Melatonin Levels and LowFrequency Magnetic Fields in Humans and Rats: New Insights From a Bayesian Logistic Regression

Melatonin Levels and Low-Frequency Magnetic Fields in Humans and Rats: New Insights from a Bayesian Logistic Regression

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Abstract

Background: The present analysis revisit the impact of extremely low-frequency magnetic fields (ELF MF) on melatonin (MLT) levels in human and rat subjects using both a parametric and non-parametric approach. **Method:** In this analysis, we use 62 studies from review articles. The parametric approach consists in a Bayesian Logistic Regression (LR) analysis and the non-parametric approach consists of a Support Vector analysis which are both robust against spurious/false results. **Results:** Both approach reveal a unique well ordered pattern, and show that humans and rat studies are consistent with each other once the MF strength is restricted to cover the same range (with $B \lesssim 50\mu T$). In addition, the data reveal that chronic exposure (longer than ~22 days) to ELF MF appears to decrease MLT levels only when the MF strength is below a threshold of ~30μT ($\log\left(B_{thr}/\mu T\right)=1.4^{+0.7}_{-0.4}$), i.e. when the man-made ELF MF intensity is below that of the static geomagnetic field. **Conclusions:** Studies reporting an association between ELF MF and changes to MLT levels and the opposite (no association with ELF MF) can be reconciled under a single framework.

Keywords: Statistics: Bayesian ; Epidemiology ; Non-ionizing Radiation; Electro-Magnetic field (EMF) ; Melatonin

Introduction

Since the epidemiological study of Wertheimer and Leeper (1979), concerns for an adverse health effect (in particular for childhood leukemia) due to electrical and magnetic fields (MFs) generated in the Extremely Low Frequency [ELF] regime (<300 Hz, but mostly at 50-60 Hz) by power lines have been raised in the west and also from case-reports of electrical substation workers in the former Soviet Union (e.g. Zhadin, 2001). This potential association between residential exposure to ELF Magnetic Fields (ELF-MF) and childhood leukemia has remained from the various pooled analysis of the numerous epidemiological studies (Ahlbom et al., 2000; Savitz, 2003; Draper et al., 2005; Kheifets and Shimkhada, 2005; Schüz et al., 2007; Sermage-Faure et al., 2013; Kheifets et al., 2013; Schüz et al., 2016) which revealed that the relative risk for leukemia is approximately 2x for MF of intensities ≥0.4 μT. This elevated risk for childhood leukemia has led to the World Health Organization to label ELF MF as possible carcinogen 'class 2B' based on International Agency for Research on Cancer (IARC) report on the subject (IARC, 2002), a conclusion recently re-affirmed by the IARC chair on non-ionizing radiation (Schüz et al., 2016).

Historically, Stevens and Davis (1996) proposed the so-called melatonin hypothesis in the context of breast cancer involving ELF MFs discussed in the 90s (as reviewed in Brainard et al., 1999; Kliukiene et al., 2004). Under this hypothesis, the well-known melatonin (MLT) hormone produced by the pineal gland that controls the body's sleep/wake cycle (e.g. Reiter, 1985, 1991), would be an intermediary agent where ELF MF would somehow impact MLT levels and this in turn would increase the risk of developing a disease or cancer. This hypothesis was put forward because

(i) it was known by Stevens and Davis (1996) that somehow the pineal gland responds to artificial EMF (since the 80s: Stemm et al., 1980; Wilson et al., 1989, 1990; Reiter, 1992, 1993, 1994), and (ii) because MLT is an effective anti-oxident agent, free radical scavenger, and a potent oncostatic agent (e.g. Panzer and Viljoen, 1997; Allegra et al., 2003; Rodriguez et al., 2004; Henshaw and Reiter, 2005; Jung and Ahmad, 2006; Reiter et al., 2016). Thus reduced MLT levels could lead to an increase risk of cancer (e.g. Guénel et al., 1996; Kliukiene et al., 2004; Koeman et al., 2014) and other neurodegenerative illnesses (e.g. Feychting et al., 2003; Huss et al., 2008; Davanipour et al., 2014) by increasing the oxidative stress as described in Mevissen et al. (1998) and reviewed in Consales et al. (2012).

This hypothetical connection made by Stevens and Davis (1996) between circadian rhythm disruption and certain illnesses has been revisited in the context of childhood leukemia by Henshaw and Reiter (2005). While this connection between MLT levels and ELF-MF lacked a clear mechanism, it seems to be related to the visual system since rats with severed optical nerves not longer respond to ELF-MF (Olcese and Reuss, 1985). The exact mechanism with magneto-receptors in the retina is now a plausible scenario in light of recent developments in the study of magneto-reception from behavioural (e.g. Kirschvink and Kirschvink, 1991; Phillips and Borland, 1992; Ritz et al., 2004, 2009; Johnsen and Lohmann, 2005; Gegear et al., 2008; Malkemper et al., 2015; Yoshii et al., 2009; Bazalova et al., 2016; Wiltschko et al., 2005; Winklhofer et al., 2013; Wiltschko and Wiltschko, 2014; Wiltschko et al., 2016; Sherrard et al., 2018) and theoretical investigations (e.g. Ritz et al., 2010a; Hore and Mouritsen, 2016) where the cryptochrome CRY proteins discovered in the 90s (Ahmad, 1993; Ahmad et al., 2007; Ahmad, 1999; Chasmore et al., 1999; Chaves

et al., 2011; Ahmad, 2016) would provide the radical pair mechanism postulated by Schulten et al. (1978) and be the (light-dependent) MF receptor (Ritz et al., 2010b; Liedvogel and Mouritsen, 2010; Hore and Mouritsen, 2016; Michael et al., 2017). CRY proteins are widely expressed in cones and amacrine cells of the retina (e.g. Foley et al., 2011; Wong et al., 2018) and are thought to be the prime MF receptors involved in avian compass.

As discussed in Lagroye et al. (2011), CRYs which are ubiquitous, and recently discovered (blue) light dependent magneto-photoreceptor, should be assessed as a plausible mechanism behind some of the biological effects of ELF MFs. CRYs are also involved in the regulation of circadian biorhythms (e.g. van der Horst et al., 1999; Yoshii et al., 2009; Ono et al., 2013; Wong et al., 2018), which led Vanderstraeten et al. (Vanderstraeten and Burda, 2012; Vanderstraeten et al., 2012, 2015; Vanderstraeten, 2017) to revive the MLT hypothesis for childhood leukemia and to formulate the cryptochrome hypothesis in the context of the epidemiological results cited above (see also Lagroye et al. (2011); Juutilainen et al. (2018)). Under this hypothesis, weak MFs in the micro-tesla range disrupt the biorhythms, leading to disrupted MLT production rendering MLT as an effective marker to be used in relation to weak MFs. Moreover, it has been shown that pulsed MFs (PMF) can also stimulate a rapid accumulation of reactive oxygen species (ROS) —a metabolite implicated in stress response and cellular ageing— but only in insect cells expressing CRY (Sherrard et al., 2018) leading Landler and Keays (2018) to postulate that carcinogenesis associated with power lines, PMF-induced ROS generation, and animal magnetoreception share a common mechanism.

However, the epidemiological and laboratory studies on MLT levels and ELF MF are often contradictory (see reviews by Henshaw and Reiter, 2005; Jahandideh et al., 2010; Touitou and Selmaoui, 2012; Halgamuge, 2013; Lewczuk et al., 2014). In this paper, we use both a Bayesian parametric regression and a non-parametric approach on a compilation of 62 studies the evolution of MLT levels on humans and rats exposed under weak ELF MFs. Given that these studies are often inconsistent (in reporting variation or no changes in MLT levels), we are making sure to include both types of results.

Materials

Here, we present the compilation of 62 studies reporting MLT levels on humans and rats and our Bayesian methodology.

Melatonin Data on humans

Halgamuge (2013) compiled various studies on humans exposed to ELF published in the last 15-20 years where MLT levels —mostly 6-sulfatoxymelatonin in urine samples (24hr)— were reported. These authors included both laboratory (short term) and epidemiological (long term) studies. From their collection of 33 studies, we noticed that some were duplicates, which were removed (e.g. their entries 13, 24, 25 are duplications of their 11, 13 and 23, respectively). We verified each entry listed in Halgamuge (2013) (their Table 4) regarding MF field strength and exposure duration, leading to some differences between their listing and this work.

Since our focus is on studying the putative effect of environmental/ambient (i.e. large scale) MF on human MLT levels, mostly from power lines where the entire body is subject to the MF, we did not consider studies that involved very localized ELF such as those from electric blankets, video displays, nor cell phone usage. Furthermore, we did not consider those regarding geomagnetic storms, in-vitro studies, or involving static magnetic field.

Table 1 lists the studies from Halgamuge (2013) used in this analysis. Note that it includes the 14 studies listed in the review of Henshaw and Reiter (2005), and we included a few studies not included in the original review of Halgamuge (2013) but in the review article of Touitou and Selmaoui (2012), such as Griefahn et al. (2001);

Kurokawa et al. (2003); Cocco et al. (2005); Davis et al. (2006) and Warman et al. (2003). The only study we rejected is that of Touitou et al. (2003) which is based on a small sample (30) of individuals/electrical workers preselected not to have any sleep disturbances, i.e. is biased against finding any sleep/MLT perturbation from ELF MF. We note that last study is in contrast to the recent work of Liu et al. (2014) on 854 workers showing an increase of sleep disturbance in some utility workers (see also Monazzam et al. (2014) on this subject).

In Table 1, some studies claim that MLT levels are affected, but the changes are invariably in the sense of a decrease of the MLT production or a phase shift. In contrast, other studies claim that the MLT level is not affected by MFs. The effect/no-effect outcome naturally leads to logistic modelling (described in the Methods section) appropriate for such binary situations (Hosmer, D. W. and Lemeshow, S., 2000). The logistic approach makes no implicit assumption and is simpler than invoking a model that assumes a linear relation between MLT levels, exposure duration, etc.

Unfortunately, MLT studies are heterogeneous and there is no universal way to quantify the amount of decrease in MLT production across these studies. Thus, we assign the outcome of the studies listed in Table 1 a 1(0) depending on whether the original authors reported change (no change) in MLT levels, respectively. When the study reported ‘some’ change, we assign the outcome of the study a 0.5. This would correspond to, for instance, when changes were observed only for a sub-group of the study.

Melatonin Data on rats

Jahandideh et al. (2010) compiled various laboratory studies on the putative effect of ELF MF on rat MLT, whose list is reproduced in Table 2. We removed the entries that were not consistent with the original study, e.g. the entries with ID 13,14 and 15 from John et al. (1998). In addition, we added the study of Loscher et al. (1994) and Löscher et al. (1998). As in the previous section, we assign rat studies a 1(0) depending on whether the authors reported change (no change) in MLT levels, respectively.

Jahandideh et al. (2010) investigated whether the MF exposure duration, MF polarization and other factors play a role. They concluded that the only factor that seemed to be the most significant is the duration of exposition to ELF MF, albeit with a P-value of 0.07 implying that this factor is not significant at more than >95% level, using a model linear with exposure duration and with field strength.

Methods

A parametric bayesian analysis

As discussed in Jahandideh et al. (2010), logistic regression (LR) is a statistical technique commonly used to examine the possible relationship between a dichotomous-dependent variable (here the effect/non-effect on MLT excretion pattern) and independent variables (such as frequency, polarization, exposure duration, and MF). In general, the probability P to observe an effect (i.e. Y=1) is given by the logistic function:

$$P(Y=1)=\frac{1}{1+\exp(-t)}=L(t) \quad (1)$$

where t is usually taken to be a linear combination of the dependent variables, X_n, i.e. $t=\alpha+\beta_1 X_1+...+\beta_n X_n$. However, one should keep in mind that such a linear combination of dependent variables makes a critical assumption: namely that these variables are independent of one another. In other words, the probability to have an effect might depend on the field exposition duration and on the magnetic field strength, but the coefficient for each of these variables are assumed to be independent of one another.

In this work, we use a logistic function ($L(t)$; Eq. 1) where t can be a non-linear function of the independent variables. $L(t)$ gives the probability to observe an effect ($p \equiv L(t)$), and the observed realization is given by the Bernoulli (Bern) probability

distribution since the observables are dichotomous, with values at 0 or 1, which can be written as (see Supplementary Material):

$$t = f(X_i; \theta) \tag{2}$$

$$p = L(t) \tag{3}$$

$$O \sim Bern(p) \tag{4}$$

where O are the simulated observables. The LR model is made robust to spurious data by including an (unknown) outlier fraction π, i.e. Eq. 3 becomes

$$p = \pi\, p_{out} + (1 - \pi) L(t) \tag{5}$$

where p_{out} is the logistic probability for outliers and π is taken from a Uniform distribution from 0 to 0.5. We use uniform priors on π and p_{out}.

Next, we will consider the following two parametric LR models. First, we use a model linear in exposure duration with log T as the single independent variable. Then, we will use a variant of the logistic model where the slope α is a function of the MF strength in a dichotomous fashion for reasons that will be clearer in the Results section. To summarize, the two parametric models are

model A: $$t \equiv \alpha_T (\log T - \beta_T) \tag{9}$$

model B: $$t \equiv \alpha, \gamma (\log T - \beta) \quad \text{if} \quad B \le B_{thr}, B > B_{thr} \tag{10}$$

where α,γ are the linear slope, β the transition point of the logistic function, and B_{thr} is the threshold level for model B.

In order to find the best parameters $\hat{\theta}$ for our model, we use a Markov Chain Monte Carlo (MCMC) algorithm. Because traditional MCMC algorithms are somewhat sensitive to the step size and the desired number of steps. In what follows, we use the No-U Turn Sampler (NUTS) of Hoffman and Gelman (2014), a self-tuning variant of Hamiltonian Monte Carlo (HMC), except when the model is not continuous (as in model B) where we revert to the traditional Metropolis-Hasting sampling method. We typically use 2 MCMC chains per run and 15,000 iterations to 25,000 iterations per chain.

In order to investigate the inherent limitations of our parametric approach (as in any regression), we applied a non-parametric supervised classification algorithm to the data sets in order to determine whether there are robustly-defined regions in the parameter space that divide studies reporting a change in MLT levels with those that reported no change. We chose to apply the Support Vector Classification (SVC) algorithm (Cortes and Vapnik, 1995) implemented in the SVM module of the SCIKIT-LEARN python package v0.19.1 (Pedregosa et al., 2011). Non-linear regions were investigated, using a Gaussian RBF (Radial Basis Function) kernel which uses a Gaussian similarity measure between points in the parameter space. The use of the RBF kernel depends on two quantities, *C*, the penalty parameter which describes the way in which smoothness of the boundaries of the classification regions in parameter space is traded off with misclassifications of the studies, and γ, the kernel coefficient which defines how much influence each individual study has. We used γ to be 1/number of features, and used a cross-validation technique to determine the penalty parameter which is $C \simeq 3$. This non-parametric approach is merely used to provide a

‘sanity check’ to the parametric approach, as it does not directly give a probability of classification to each of the studies considered.

Results

Magnetic field strengths

Figure 1 shows the histogram of mean MF strengths for the studies compiled on humans (hatched) and on rats (solid). The strength of the static Earth magnetic field $B_{\odot} \sim 50\,\mu T$ is indicated with the vertical dotted line, but the local strength varies from ∼30 to 60 μT, depending on the latitude.

This figure shows that human studies cover the range of MF of strength from 0.1 to 50μT, while rat studies are involving MF of higher strengths from 1 to 1000 μT. The MF distributions for human and rat studies appear to be significantly different as a Kolmogorov Smirnov(KS)-test indicate the two histograms are not drawn from the same parent population, with a P-value of 0.01. This difference is perhaps due to an implicit bias induced by researchers looking to bring out a signal in the lab, i.e. induced by a dose-response expectation as in Warman et al. (2003).

Results on human studies

Regarding model A (described in the Methods section), we use the following (uninformative) priors for the slope α and zero-point β:

$$\alpha_T \sim N(0,10)_{lo=-5}^{up=5} \qquad \beta_T \sim U(-2,3.5) \tag{11}$$

where the $N(\mu,\sigma)$ is the normal distribution truncated on the interval [-5,5] and U is the Uniform distribution. The best fit parameters of model A with their 95% credible intervals are $\beta_T = 1.4^{1.7}_{-1.0}$ and $\alpha_T = 2.5^{+2.4}_{-1.8}$ (Table 3).

Figure 2(left) shows the result from the LR model A applied on the 28 human studies reporting change or no change to human MLT levels. The top panel shows the data in the plane log B—log T where the model predictive values are represented by the grey scale. The vertical line represents the best fit β_T parameter, i.e. where the probability to have an effect is modeled to be 0.5. The bottom panel shows the model prediction (red solid line) as a function of exposure duration T where vertical dotted-dashed lines indicating a day, a month, and a year. The shaded gray region represents the 95% posterior uncertainties, calculated using the Wilson (1927) score confidence interval for binomial distributions, verified to be a continuous representation of the uncertainties found from the MCMC posteriors. This figure shows that ELF-MFs start to have an effect on MLT levels with a probability larger than 50% at around $\sim$22 days.

Figure 2(right) shows the same 28 human studies where we applied a non-parametric SVC algorithm and studies reporting change, partial change and no change on MLT levels are shown in red, yellow and blue respectively. This figure confirms that the studies reporting changes in MLT levels are predominantly in the region of parameter space with long exposure duration, supporting the results from the parametric LR shown on the left panel, and is not driven by a few rogue false data points.

Results on rat studies

We performed a similar analysis on the studies available on laboratory rats (described in Materials) and the results are listed in Table 4. One notable difference between studies involving humans or rats, is that the duration coefficient α_T appears to be much weaker in the case of rat studies ($\alpha_T \simeq 1.2$) than in the case of humans ($\alpha_T \simeq 2.5$) and α_T is much less significant for rats. However, we remind the reader that, as shown in Figure 1, only a handful of human studies have MF strength above $\sim$50 μT, while about half of the studies on rats have MFs above this level.

Towards a unified framework

Given that human and rat studies differ significantly in the field strengths, we show in Figure 3 the results for studies on laboratory rats when the MF strength is below (above) 45μT (chosen to avoid the four studies which are at 50.0μT), shown in the bottom (top) panels, respectively. These two panels clearly show that the effect on MLT levels becomes random with respect to exposure duration *T* when the MFs are above $\sim$50μT. In both panels, the red solid line represents the best model (model A) obtained from the LR Bayesian analysis whose parameters are listed in Table 4.

Comparing Table 4 with the results of model A on humans in Table 3, one sees that the statistics of change/no-change on MLT levels in rat and human studies are consistent with each other, **only** *after restricting animal and human studies over the same range of MF strengths*. The time-dependent factor is $\alpha_T = 2.5^{+2.4}_{-1.8}$ for

human studies and $\alpha_T = 3.0^{+1.9}_{-2.4}$ for rat studies. Furthermore the exposure duration where the MF exposure becomes significant (with a probability to affect MLT levels greater than 50%) is in both cases close to $\beta_T \simeq 1.2$, corresponding to $\sim$16 days.

Inspired by these results, we extended our LR model to include some (unknown) threshold MF, B_{thr} , i.e. model B introduced in the Methods section. Figure 4(left) shows the data in the log *T*–log *B* plane along with the model predictions represented as the grey scale. Figure 4 (right) shows the non-parametric SVC analysis, and strongly supports the results from the Bayesian parametric LR. Figure 5 shows that posterior distribution on each of the parameters for model B, whose best parameters are listed in Table 4.

The best threshold value determined by the data is $\log B_{thr} = 1.4^{+0.7}_{-0.4}$ (68% CL), i.e. the magnetic threshold is $B_{thr} \simeq 10 - 65$ μT. We note that the transition field strength of $\sim$50μT corresponds to two different regimes, one where the ELF MF are a mere perturbation to the ambient static terrestrial MF, which has an amplitude of $B_{\odot} \simeq 50 \mu T$, and the other where time varying ELF MF are the sole dominant contribution. We discuss the implications of this in the next section.

Discussion

In the context of our result of a threshold-dependent impact of man-made ELF MFs on MLT levels it is relevant to discuss the functional window discussed by Wiltschko and Wiltschko (2014) in the case of the avian magnetic compass. The functional window at ~50μT has been shown to be adaptable to variations in the static field. Indeed, Wiltschko and Wiltschko (2014) and collaborators have shown that, after a few hours, migratory birds regain their magnetic sense at other intensities both low (e.g. Winklhofer et al., 2013, as low as 4μT) and high (Wiltschko et al., 2006, up to 92μT). Note the coupling between such a weak field and biological organisms (e.g. Ritz et al., 2000; Vanderstraeten and Gillis, 2010; Vanderstraeten, 2018; Hore and Mouritsen, 2016; Kattnig and Hore, 2017) is far more complex than having an 'internal compass' in their beak and appears to involve chemical reactions on spin-correlated radical pairs, even though little is understood on the downstream signalling cascade mechanism(s) (as reviewed in Nordmann et al., 2017).

Our result of a threshold-dependent impact of man-made ELF MFs on MLT levels at intensities at or below $B_{\odot}$ calls for a possible role of the geomagnetic field. Indeed, the amplitude of the static Earth MF $B_{\odot}$ is not constant with time as there are fluctuations on a range of time-scales, from daily fluctuations to monthly, annual variations and up to time-scales of millions of years (see e.g. Courtillot and Le Mouel, 1988) due to complex interactions between the solar wind and the magnetosphere. The daily variations are of the order of 20 to a few hundreds of nT (i.e. 1000× smaller than the field strength) due to the impact of the solar wind

pressure in the upper atmosphere (e.g. Hitchman et al., 1998), and this led Liboff (2014) to suggest that the biological genesis for interactions between living beings and weak ELF could originate from these tiny (∼50 nT) daily swing in the geomagnetic field because it is a remarkably constant effect exactly in phase with the solar diurnal change. Hence, as argued in Liboff (2014), the widespread sensitivity of biological systems to weak ELF magnetic fields could be derived from the diurnal geomagnetic variations. However, while numerous studies show that MF can influence the circadian system, no study has experimentally established that the natural GMF variations can act as a reliable secondary zeitgeber.

Possible Limitations

Our study did not consider other possible parameters that may influence MLT excretion levels due to the lack of consistency in the parameters reported in MLT studies. In light of the mechanisms of interaction between MF and biological systems discussed in the introduction such parameter might include (1) the MF polarization, (2) the amount of light and more importantly, whether or not the spectrum includes blue photons as magneto-reception appears to be blue-light dependent (e.g. Chasmore et al., 1999; Ritz et al., 2000; Gegear et al., 2008; Chaves et al., 2011; Michael et al., 2017; Vanderstraeten, 2018), (3) the intensity of blue-light (as magneto-reception might be inversely proportional to the photon flux, e.g. Vanderstraeten, 2018), (4) the time of exposure with respect to MLT rise (as suggested by Wood et al., 1998; Vanderstraeten and Burda, 2012), (5) the MF orientation with respect to the geomagnetic field since the radical pair (RP) mechanism involved in CRY might depend on the direction of the field line (Wiltschko and Wiltschko, 2014; Zhang et al., 2015), (6) the (blue) light polarization (as discussed in Stoneham et al., 2012; Hore and Mouritsen, 2016), (7) the possible adaptation time reported by Wiltschko and Wiltschko (2014) for the avian magnetic compass, (8) the age (Vanderstraeten and Burda, 2012) and genetic factors as Fedrowitz et al. (2004) indicated that significant differences might occur from different substraints of rats.

Conclusions

From our analysis of 62 studies on the possible variations of MLT levels in humans and rats from Jahandideh et al. (2010); Touitou and Selmaoui (2012); Halgamuge (2013), we examined the possible relationship between a dichotomous dependent variable (corresponding to studies showing an effect or no effect on MLT excretion pattern) and independent variables such as exposure duration and magnetic field strength using a Bayesian approach and a simple logistic regression model. We find that :

- the MF exposure duration is the most significant parameter in causing changes in MLT levels both in human (Fig. 2) and rat (Fig. 4) studies, as others have reported (e.g. Savitz, 2003; Kurokawa et al., 2003; Selmaoui and Touitou, 1995; Jahandideh et al., 2010; Vanderstraeten et al., 2012);
- human and rat studies are entirely consistent with one another, but *only after matching the MF strengths* to similar ranges, i.e. $B \lesssim 50\mu T$;
- there seems to be no dose-dependence between any change in MLT levels with MF strengths ranging from 0.5 to 100μT as others have reported (e.g. Kato et al., 1993; Reiter, 1993; Pfluger and Minder, 1996; Halgamuge, 2013);
- the impact of MF on MLT levels **does**, however, depend on the ELF MF strength, in the regime where ELF MFs are weaker than $B_{thr} \sim 30\mu T$ (Fig. 5). Such a window effect was already discussed in Löscher et al. (1998).

In light of these results, we suggest to perform additional research on rats with ELF MF with intensities in the range from 20nT to 20μT, while controlling the additional factors listed earlier in the section Limitations, because epidemiological

studies have indicated that adverse effects on human health become noticeable at ∼0.4μT. But so far very few rat studies involved ELF MF with intensities below 5μT. This range 20nT to a few μT covers the regime experienced by humans in man-made and natural environments. Indeed, the natural variations of the geomagnetic field ranges from 20nT to a few hundreds of nT (Hitchman et al., 1998).

Because MF strengths >50μT are not found in nature, studies on rats with MF strengths >50μT, or mT levels, might reveal a different (likely acute effect) than the duration-dependent effect discussed here, where perhaps one of the other factors discussed earlier has become dominant.

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Conflict of Interest: The authors have no conflict of interest.

Software: This work made use of the following open-source software: NUMPY (Van Der Walt et al., 2011), SCIPY (Jones et al., 2001), MATPLOTLIB (Hunter, 2007), PYMC3 (Salvatier et al., 2016) and SCIKIT-LEARN (Pedregosa et al., 2011).

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Figure 1: Histogram of MF strength for studies involving human (hatched) and rats (solid). The vertical dotted line represents the geomagnetic field B_E at 50μT. A KS-test indicate the two histograms are not drawn from the same parent population, with a P-value of 0.01.

Figure 2: *Left*: Bayesian Logistic Regression (model A) on human studies. The top panel shows the data in the log *T*–log *B* plane along with the model A prediction (grey scale). The vertical line shows the best fit β_T parameter, i.e. where the probability *p* for having an effect is 0.5. The bottom panel shows the data as a function of exposure duration log *T* and the red solid line represents the best fit logistic model with the shaded region representing the 95% posterior predictive interval. *Right:* Non-parametric Support Vector Classification (SVC) using a Radial Basis Function (RBF) kernel with penalty parameter *C*=3.2 determined by cross-validation. In both panels, the *x*-values have been offseted by a small (random) amount to help distinguish overlapping data points.

Figure 3: Bayesian Logistic Regression (model A) on rat studies with magnetic field strength *B* above (below) 45μ*T* shown in the top (bottom) panel respectively.

Figure 4: *Left:* Bayesian Logistic Regression (model B) on laboratory rat studies shown in the *log T*–log *B* plane shown along with the model predictions (grey scale). The horizontal dot-dashed line represents the best fit threshold inferred by the model and the vertical solid line represents the best fit β parameter, i.e. where the probability *p* for having an effect is 0.5. *Right:* Non-parametric Support Vector Classification (SVC) using a RBF kernel with penalty parameter *C*=3.2 determined by cross-validation. In both panels, the *x*-values hasve been offseted by a small (random) amount to help distinguish overlapping data points.

Figure 5: MCMC posterior distribution for the parameters of LR model B applied on MLT levels in rats.