Developmental Effects of 7 Hz, Square Wave Magnetic Fields and Nitric Oxide Modulation on Organ Systems

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Abstract: Prenatal or perinatal exposure to physiologically-patterned magnetic fields (MFs) affects behaviour in weanling (22d) and young adult (90d) rats. However, the long-term (120d-730d) biological effects of these MFs have not been examined. In the current study, the long-term effects of developmental exposure to a physiologically-patterned MF, and their dependence on nitric oxide (NO) activity, were investigated. Pregnant dams were exposed from 2d before to 14d after parturition to square wave, 7 Hz MF and to either water or nitric oxide (NO) modulation in tap water with NO precursor 1.0 g/L L-arginine or 0.5 g/L NO inhibitor n-methylarginine. To assess the possibility of intensity-windowing of any effects, MF intensities of <1, 1, 5, 10, 50 and 500 nT were employed. Male offspring were euthanized for post-mortem examination and wet organ weights were then taken. Analysis showed increased brain weight in 10 and 50 nT-treated groups, increased bodyweight in 50 nT-treated groups and suggested increased testicular weight in 5, 10 and 50 nT-treated groups. Few effects of NO modulation were evident in these rats, reinforcing the idea that these are short-term and reversible. These findings suggest that subtle long-term changes in organ structure can arise from developmental exposure to physiologically-patterned MFs.

INTRODUCTION

The prenatal period is characterized by rapid division, differentiation and heightened sensitivity of cells. Overlapping this timeframe and extending into the weeks that follow is the perinatal period, where further growth and refinements occur that are heavily influenced by the environment [1, 2]. Together these phases determine the majority of the organism's phenotype; dramatic redirection in phenotype can occur if specific stimuli are applied during either phase. Even if these stimuli are normally innocuous to the adult they may be dangerous to the neonate, with the developing central nervous system being particularly vulnerable [3].

Since the outset of industrialization there has been intense investigation into the developmental effects of power frequency magnetic fields (MFs of 50 and 60 Hz) which are generated by appliances and their wiring. Developmental toxicology studies in the fruit fly [4], chick [5, 6], fish [7], mouse [8, 9], rat [10-12] and multiple avian species [13] have been done using these frequencies and do not suggest reliable biological correlates to fields of low intensity. Subtle effects on skeletal morphology have been the only consistent effect in rodent species [14]; external or visceral malformations do not appear to be enhanced in exposed offspring.

Power frequencies represent only a portion of the frequencies encountered in nature. An examination of the developmental effects of physiologically-patterned MFs [15] strongly suggests that even extremely weak (< μT) MFs can be dangerous to the neonate if they are of a specific pattern. Physiologically-patterned fields, which are modeled after the rhythms of natural processes, have multiple biological long-term effects in exposed offspring. Examples of physiologically-relevant patterns include waveforms modeled after hippocampal theta rhythms [16] and waveforms modeled after geomagnetic micropulsations [17] as they are both naturally occurring patterns of magnetic activity. Brain structure appears sensitive to these fields: reductions in the density of the medial preoptic nucleus in males [18, 19] and parasolitary nucleus in both sexes [17] have been reported as have alterations in the gross [20] and fine structure of the hippocampus [16]. Changes in testicular weight [19] and thyroid weight [21] might also occur. One field configuration increased the weight of exposed offspring by nearly 33% [22]. Unpublished studies suggest these fields could influence organ structure [23]; the same does not appear true of power frequency fields [10]. Most remarkable is that these physiologically-patterned MFs can have effects at extremely low intensities (nT) that are nearly a million times lower than recommended public and occupational thresholds (~0.5 mT).

The waveforms applied in electromagnetic medicine [24] are not always within the 50-60 Hz range and often fall into the range of the physiologically patterned frequencies (≤10 Hz). This is true of exploratory therapies such as those for multiple sclerosis [25, 26] and established therapies such as repetitive transcranial magentic stimulation [27]. A comprehensive examination of the developmental effects of the latter is warranted as the behavioural and biological effects of any MF are specific to the temporal pattern of its frequency or complex frequencies [15] and are not typically identical to those of 50 and 60 Hz frequencies.

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In order to resolve these concerns, a wide-scale, comparative investigation of biological variables following developmental MF exposure is in order. This insight compelled the current study. Rats were exposed during development to a 7 Hz, square wave MF previously shown to be effective [22] during the perinatal period (2d before to 14d after birth) and then examined for general biological responses in adulthood. The involvement of NO activity in the MF's effect [28] was addressed by applying either NO donour amino acid L-arginine (LA; 1.0g/L) or NO inhibitor n-methylarginine (NMA; 0.5g/L) along with the field. This design also permitted the examination of the effects of perinatal NO modulation independent of MF. Among the potential chemical effectors of MFs, NO and opiates are the most widely implicated [15]. NO metabolites, as opposed to opiate indicators, are often up-regulated following exposure [14,29]. Exposed rats were observed from birth to late adulthood and then sacrificed for post-mortem examination. Wet organ weights were taken as were qualitative observations of health and behaviour prior to euthanasia.

If physiologically-patterned MFs have long-term biological influences as the research suggests, detectable changes in organ weight or structure, particularly in the thyroids or sex organs, should be observable in adult rats as these effects have been reported for other fields. If MFs induce NO activation, any changes shown in animals exposed to the 7 Hz, square wave MF should be similar to those induced by LA application and should be counteracted by NMA [22].

MATERIALS AND METHODS

Subjects

The procedures employed have been described previously [22]. Briefly, pregnant dams received a 7 Hz, square wave MF of either <1, 1, 5, 10, 50 or 500 nT in strength during the perinatal period (2d before to 14d after birth). To assess the contribution of NO to the effectiveness of the MF, these six groups also received one of three solutions during the MF exposure period: either tap water (control), 1.0g/L NO donour L-arginine (Sigma) or 0.5g/L NO inhibitor n-methlyarginine (Sigma). The offspring of these dams were maintained in standard colony conditions with food and water available *ad libitum*. At ages between 200-730d male rats were selected for sacrifice. Rats fit into one of four age groups: 1) 200-300d; 2) 300-400d; 3) 400d-500d and 4) 500d or older. These groups were equally weighted and each accommodated 25% of the design.

Organ Sampling

Following carbon dioxide euthanasia (≤2 minutes), key organs were harvested and trimmed of fat and connective tissue. The brain, pituitary gland, thyroids, pancreas, spleen, adrenals, kidneys and testicles were all removed in consistent order. Wet tissue weights were taken using a balance accurate to ±0.1 mg. Separate left and right weights were taken for large paired organs (adrenals, kidneys, and gonads). The extraction process took an average of 30 minutes. Prior to euthanasia, the animal was weighed.

Qualitative Observations

Any abnormal behaviours (such as over-grooming or lethargy) or health conditions (such as development of sores or tumours) were recorded during daily monitoring of the animal. These assessments were made by an animal care technician. Inspection of the body for subtle effects, such as hair loss (which can occur during many health problems including over-grooming) was also performed regularly. During post-mortem, any internal qualitative anomalies suggesting aberrant or damaged tissue were recorded.

Statistical Analysis

As there were three drug groups (either water, LA or NMA) and six intensity groups (either <1 (Sham), 1, 5, 10, 50 or 500 nT), a 3 (drug) x 6 (intensity) two-way ANCOVA was performed on all measures. Age and bodyweight were used as covariates. Prior to analysis, extreme outliers (≥ +2 SD or ≤ -2 SD) were omitted. This was to exclude tumourous organs and atrophied organs. When appropriate, Chi-square analysis was performed on qualitative observations. *Post-hoc* analysis was performed on the residuals of the ANCOVA using the tukey multiple ranges test with significance set at $p = 0.05$. All analysis was performed using SPSS on a VAX 4000 computer. For significant analysis, the effect size (η^2), defined as the variability in the dependent variable explained by the independent variable (or the treatment), is provided. This value is a measure of the strength of the effect of the treatment and is equivalent to the r^2 value in correlations.

RESULTS

Mean and standard error of the mean (SEM) for bodyweight and organ weights by group are listed in Table **1**.

Bodyweight

Two-way ANCOVA detected a main effect for field treatment on bodyweight ($F(5,86)=7.30$, $p<.001$, $\eta^2=.25$) and a field by drug interaction ($F(1,86)=2.18$, $p<.05$, $\eta^2=.15$) when accommodating age. *Post-hoc* analysis showed the source of the interaction to be the larger bodyweight of rats given 50 nT MF + water only (Fig. **1**).

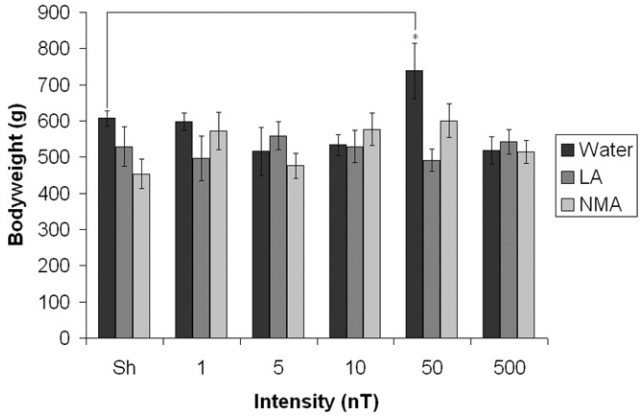

Fig. (1). Mean and SEM for bodyweight by field and drug treatment group. *Sh* = Sham. The group given 50 nT + water is elevated with respect to the control.

Brain Weight

Two-way ANCOVA detected a main effect for field treatment on brain weight ($F(5, 84)=4.40$, $p<.001$, $\eta^2=.14$)

Table 1. Mean and SEM for Bodyweight and Organ Weights (in g) by Field and Drug Treatment Group. Outliers have been omitted. *W* = Water

Group	n	Bodyweight	Brain	Pituitary	Thyroid	Spleen	Pancreas	Kidneys	Adrenals	Testicles
Sh/W	4	607.1 (20.9)	2.16 (0.006)	0.013 (0.001)	0.029 (0.002)	1.12 (0.13)	1.27 (0.16)	4.22 (0.39)	0.072 (0.004)	4.13 (0.35)
Sh/LA	4	637.3 (14.5)	2.16 (0.042)	0.010 (0.001)	0.030 (0.005)	1.39 (0.10)	1.19 (0.03)	4.57 (0.24)	0.070 (0.006)	3.78 (0.24)
Sh/NMA	3	517.7 (48.3)	2.12 (0.038)	0.011 (0.001)	0.026 (0.006)	1.04 (0.19)	1.14 (0.19)	3.57 (0.25)	0.054 (0.001)	3.86 (0.09)
1 nT/W	6	598.0 (24.6)	2.23 (0.054)	0.020 (0.003)	0.032 (0.003)	1.91 (0.24)	1.75 (0.23)	5.99 (0.82)	0.095 (0.012)	3.33 (0.24)
1 nT/LA	2	718.8 (93.8)	2.34 (0.020)	0.013 (0.050)	0.040 (0.006)	1.74 (0.21)	1.10 (0.01)	5.22 (0.90)	0.099 (0.033)	2.44 (0.39)
1 nT/NMA	5	571.7 (51.9)	2.26 (0.030)	0.019 (0.001)	0.034 (0.002)	1.44 (0.15)	1.97 (0.29)	4.91 (0.48)	0.087 (0.011)	3.84 (0.55)
5 nT/W	2	576.5 (52.5)	2.28 (0.010)	0.012 (0.001)	0.029 (0.002)	1.21 (0.03)	1.15 (0.11)	4.61 (0.25)	0.067 (0.018)	4.66 (0.22)
5 nT/LA	4	559.0 (38.9)	2.16 (0.025)	0.011 (0.002)	0.031 (0.006)	1.11 (0.08)	1.08 (0.07)	3.85 (0.15)	0.074 (0.006)	3.92 (0.33)
5 nT/NMA	5	528.8 (36.9)	2.17 (0.027)	0.015 (0.003)	0.022 (0.001)	1.00 (0.05)	1.00 (0.06)	3.62 (0.12)	0.062 (0.002)	3.70 (0.22)
10 nT/W	13	641.0 (36.2)	2.37 (0.022)	0.018 (0.002)	0.048 (0.003)	1.87 (0.17)	1.90 (0.18)	6.71 (0.48)	0.116 (0.019)	4.33 (1.15)
10 nT/LA	11	637.7 (42.4)	2.35 (0.039)	0.017 (0.001)	0.040 (0.005)	1.98 (0.04)	1.55 (0.25)	6.04 (0.45)	0.212 (0.134)	3.61 (0.23)
10 nT/NMA	7	796.4 (41.6)	2.46 (0.054)	0.018 (0.002)	0.043 (0.005)	1.97 (0.14)	1.97 (0.29)	6.26 (0.46)	0.074 (0.006)	3.86 (0.11)
50 nT/W	3	738.2 (76.6)	2.36 (0.024)	0.016 (0.005)	0.050 (0.011)	2.26 (0.58)	1.21 (0.50)	6.88 (0.35)	0.129 (0.048)	3.77 (0.31)
50 nT/LA	3	566.7 (58.8)	2.31 (0.007)	0.013 (0.001)	0.043 (0.008)	2.02 (0.34)	1.29 (0.16)	10.16 (2.92)	0.089 (0.004)	3.56 (0.51)
50 nT/NMA	6	614.1 (52.7)	2.36 (0.056)	0.017 (0.004)	0.032 (0.004)	1.54 (0.22)	1.48 (0.39)	5.05 (0.44)	0.292 (0.184)	2.68 (0.15)
500 nT/W	9	625.0 (27.7)	2.33 (0.049)	0.018 (0.002)	0.033 (0.002)	1.60 (0.12)	1.88 (0.25)	5.30 (0.19)	0.086 (0.007)	4.36 (0.22)
500 nT/LA	10	650.5 (40.8)	2.41 (0.053)	0.018 (0.001)	0.047 (0.003)	1.62 (0.19)	1.38 (0.11)	6.65 (1.03)	0.091 (0.006)	3.04 (0.37)
500 nT/NMA	8	610.8 (50.8)	2.29 (0.039)	0.015 (0.001)	0.034 (0.006)	1.51 (0.23)	1.34 (0.20)	4.94 (0.37)	0.151 (0.071)	3.49 (0.18)

but no drug effect or interaction. *Post-hoc* analysis of the residuals showed that brain weight was elevated in 10 and 500 nT 7 Hz groups (Fig. **2**). The difference in the case of 5 nT was marginal but not statistically significant. In a polynomial analysis, the relationship between intensity and brain weight was shown to possess a statistically significant quartic term which was weighted more heavily than the linear term.

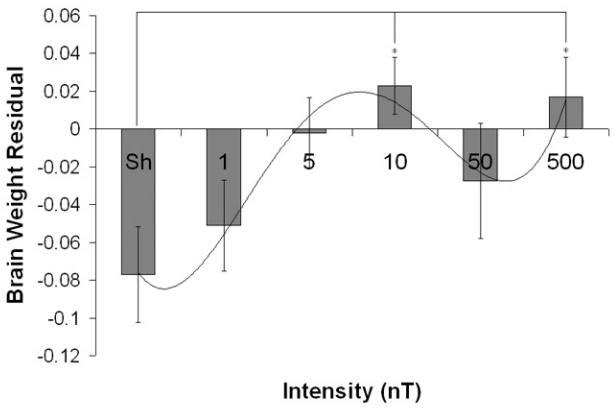

Fig. (2). Residual mean and SEM for brain weight by field treatment group. Superimposed on the means is the quartic function for the relationship.

Thyroid Weight

Two-way ANCOVA found no significant main effects or interactions of the treatments on thyroid weight. The two main effects ($p<.15$) and interaction ($p<.10$) were marginally significant but had weak effect sizes ($\eta^2<.10$).

Kidney Weight

Two-way ANCOVA detected a main effect for field ($F(5,84)=2.32$, $p<.05$, $\eta^2=.05$) and drug ($F(2,84)= 3.69$, $p<.05$, $\eta^2=.08$). *Post-hoc* analysis showed that kidneys from groups given 10 nT fields were heavier than those given 1 nT fields but were not different than controls. A significant quartic relationship between intensity and residual kidney weight was also extracted using polynomial analysis (Fig. **3a**). Further analysis showed the source of the drug effect to be the reduced kidney weights of animals given NMA compared to those given water (Fig. **3b**).

Testicular Weight

Two-way ANCOVA detected a main effect for drug ($F(2,84)= 10.93$, $p<.001$, $\eta^2=0.14$) and a significant field by drug interaction ($F(2,84)= 2.11$, $p<.05$, $\eta^2=0.14$) when covarying for age and bodyweight. Animals given 1 nT field + LA, 50 nT + NMA or 500 nT + LA all had reduced testicular weight relative to the other groups. Several field-treated

groups fed water (5, 10 and 500 nT + water) tended to have increased weight compared to controls (Fig. **4**).

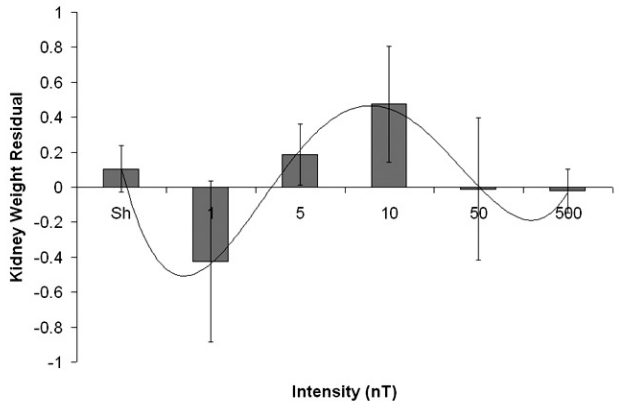

Fig. (3a). Residual mean and SEM for kidney weight by field treatment group. Superimposed on the means is the quartic function for the relationship.

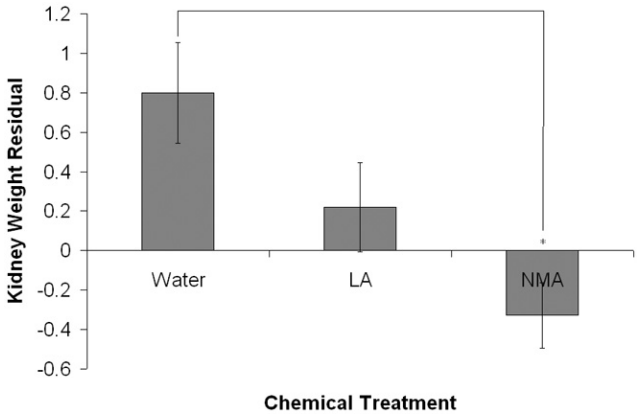

Fig. (3b). Residual mean and SEM for kidney weight by drug treatment group.

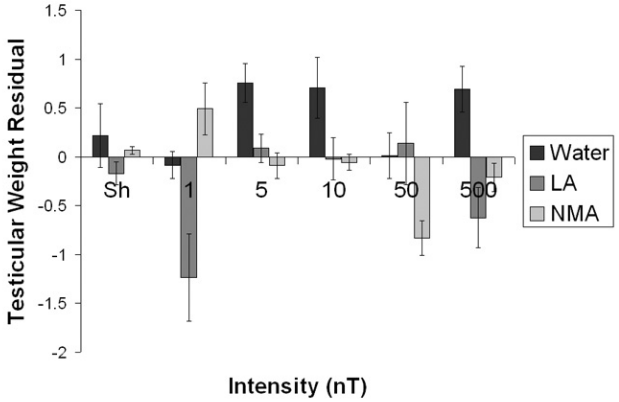

Fig. (4). Residual mean and SEM for testicular weight by field and drug treatment group.

Other Organs

Two-way ANCOVA detected no main effects, interactions or trends of field or drug treatment on pituitary, spleen, pancreas or adrenal weight.

Symmetry of Large Paired Organs

Two-way MANOVA was used to examine the effect of treatment on symmetry of large paired organs (adrenals, kidneys and testicles). No significant findings were obtained at the sample size employed.

Incidence of Health Ailments

Chi-squared analysis was performed on all qualitative observations. These included: 1) presence of external tumours; 2) presence of pituitary tumours; 3) occurrence of sudden deaths; 4) general symptoms (such as weight loss or respiratory distress). No significant findings were obtained.

DISCUSSION

Current MF exposure studies predominantly utilize power frequencies and are conducted within a limited timeframe (<90d). Here, physiologically-patterned MFs were used in a developmental investigation with an observation period that extended into late adulthood. This expanded scope showed long-term MF effects on bodyweight and brain weight of significant statistical power. Previously noted increases in testicular weight were also suggested. NO modulation tended to reduce kidney weight, but otherwise was inert and failed to show evidence of interactions with the MF.

One of the most revealing results, in addition to the finding that persistent effects resulted from a relatively brief exposure to weak MFs, was that a non-linear relationship existed between the effects of the MF and its intensity. If the quartic (sine wave) function shown in Figs. (**2** and **3a**) holds, it is possible that MFs may be much more effective than expected. MF intensities which traverse this range – including effective and non-effective intensities – might produce an "averaged" zero effect in the organism. This null or weak result could create the misleading impression that the MF is not biologically active. Similarly, MFs with intensities lying within the "zero" regions of the sine function – and not the "peak" or "trough" regions - would show no effect and appear benign. While the plot is technically non-linear, the lower intensity ranges (from 1-10 nT) are close in sequence and tightly adhere to the generated curve. Before definitive conclusions can be drawn about the 10-50 and 50-500 nT ranges, the intermediate intensities will have to be tested.

The concept that a large amount of substance produces a mild effect while a small amount of the same substance produces a large, specific effect is well-known in pharmacology. Within the range of high affinity to low affinity receptor subtypes, various concentrations of the same ligand can induce powerful and even opposite effects. This concept, clearly articulated in experiments on the cholinergic system and its associated muscarinic and nicotinic receptors, has been known to pharmacology for nearly 100 years but has yet to be embraced by bioelectromagnetics. These effects, while small in size, are very relevant when one considers the size of the populations that could potentially be exposed to these MFs.

As weanlings, rats exposed to 5, 50 or 500 nT 7 Hz MF show increased bodyweight [22]. Here, weight increases were found in very late adulthood. When age was accommodated, it was shown that exposure to only 50 nT 7 Hz MFs – and not 5 or 500 nT – increased bodyweight. Weight

changes with developmental MF exposure have not been widely reported and are likely specific to this waveform.

The basis of these bodyweight increases is difficult to ascertain. While changes in thyroid structure with MF exposure have been suggested [21], they are not evident in all cases [30] and their involvement here is unlikely. The 50 nT group which displayed the prolonged bodyweight increase did not appear to have heavier or otherwise abnormal thyroids. In future replications, the pursuit of behavioural correlates might be more revealing. Decreased overall activity may be a factor as might increased nutrient consumption.

Brain weight was increased by 10 and 50 nT 7 Hz MF independent of NO modulation. This increase was equivalent to the gender difference in brain weight between males and females (approximately 3%) in terms of strength but its source is unknown. If, as suggested by St-Pierre and Persinger [20] extra-cellular fluid volume is affected by developmental MFs, then the weight increase might be an increase in fluid rather than cells. The involvement of MF-induced increases in vasculature is a further possibility [31]. Lack of interaction of this MF effect with NO modulation in developing rats is consistent with past findings that suggest the brain is insensitive to NO inhibition [32] and L-arginine administration [33]. The absence of effects of NO modulation in this long-term study is notable when one considers the drastic effects that are observed shortly after the end of the treatment period, particularly in the case of perinatal NO inhibition [22,28,32,34]. With perinatal NO inhibition, strong reductions in size or growth [22,28,34] and changes in behaviour [22,28,32] are found. This study suggests that at least some of these effects are partly reversible.

In general, the effects of NO modulation were few and weak in strength. It is proposed that the long timeframe of the study (200-730d) eclipsed the window of sensitivity to NO modulation. Whereas relatively brief MF exposure produced a permanent alteration, prolonged NO inhibition might be required to induce an equivalent effect or interact with the MF effect. The only notable effect of perinatal NO modulation was the ability of NMA to decrease kidney weight. Interestingly, this trend is the reverse of what has been found to occur with chronic NO inhibition administered in adulthood [35]. The time at which NO modulation occurs might therefore determine the vector of effect on kidney mass.

Exposure to 5, 10 and 500 nT MFs tended to increase testicular weight while any NO modulation tended to reduce it. Selected field-treated groups given water (5, 10 and 500 nT) strongly tended to have increased testicular weight. This is in partial confirmation with past findings [19,21,36]. Age was shown to be a significant covariate and negatively correlated with testicular weight ($r = -.35$, $p<.001$). It is therefore possible that age-related decreases in testicular mass masked the MF's effects on these tissues.

Perhaps counter-intuitively, field intensity did not have a linear relationship with the effect of the MF. In the case of brain weight (Fig. **2**) and kidney weight (Fig. **3a**) the relationship was quartic. While non-linear relationships were described by Adey [37] decades ago there has been resistance to accommodating them in design and little progress in describing them using mathematical relationships. Predicting the efficacy of an MF using such relationships could optimize clinical therapies and minimize safety risks.

CONCLUSIONS

There has been relatively little variation in the design of MF developmental toxicology studies since the birth of bioelectromagnetics. The empirical evidence that physiologically-patterned MFs have heightened penetrability and the growing use of these fields in MF-based therapies suggests that investigations into their safety be performed and interpreted within their own context. Past findings of 50 and 60 Hz exposure studies do not appear applicable to these MFs, which have multiple biological effects not reported for power frequency fields. That these effects were noted at such a weak intensity and followed non-linear relationships testifies to the complexity of the interactions between MF and the biological system.

The findings herein suggest that physiologically-patterned MFs, and any other MFs in widespread use, must be explored specifically in custom-designed, long-term studies. They also reinforce the idea that peripheral and central changes can result from perinatal and prenatal MF exposure and that these may be as powerful and persistent as those arising from exposure to chemical teratogens.

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