of the study, please do not hesitate to contact Alexandre Legros (Ph.D., Associate Professor, Bioelectromagnetics Scientist, Principal Investigator, LHRI) at [redacted]

If you have any questions/concerns about your rights as a research participant or the conduct of this study, please contact: St. Joseph's Health Care London Patient Relations Consultant at [redacted]

Initials: _____

Consent to participate in the study entitled:

Extremely Low Frequency Magnetic Field Threshold for Magnetophosphene Perception and Associated EEG Modulations

Identification Number:

I, _____, have read the Letter of Information, have had the nature of the study explained to me, and I agree to participate.

All questions have been answered to my satisfaction.

_____	_____	_____
PRINT NAME	SIGNATURE	DATE
_____	_____	_____
PRINT NAME OF TRANSLATOR (IF APPLICABLE)	SIGNATURE	DATE
_____	_____	_____
PRINT NAME OF PERSON OBTAINING CONSESNT	SIGNATURE	DATE

Appendix D: Advertisement for Study Participation

VOLUNTEERS NEEDED

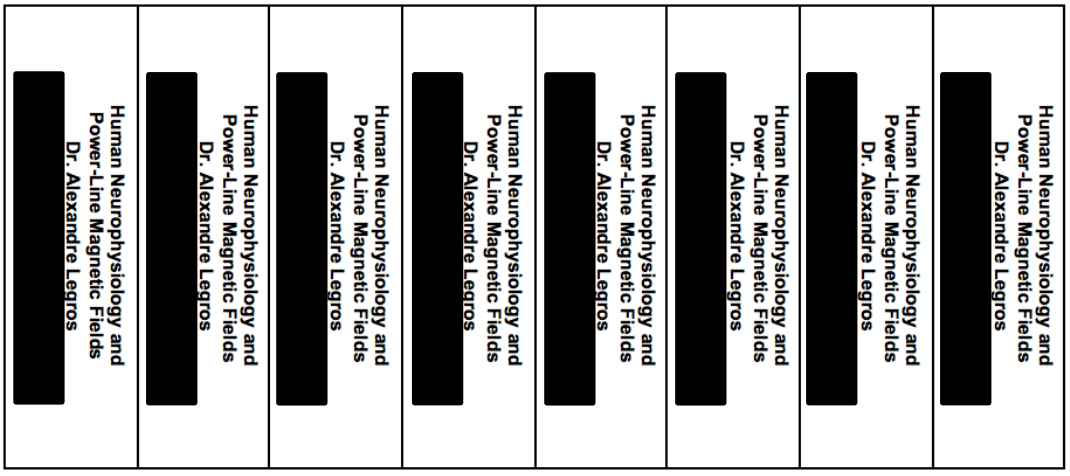
Healthy volunteers needed to participate in a study investigating the effects of a power-line frequency magnetic field on human neurophysiology

Those between the ages of 18 and 55 inclusive are eligible to participate.

You should not take part if you have a limitation of movement, if you have ever experienced epileptic seizure, if you suffer from chronic illness (e.g., diabetes, psychiatric or severe cardiovascular or neurological diseases), if you have a history of head or eye injury involving metal fragments, if you have ever worked in a metal shop or been a soldier, if you have some type of implanted electrical device (such as a cardiac or cerebral pacemaker), if you use illicit drugs regularly, if you are wearing metal braces on your teeth, if you have a permanent piercing, if you could be pregnant, or if you have an intrauterine device.

For more information please contact (e-mail preferred):

[redacted]



Appendix E: Phone Questionnaire

Phone Questionnaire

To participate in this study, you must be between the ages of 18 and 55 inclusive. To determine whether or not you are a potential candidate for this study, we would ask you to answer the following questions:

1. Do you suffer from limited movement of your hands or fingers? Yes No
   If yes, of what nature? ……..
2. Do you currently suffer from a chronic illness that requires that you regularly take medication(s)? If yes, which one(s)? ……. Yes No
3. Are you currently experiencing psychiatric illness or difficulties? (ex. Depression, anxiety) Yes No
4. Have you ever had an epileptic seizure? Yes No
5. Are you claustrophobic? Yes No
6. Do you wear an implanted electric device, or do you have a metal implant in your head or chest? Yes No
7. Do you have any permanent piercing? Yes No
8. Are you wearing a hearing aid system? Yes No
9. Do you wear glasses or contacts? Is it possible for you to wear contacts throughout the duration of the study? Yes No
10. Do you regularly use illicit drugs? Yes No
11. Do you smoke? Yes No
12. The experiment requires that you not be under the influence of tobacco, alcohol or coffee during the test. Is it impossible for you to abstain from smoking, consuming alcohol or drinking caffeinated beverages from midnight the night before the experiment until the next afternoon (expected end time of the experiment)? Yes No
13. Is there a chance of pregnancy? Yes No
14. Dominant hand:
15. Date of birth:
16. Weight:
17. Height:

Identification number: ……

NOTE: This information will be used to ensure you are meeting the study's inclusion criteria, and to categorize the data when analyzed. If you sign the consent form, the information you provide on this questionnaire will be kept, locked and stored for seven years and then shredded and/or mulched using a standard hospital protocol for document destruction (even in the event you withdraw from the study before having completed it). Should you discontinue participation in this study prior to signing the consent for, the information you provide on this questionnaire will be instantaneously discarded.

✂----------

Last Name:…….…… First Name:…….

Address:…….. City:……

Home phone number:……..…….. Work:……..…

E-mail address:……..

Sex:…….…….…… Date of birth: ……

Identification number: ……..... (To be filled out by a member of the research team)

Appendix F: Field Status Questionnaire (FSQ)

DETECTION SURVEY

Identification Number: ……..

In your opinion, was the magnetic field generated during this test, or not?

Yes (generated)

No (no field)

With what degree of certainty do you assert that opinion (from 1 to 5)?

Answer:

On what do you base your opinion?

Did you feel that this situation (sitting in the exposure coils) was:

Stressful ——————— Relaxing

Comfortable ——————— Uncomfortable

Did you feel/perceive anything specific during this experiment?

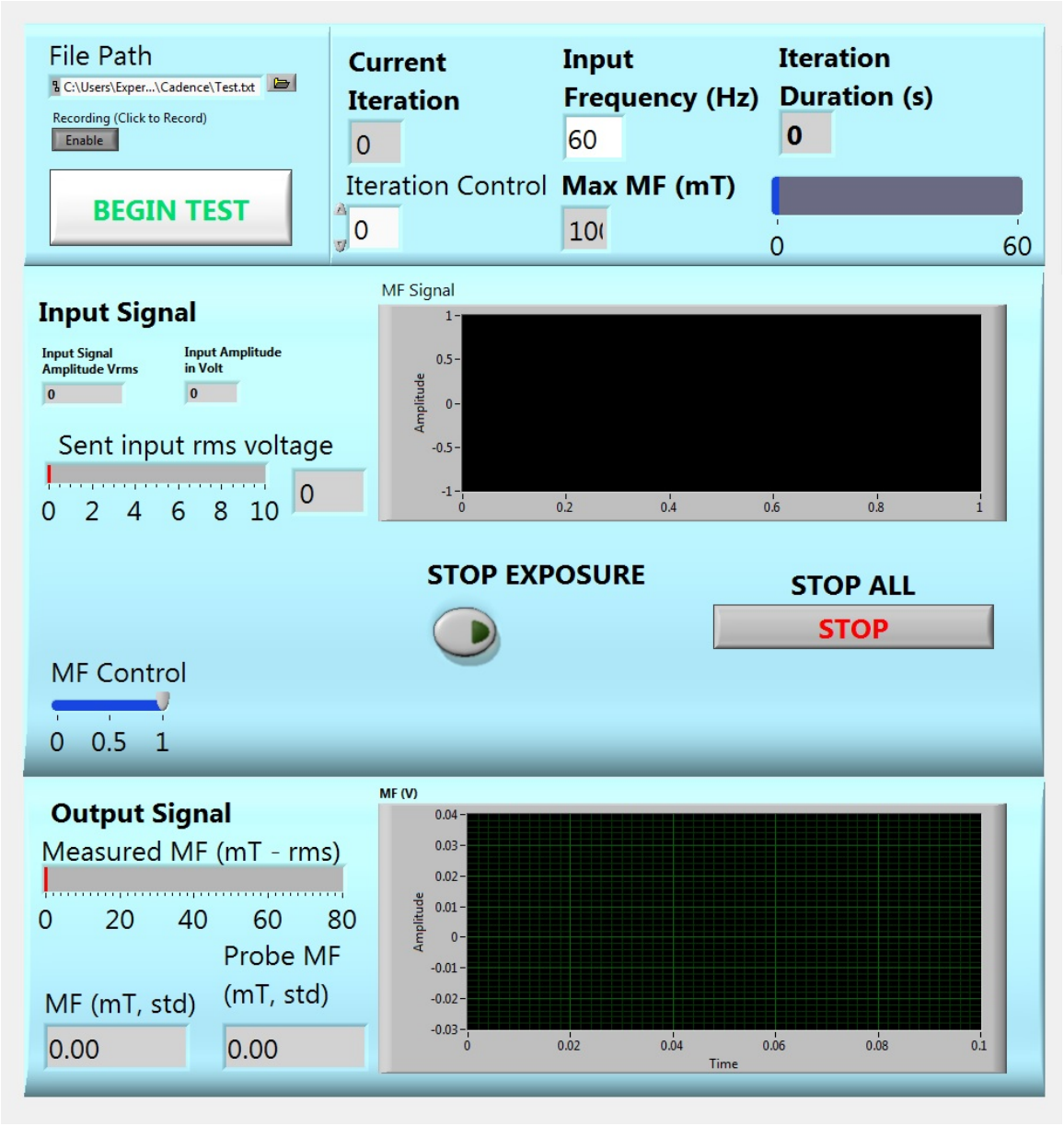
If yes, how would you describe it?

Other comments:

Appendix G: Raw Data - Magnetophosphene Threshold Values, Reported in mT_{rms}

	Frequency																
	5	**10**	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**
P1				12.71	11.25	20.60	21.99	20.81	28.59	28.70	44.21	43.84	44.05	53.09			
P2				24.41	16.47	18.88	13.91	14.54	20.20	20.16	23.09	23.96	24.37	26.25	34.50	37.79	46.19
P3				33.42	25.49	19.32	22.19	20.47	23.02	29.25	27.62	27.63	33.23	31.24	43.53	33.54	43.23
P4				22.59	12.60	24.73	16.58	15.80	24.58	20.92	22.92	29.88	30.87	30.94	35.59	47.52	55.40
P5				39.31	4.46	8.02	11.93	14.20	13.85	19.93	23.07	23.87	23.65	21.81	27.82	23.75	37.72
P7				23.74	21.46	6.69	10.91	13.31	15.00	17.51	20.13	22.79	21.35	17.87			
P8				20.38	23.22	13.54	14.15	21.12	29.10	24.27	29.74	24.04	29.18	33.02	40.82	59.63	59.63
P9				43.54	30.13	40.72	25.45	30.25	34.20	41.82	37.24	39.29	36.62	42.77	36.47	56.51	
P10				34.29	14.50	11.89	17.23	28.60	39.22	32.44	30.55	39.71	55.93	51.97		32.18	59.64
P12				14.09	19.09	17.51	19.54	17.66	20.95	23.51	32.00	34.16	42.91	37.51	45.40	53.03	54.78
P13	31.69	5.77	17.16	6.35	17.89	14.40	9.48	12.33	12.99	16.89	21.86	12.78	15.41	11.98	14.60	14.27	20.39
P14	26.02	20.74	17.11	19.96	14.47	21.67	23.83	21.82	21.03	27.02	26.69	34.10	23.54	24.65	27.85	27.81	23.53
P15		33.28	31.35	34.14	16.68	21.52	27.79	23.45	33.45	29.81	21.33	33.47	27.90	35.04	36.92		
P16	39.61	17.69	12.26	11.67	15.77	22.07	13.20	15.59	12.90	11.86	14.87	29.15	25.96	24.12	22.99	24.55	31.74
P17	43.03	13.93	16.93	24.85	32.98	49.50	38.07	40.89	39.38	39.78				29.69			
P18	38.06	24.22	21.63	18.09	13.96	20.65	10.10	13.43	18.52	19.11	22.10	21.57	17.19	21.45	26.30	26.63	30.08
P19	42.85	19.11	18.57	24.08	21.57	26.52	22.51	18.18	23.75	27.41	42.95	28.91	36.93	26.39	32.74	42.31	
P20	45.48	36.44	28.78	26.25	19.24	12.41	18.51	25.45	27.84	25.76	35.95	24.30	23.20	29.26	22.53	23.22	31.34
P21	45.38	31.42	21.98	22.82	16.99	13.63	10.90	10.98	14.69	18.43	24.31	27.90	27.41	32.95	41.67	41.49	42.13
P22	44.20	21.90	38.30	16.26	16.61	13.66	19.37	20.83	26.91	21.64	40.02	32.12	34.52	30.23	39.72	40.83	20.55
P23		29.42	19.48	16.47	11.96	15.65	17.14	12.01	15.72	18.12	15.79	21.37	15.88	21.98	14.68	23.21	
P24		29.40	25.63	22.84	31.56	20.82	18.67	16.26	25.40	26.59	23.77	22.50	19.55	23.41	34.28	41.77	42.43
P25		31.20	26.44	26.74	13.23	28.69	22.78	23.91	30.69	29.51	41.02	46.41	28.76	31.92	42.32		
P26	49.50	29.75	37.56	42.19	19.43	19.14	22.22	18.90	33.82	24.51	34.00	28.54	31.43	35.39		24.37	
P27	45.49	10.75	5.88	7.56	10.80	11.20	12.38		12.38	13.17	15.98	16.66	21.71	21.58	27.52	28.90	
P28	49.50	33.35	27.76	16.56	7.85	8.34	4.81	7.41	11.76	12.10	14.20	12.28	20.41	10.58	21.55	11.80	5.15
P29		30.41	22.73	22.10	18.06	10.44	18.06	20.72	24.66	23.52	25.54	39.07	30.44	39.22	34.12	38.70	
P30	43.25	23.72	10.79	14.68	13.42	17.53	15.76	24.50	20.54	28.05	36.85	48.75	25.49	29.92	27.28	36.32	30.50
P31	46.25	30.85	10.23	16.74	16.65	25.08	11.55	9.41	11.13	22.32	27.23	26.69	19.68	17.52	22.63	26.64	28.72
P32		26.21	17.97	21.17	22.38	21.05	17.40	25.86	28.29	27.41		43.43					
P33	49.50	27.86	25.07	19.21	19.10	15.60	17.08	16.10	14.85	33.58	27.62	27.19	30.36	30.61	33.20	42.43	
P34	16.48	11.72	11.21	15.82	13.24	12.08	17.88	14.94	19.53	24.06	21.81	25.94	28.41	23.89	20.96	42.43	32.93
P35		40.69	27.87	16.72	13.57	10.93	11.21	15.30	16.30	15.56	24.55	23.33	22.65	33.65	41.49		
P36	47.48	40.13	29.16	31.02	25.74	12.10	19.29	22.67	17.19	22.42	17.32	27.66	38.43	36.89	33.32	41.22	41.65
P37	46.07	31.30	16.34	21.60	17.48	13.75	16.19	15.48	18.96	25.55	34.47	23.06	30.86	27.96	37.97	42.43	
P38	49.50	43.79	22.65	19.93	18.54	17.36	13.57	12.55	14.08	17.52	17.44	25.03	19.60	16.79	14.98	16.49	21.95
P39		49.50	49.50	49.50	45.75	49.00	41.13	37.54	49.50	48.40	39.45	49.50		42.43		42.43	
P40		21.25	13.77	17.22	23.77	20.61	12.36	17.90	20.58	28.47	35.47	30.87	42.33	42.43			
P41	29.45	16.08	14.81	10.61	14.14	9.41	9.13	9.28	11.73	11.97	14.22	16.11	19.11	16.47	22.07	16.28	14.12
P42	47.14	28.02	20.17	17.48	18.04	15.72	18.75	16.39	18.41	19.04	29.71	32.51	23.95	32.84	30.46	37.55	39.17
P43		23.57	9.17	19.55	19.00	14.76	15.42	15.82	13.34	18.83	25.52	26.00	26.67	30.83	36.79		
P44		24.92	25.83	20.04	18.27	12.41	14.02	15.64	19.97	15.82	15.63	16.67	21.66	19.36	28.05	31.16	
P45	9.82	16.32	14.21	9.52	15.87	6.34	9.52	14.95	18.69	7.12	14.95	14.89	15.09	22.83	18.76	25.59	31.32
P46	36.53	23.48	23.76	21.91	16.24	12.02	12.09	15.56	21.30	21.25	24.31	21.16	23.94	34.24	26.11		
P47	43.84	17.11	14.82	13.98	13.20	14.29	15.65	23.54	26.02	30.22	22.44	25.27	30.53	29.90	18.68	26.34	31.39
P48		30.48	26.20	17.03	15.88	22.78	20.77	23.35	21.04	32.21	28.30	24.05	27.87	30.07	32.07		
P49	49.50	25.48	16.19	17.31	16.28	31.22	20.81	16.48	16.39	21.97	24.05	26.56	24.68	24.19	22.91	30.28	34.68
P50	43.40	3.54	2.21	3.50	2.10	3.23	8.05	11.57	12.24	13.07	13.69	11.00	19.04	14.72	8.23	9.20	
P51	45.45	22.19	31.28	22.20	21.09	11.52	13.72	16.25	13.62	14.91	19.07	14.00	18.19	23.89	27.59	27.17	29.74
P52		19.24	25.90	17.24	11.36	7.29	10.58	10.60	11.83	13.90	17.46	15.75	17.66	21.77	21.79	19.22	17.42
P53		31.71	22.20	20.68	15.96	19.99	22.18	22.91	28.04	31.06	24.17	23.00	23.50	26.31	27.64	30.82	34.57
P54	21.04	11.95	11.29	12.95	6.69	7.73	9.41	7.76	11.78	15.84	18.10	15.52	15.68	15.50	9.86	13.45	14.24
P55	44.62	21.93	16.82	19.84	18.20	7.34	14.17	13.98	11.80	15.42	17.16	17.66	24.47	26.61	24.44	32.29	
P56	39.56	28.25	35.49	25.69	18.76	10.79	12.46	13.37	15.57	13.24	17.90	13.40	18.36	24.73	23.43	30.77	
P57	41.79	10.85	19.03	15.61	10.98	11.36	10.09	9.98	10.82	14.72	15.72	14.15	16.46	18.75	19.17	20.46	26.96
P58		43.52	45.33	25.45	29.81	33.06	34.70	31.61	31.32	42.32	39.07	44.94	32.22	42.19	42.43	41.97	
P59	35.44	18.06	7.06	11.55	10.70	22.50	22.29	17.77	18.86	18.09	19.89	23.28	27.39	25.74	34.05	16.91	
P60	32.62	14.58	8.76	17.16	7.22	10.07	10.44	10.66	12.22	14.18	16.52	19.70	17.11	20.19	21.24	25.45	
Mean Threshold (mTrms)	**39.98**	**24.94**	**21.14**	**20.87**	**17.36**	**17.43**	**16.92**	**18.05**	**20.87**	**22.80**	**25.20**	**26.45**	**26.25**	**28.06**	**28.63**	**31.47**	**33.33**

Appendix H: LabVIEW Front Panel



Curriculum Vitae

Cadence Baker, BSc.
MSc. Candidate, School of Kinesiology, Faculty of Health Science, Western University

Education:

2016 – MSc. Candidate; Kinesiology, Western University, Canada

2012 – 2016 Bachelor of Science; Kinesiology, Western University, Canada

Employment / Academic History

2016 – 2018 Teaching Assistant: Functional Human Anatomy (Anatomy and Cell Biology 2221). Western University, London, ON, Canada

2016 Summer Research Assistant, Lawson Health Research Institute, London, ON, Canada

Awards, Honors, Scholarships:

2018 Faculty of Health Science Graduate Conference Travel Award (Spring 2018 Competition), Faculty of Health Sciences, Western University, London, ON, Canada ($500)

Kinesiology Graduate Conference Travel Award (Spring 2018 Competition), School of Kinesiology, Western University, London, ON, Canada ($600)

BioEM2018 Meeting Student Support Award ($300)

2017 Faculty of Health Science Graduate Tri-Council Scholarship Incentive ($1000)

Faculty of Health Science Graduate Conference Travel Award (Spring 2017 Competition), Faculty of Health Sciences, Western University, London, ON, Canada ($330)

Kinesiology Graduate Conference Travel Award (Spring 2017 Competition), School of Kinesiology, Western University, London, ON, Canada ($600)

BioEM2017 Meeting Student Support Award ($300)

People's Choice Poster Award, Western Research Forum, Western University, London, ON, Canada ($50)

2016 Lawson Internal Research Fund Studentship Award Recipient ($15 000)

Peer reviewed articles (2 total)

2017 Davarpanah Jazi S., Modolo, J., Baker, C., Villard, S., Legros, A. Effects of a 60 Hz Magnetic Field of Up to 50 milliTesla on Human Tremor and EEG. *International Journal of Environmental Research and Public Health.* (2017).

2016 Baker CM, Barkwell GE. Regulation of Balance After Spinning: A Comparison Between Figure Skaters and Controls. *WURJ: Health and Natural Sciences*. 2017;7(1):Article 5 (7 pages).

Conference Peer Reviewed Abstracts and Presentations (13 total)

2018 **Baker C.**, Villard, S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros A. Dépendance en fréquence du seuil de perception de magnétophosphènes chez l'humain exposé à un champ magnétique EBF. *Société Française de Radioprotection, Montpellier, France. October 2nd , 2018 (Poster Accepted).*

Baker C., Villard, S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros A. Frequency Specific Magnetophosphene Thresholds in Humans Exposed to ELF Magnetic Fields. *Bioelectromagnetics Conference, Piran, Portoroz, Slovenia. June 25-29th 2018 (Oral Presentation).*

Baker C., Villard, S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros A. Frequency Response of Magnetophosphene Perception in Humans Exposed to Extremely Low Frequency Magnetic Fields and Associated Occipital Cortex Electroencephalography. *London Health Research Day, London, ON, Canada. May 10th, 2018 (Poster Presentation).*

2017 Legros A**.**, Modolo M., Davarpanah Jazi S., **Baker C.,** Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Thomas A. W. Acute Neurophysiological Response to ELF MF exposure in human, 32nd URSI GASS, Montreal, August 19-26th 2017.

Legros A., Modolo J., Corbacio M., Davarpanah Jazi S., **Baker C.M**., Villard S., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Thomas A. W. Experimental threshold for magnetophosphene perception triggered by retinal magnetic induction. European Medical and Biological Engineering Conference (EMBEC) and the Nordic-Baltic Conference on Biomedical Engineering and Medical Physics (NBC), Tampere, Finland, June 11th – 15th, 2017.

Baker C., Davarpanah Jazi S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros,

A. Magnetophosphene Frequency-Response in Humans Exposed to Extremely Low Frequency Magnetic Fields. *Bioelectromagnetics Conference*, *Hangzhou*, *China. June, 2017 (Oral Presentation).*

Davarpanah Jazi, S., **Baker, C.**, Corbacio, M., Goulet, D., Plante, M., Souques, M., Deschamps, F., Ostiguy, G., Lambrozo, J., & Legros, A. Magnetophosphene perception threshold increases as a function of time spent in the dark in humans exposed to extremely low frequency magnetic fields. *Bioelectromagnetics Conference*, *Hangzhou, China. June, 2017.*

Legros A., Modolo M., Davarpanah Jazi S., **Baker C**., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Thomas A. W. Sixteen years of UTIC supported science: Overview of human physiological, neurophysiological and behavioural responses to ELF MF exposures up to 100,000 μT. Annual Joint Meeting of the Bioelectromagnetics Society and the European BioElectromagnetics Association – *BioEm2017*, Hangzhou, China, June 5th – 9th 2017.

Baker C., Davarpanah Jazi S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros, A. Frequency Response of Magnetophosphene Perception in Humans Exposed to Extremely Low Frequency Magnetic Fields**.** *Bodies of Knowledge, University of Toronto, Toronto, ON, Canada. May 11-12, 2017 (Oral Presentation).*

Baker C., Davarpanah Jazi S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros A. Frequency-Dependent Threshold for Magnetophosphene Perception in Humans Exposed to Extremely Low Frequency Magnetic Fields. *London Health Research Day, London, ON, Canada. March 28th, 2017 (Poster Presentation).*

Davarpanah Jazi S., **Baker C.**, Corbacio M., Goulet, Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros A. Magnetophosphene Perception Threshold as a Function of Adaptation to Darkness in Humans Exposed to Extremely Low Frequency Magnetic Fields. *London Health Research Day, London, ON, Canada. March 28th, 2017.*

Baker C., Davarpanah Jazi S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros. Acute Impact of an Extremely Low Frequency Magnetic Stimulus on Human Neurophysiological Function - Magnetophosphene perception. *Western Research Forum, London, ON. March 10th, 2017 (Poster Presentation).*

Legros A., Modolo J., Corbacio M., Davarpanah Jazi S., **Baker C.M.**, Villard S., Goulet D., Plante M., Souques M., Deschamps F.,

Ostiguy G., Lambrozo J., Thomas A. W. Magnetophosphenes: Human acute neurophysiological responses to magnetically-induced alternating current densities of up to 100 mA.m2. *2nd International Brain Stimulation Conference, Barcelona, Spain. March 5th – 8th, 2017.*

Non-Peer-Reviewed Presentations (3 total)

2018 **Baker C.**, Villard, S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros A. Modulations of Visual Perception with Magnetic Stimulation: Flickering Lights in the Dark. *EuroMov, Université de Montpellier, France. June 21st, 2018 (Oral Presentation).*

2017 **Baker C.**, Davarpanah Jazi S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros, A. Acute Impact of an Extremely Low Frequency Magnetic Field on Human Magnetophosphene Perception. *Kinesiology Graduate Student Association Symposium, Western University, Canada, April 21, 2017 (Oral Presentation).*

Baker C., Davarpanah Jazi S., Corbacio M., Goulet D., Plante M., Souques M., Deschamps F., Ostiguy G., Lambrozo J., Legros, A. Acute Impact of an Extremely Low Frequency Magnetic Field on Human Magnetophosphene Perception. *Talks on Fridays, St. Joseph's Hospital, London, ON, Canada, March 31, 2017 (Oral Presentation).*

Service/Volunteer Experience

2017 – Vice-President Social, Kinesiology Graduate Student Council. Organized social and networking events for kinesiology graduate students

2016 – Volunteer with Big Brothers Big Sisters of London Area. Volunteer with a youth for four hours per week, helping enrich my "Little Sister" in her growth and development

2016 Research Assistant Volunteer. Volunteered in the Human Threshold Research Group assisting with data collection.

2015 – 2017 Orientation Leader, Western University. Served as a mentor to incoming first year students (yearlong commitment)

2013 – 2016 Leadership and Mentoring Team Leader, Western University. Served as a mentor and team leader to first year kinesiology students.