Possible Effect of Geomagnetic Fluctuations on the Timing of Epileptic Seizures

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Key words: epilepsy; geomagnetism; magnetic field; seizure
Running head: Geomagnetism and epileptic seizure.

Summary

Some reports have suggested that epileptic seizures might occur more frequently at times of enhanced disturbance of the geomagnetic field. This study examines this putative association using 4101 seizures from 22 epileptic patients where the seizure times were known to within a day or better. A measure of the geomagnetic fluctuation level for the seizure day, and the days preceding the seizures, was derived from the geomagnetic index *ap*. This daily index was significantly higher on the seizure days than on the day prior to the seizures ($p = 0.007$) and slightly higher than for the preceding 10 days ($p = 0.1$). The effect size for the increase of geomagnetic activity on seizure days from the previous days was inhomogeneous across this group of patients ($p = 0.04$), suggesting an uncontrolled factor. However, a regression of age, sex, seizure type and frequency onto effect size failed to reveal any significant loadings.

Introduction

The reasons for the precise timing of epileptic seizures in most patients remain largely unknown. Statistical studies of seizure timing have failed to identify clearly non–random patterns such as clustering or periodicity in many patients (Taubøll et al., 1991; Milton et al., 1987). Several explanations for this have been suggested, including the postulation of an inherently random endogenous mechanism (Binnie, 1985) and the possibility that seizure occurrence might be more or less tightly coupled to an exogenous variable which itself had nearly random statistics. In considering the second of these hypotheses several workers have looked for a suitable environmental stimulus in the very low frequency region of the electromagnetic (EM) spectrum. EM waves with frequencies of 10^4 Hz or less have several natural sources, including lightning discharges and ionospheric phenomena, and exhibit a complex distribution in time (Matsushita & Campbell, 1967). These long wavelength EM emissions are detectable everywhere on the globe and penetrate buildings and conducting structures with little attenuation. Additionally there is some evidence that such low frequency EM fields can interact with the functioning of biological systems, though the question is far from settled (Adey, 1981: Marino et al., 1977). A connection between the triggering of epileptic seizure and low frequency EM radiation therefore has a certain *prima facie* plausibility.

Some reports have suggested that epileptic seizure frequency may be correlated with disturbances of the geomagnetic field (GMF) (Venkatraman, 1976; Rajaram & Mitra, 1981; Keshavan et al., 1981). Fluctuations in the GMF are primarily driven by changes in the sun's activity and major solar storms give rise to magnetic field changes of up to 1000 nT at the earth's surface and cover a range of frequencies from approximately 20 μHz to 10 Hz (Matsushita & Campbell, 1967). The literature on the effects of magnetic field exposure upon epileptic seizure, while not extensive, contains some suggestive avenues of research. Venkatraman (1976) originally suggested that there might be an association between magnetic storms and epileptic attacks but did not provide any statistics to support this conclusion. Rajaram & Mitra (1981) reported that monthly averages of admissions of epileptic cases rose during periods of increased GMF variation. However, no attempt was made to control for other factors which influence hospital admissions. According to Keshavan et al (1981) a decrease in convulsive threshold in rats was observed during the GMF variation associated with a solar eclipse. Persinger (1988) has suggested that increases in the GMF noise level suppress nocturnal melatonin levels, precipitating seizures and consequent cardiovascular instability. Significant correlations have also been reported between epileptic seizure onset and 10 kHz and 28 kHz atmospherics (Ruhenstroth–Bauer et al., 1984). However a laboratory study of audiogenic seizure susceptible rats failed to find an association between EM at these frequencies and seizure timing (Juutilainen et al., 1988). There is also evidence that exposure to relatively intense (10^5 nT) 60 Hz magnetic fields may actually inhibit electrically kindled seizures in rats (Ossenkopf, 1988).

Numerous biological effects from exposure to weak VLF and ULF magnetic fields have been reported, as is demonstrated in reviews of this literature such as those by Adey (1981) and Marino and Becker (1977). Interest in the area has recently been stimulated by concern with the possible carcinogenicity of the 50 and 60 Hz magnetic fields associated with power generation and distribution.

However, the physical mechanisms which might account for biological sensitivity to weak, low frequency, magnetic fields such as the GMF remain obscure. Adair (1991) has calculated the electric fields and other effects in cells and cell membranes consequent upon 60 Hz magnetic fields of larger amplitude (and frequency) than GMF fields. He finds that the induced electric fields are considerably smaller than the fields due to thermal noise. However his arguments do not entirely rule out interactions involving larger multicellular receptors. It is also possible that the putative association between enhanced GMF disturbance and epileptic seizure may not be caused by the magnetic field itself, but rather by some other environmental parameter (Bucha, 1991) which co–varies with the GMF changes. The physics of possible mechanisms for electromagnetic triggering of epileptic seizure is not well enough understood to suggest what frequency or amplitude of EM radiation might be responsible for such an effect. While the epidemiological literature suggests that a weak connection between seizure timing and enhanced GMF activity may exist, the evidence is not statistically assessable.

This study examines one of the hypotheses raised by the earlier literature, specifically whether epileptic seizure timing in humans is associated with increased GMF fluctuations at the time of the seizures. Seizure diaries from 22 epileptic patients, containing timings of 4101 seizures, were analyzed to see whether these events occurred at times of enhanced GMF activity. By using seizure diaries, rather than hospital admission records, many potentially confounding factors can be avoided. In the light of the earlier studies it was hypothesized that the days on which epileptic seizures occurred would show higher levels of GMF activity than that of the preceding days.

Methods

Patients

Seizure data consisting of dates, and in some cases times and dates, of seizures were obtained for a total of 22 patients. Data for patients 1 through 17 were collected from a study of the statistics of seizure timings (Taubøll et al., 1991). This data, referred to as TLG, comprised diaries of patients on a stable regimen of antiepileptic medication who recorded the daily number of seizures along with details of unusual activities, stress and alcohol consumption. In the TLG study, data from three patients was split into subsets due to medication changes, loss of data recording for a period, or intervening surgery. In this study these patients' data was treated as a unit, identically to the other patients' data, since there was no *a priori* reason to expect that the data subsets used would show a differentiation of response to GMF variations. The remaining five patient's data was collected for this study and was more heterogeneous. Patient RR1 had all seizures recorded by her parents during a 4 month period under medical supervision but prior to medication being prescribed. After being administered sodium valproate her seizures stopped. Patients NE1 to NE3 had their seizures recorded partly as in–patients and partly at home. The completeness of these recordings is not known. Finally patient WO1's seizures were recorded by a family member during two periods and are thought to constitute a complete and accurate recording. All seizures submitted were included in the analysis, except those which occurred after September 30th 1991 when *ap* index data was not available. The clinical data is summarized in table I.

Insert table I about here

Geomagnetic Field Data

The 3 hour geomagnetic *ap* index (Mayaud, 1980) was used as the primary measure of GMF activity. This index provides an estimate of the range of variation of the intensity of the GMF, in nT, during a 3 hour interval of universal time (UTC). The index is also a spatial average across the globe; the actual range of field strength variation observed at any location may be greater than the *ap* range at high latitudes and smaller at low latitudes. The *ap* index is an integer value in the range [0, 400] with the variance of the index increasing during magnetic storms. Since this behavior can violate assumptions of homogeneity of variance needed for *t* test used here, the *ap* index data was log transformed before the analysis. Owing to the persistence of the interplanetary particle storms responsible for the larger GMF disturbances, 3 hour and daily geomagnetic indices are auto–correlated. For instance the *Ap* daily index, consisting of the mean of the eight *ap* values for the day, has a Pearson correlation of $r = 0.48$ for data for 1980 though 1990 at one day's lag. This auto–correlation may ameliorate the effect of the lack of time of day information for some of the seizures.

Analysis

Since the majority of the seizures (3307 out of 4101) lacked time of day information, the temporal unit for the analysis was taken as a day and an index of geomagnetic activity for the day preceding the seizures was developed. The seizures for which a time of day had not been recorded were assigned to have occurred at 12 noon local time. This procedure results in a maximum error in the seizure time of 12 hours. All seizure times and dates were adjusted to UTC allowing for time zones and summer time where necessary. The average *ap* for the 24 hour period preceding the seizure was calculated by computing the mean of the (log transformed) *ap* values for the 3 hour UTC interval during which the seizure occurred and for the 7 preceding 3 hour intervals. The average daily indices for the previous days were computed similarly. The mean daily *Ap* index on the seizure day was compared with that for preceding two days with paired *t* tests of the log transformed indices. All statistical tests were calculated using SPSS–X software.

Results

GMF activity on the seizure days was compared with the activity of preceding days for the group of patients as a whole and for each patient separately. Grouping the data, the *Ap* index on the seizure day, 16.41 ± 20.2 nT, was slightly greater than for the preceding day, 16.01 ± 20.3 nT, (t [4100] = 1.84, p = 0.03). The index for the day prior to this, 16.09 ± 19.9 nT, was not significantly different from the seizure day (t [4100] = 0.55, p = 0.3). Neither was the index for the 10 days preceding the seizure, 16.43 ± 11.2 nT, significantly different from the seizure day index (t [4100] = 0.78, p = 0.2). The seizure diaries were recorded during intervals spanning the years 1977 to 1991 and covering more than one 11 year cycle of solar activity. Thus some diaries were recorded at periods of higher average GMF activity than others. For instance the mean *Ap* index for the 10 days prior to the seizure days for patient NE1 was 35.7 ± 16.9 nT, while that for TLG12 was 7.93 ± 2.1 nT. With the data combined into a single data set, GMF index changes between days will be masked by the large differences between the mean indices for the diaries. To avoid this, the differences in GMF index data between seizure and earlier days were analyzed for each patient separately. The results are shown in table II. The overall deviation from chance expectation for the group of patients can also be calculated from the individual patient's statistics by converting the t values to 1–tailed p values and then to z – scores which were combined by Stouffer's method. By this method, the *Ap* index for the seizure day was significantly greater than on the preceding day, (z = 2.48, p = 0.007) and greater, but not significantly so, than for the second day prior to the seizures (z = 1.21, p = 0.1), and for the mean daily index for the preceding 10 days (z = 1.08, p = 0.1). There is a wide range of patient t values ($-2.59 \le t \le 2.89$) present in the data. To analyze inter–patient differences, a measure of the difference in *Ap* index between the seizure days and the preceding days for each patient was defined which is independent of the number of seizures. The effect size $r = z / \sqrt{n}$ is such a measure, where z is the equivalent z – score for each patient's t value as computed above and n is the number of seizures recorded in the patient's diary. The overall effect size for the set of patients can be estimated as the weighted mean of the effect sizes and was found to be $\mu_r = 0.029 \pm 0.016$. This sample of 22 effect sizes was found to be inhomogeneous (χ^2 [21] = 33.3, p = 0.04) suggesting that the types of seizure or treatments represented in this data may exhibit intrinsically different responses to geomagnetic variations.

Insert table II about here

To investigate whether seizure type, sex and age of patients, or seizure frequency were significant moderating variables for the difference between *Ap* values on the seizure day, a linear regression was calculated between these variables and the patient effect size r. Using dummy variables for sex and seizure type, the regressions revealed no significant loadings for any of the variables. Given the small number of patients in the study the power of this analysis to uncover any real effects, if they exist, is small. It is perhaps worth

noting that the two patients who were unmedicated for at least part of the time of seizure data collection had relatively large effect sizes (RR1, r = 0.24 and WO1, r = 0.17, μ_r = 0.029 ± 0.016).

Discussion

The hypothesized association between epileptic seizure occurrence and increased GMF activity on the seizure day was confirmed in this data. However the observed effect size for the interaction was very small (r = 0.03). For comparison Cohen (1988) classifies effect sizes of less than 0.2 as small. Although this result has confirmed the earlier studies as regards the existence and direction of the GMF – seizure effect, the very small effect size observed and the absence of an established theoretical background for very low frequency EM fields as seizure promoters suggest that the present result should be treated cautiously. However the inhomogeneity of the sample of effect sizes suggests that there are uncontrolled factors effecting the interaction between GMF fluctuation and seizure occurrence. Whether these factors are characteristics of the patients or possibly of other environmental stimuli could not be determined in this study.

Research in neurobiology in general and epileptology in particular involves the almost impossible task of differentiating direct from indirect effects. Such unusual phenomena as seizures induced by tooth brushing or the smell of perfume but not foul odors exemplify the specificity of triggers in particular patients. Moreover, more general phenomena such as stress itself have been noted to increase the risk of seizures in many. These non–specific triggers may play only indirect roles by pathophysiologic cascades influencing neurotransmitter systems or electrical firing. Such phenomena (Neppe & Tucker, 1992) are even more difficult to determine because they may effect only a small proportion of epileptics.

These comments clearly have relevance with regard to geomagnetic influence. This could conceivably correlate with weather patterns. Cloudiness has been regarded as a possible correlate with depression. Heat intolerance can cause irritability. Indirect geomagnetic influences may turn out impossible to differentiate from direct ones but may lessen the power of tests to quantify statistically as other influences may also be confounding issues. Moreover, we know that certain patients may have their seizures triggered by events which do not influence others. Consequently, geomagnetism may play a role in a small proportion of patients and such actors as anticonvulsants may prevent this role powerfully. Thus, the profound results with the limited medicated patients may not be coincidental and serves as an excellent group for further research.

The decision not to control for anticonvulsant blood levels in our subjects merits further comment. Although serum concentrations of agents known to be pharmacologically active against seizures might appear to be the single most important variable affecting seizure frequency, there are several reasons for believing that this is probably not the case. In the majority of patients, anticonvulsant levels remain stable over time, especially when medications are administered chronically. Secondly, it is well known that patients respond differently at similar serum concentrations (Neppe & Tucker, 1992), and thus for

any given concentration, some patients will seize and others will not. Furthermore patients TLG1 to TLG17 had their antiepileptic drug levels measured at least once during the study with serum concentrations within the therapeutic range. Multiple blood samples were drawn from patients TLG1, TLG4 and TLG6 and no significant changes in the serum concentrations were observed and no relation to seizure frequency could be demonstrated. Thus variations in serum concentrations are unlikely to be a major determinant of seizure timing for the patients in this study.

Many avenues of further investigation exist. If the seizure promoting effect of GMF fluctuations is really due to very low frequency EM, a relationship between magnetic latitude and effect size might be expected, since the amplitude of geomagnetic disturbances generally increase at higher latitudes. Recently Randall (1990) reported just such a latitude dependence in correlations between GMF disturbance and conception rate. Unfortunately the seizure data studied here come from only four locations, with 17 of the 22 patients at just one latitude. Thus the question of latitude dependence cannot be tested with this data. Another promising approach would involve studying epileptic seizures in a medical facility, where precise timings of seizures and EEG monitoring and seizure detection was possible. Such observations combined with broad spectrum measurements of low frequency EM field excursions might answer the question of electromagnetic stimulation of epileptic seizures.

Acknowledgments: We thank Drs. Edwin C. May and Jessica Utts for assistance with the statistical design and Ms. Sarah Ryer for providing the original stimulus for this research.

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Table I––clinical data

Patient ID	Sex	Age	Seizure Type[a]	Medication[b]
TLG1	M	48	GTC	PTH
TLG2	F	40	CPS + 2^{o} GTC	CBZ
TLG3	M	28	CPS	CBZ + VPA
TLG4	M	31	CPS	PHT + CBZ
TLG5	F	36	A	PRIM + PB + (CZP)
TLG6	M	29	CPS	CBZ + PHT
TLG7	M	4	SPS + 2^{o} GTC	CBZ + PHT
TLG8	F	40	GTC	PHT
TLG9	M	22	CPS + 2^{o} GTC	VPA
TLG10	F	34	SPS + 2^{o} GTC	VPA
TLG11	M	14	CPS + 2^{o} GTC	CBZ + VPA + NZP
TLG12	F	21	CPS + 2^{o} GTC	CZP
TLG13	F	26	SPS	CBZ
TLG14	F	34	CPS	PHT + PB + CBZ
TLG15	M	44	CPS	PHT + PB + CBZ
TLG16	F	52	CPS	PRIM + CBZ
TLG17	F	49	CPS	PHT
RR1	F	5	A	UM
NE1	M	1	IS + CPS	ACTH + VPA
NE2	F	7	CPS + 2^{o} GTC	DPH + CBZ
NE3	F	26	GTC	DPH
WO1	F	31	CPS	UM, VPA

[a] Seizure types are designated: A, absence seizure; CPS, complex partial seizure; GTC, generalized tonic–clonic seizure; 2^{o} GTC, secondary generalized tonic–clonic seizure; IS, infantile spasms; SPS, simple partial seizure.

[b] Medications are designated: ACTH, adrenocorticotropic hormone; CBZ, carbemazepine; CZP, clonazepam; DPH, diphenyl hydantoin; NZP, nitrazepam; PHT, phenytoin; PB, phenobarbital; PHT, phenytoin; PRIM, primidone; VPA, Na–valproate; UM, unmedicated.

Table II––seizure data

Patient ID	Period of data col.	No. of seizures	Seizure freq.	Epoch –1[a] *t*	Epoch –1 *p*	Epoch –2[b] *t*	Epoch –2 *p*	Epoch –1 *r*
TLG1	205	7	0.034	1.03	0.17	3.10	.01	0.359
TLG2	574	320	0.56	0.70	0.24	–0.28	.61	0.039
TLG3	182	42	0.23	–2.59	0.99	–3.08	.998	–0.382
TLG4	300	13	0.043	2.08	0.031	1.85	.045	0.518
TLG5	268	1449	5.4	0.41	0.34	–0.50	.69	0.011
TLG6	370	130	0.35	0.30	0.38	–1.87	.97	0.026
TLG7	482	11	0.023	0.06	0.48	–0.23	.59	0.018
TLG8	174	7	0.040	1.20	0.14	0.35	.37	0.412
TLG9	293	82	0.28	0.55	0.29	–1.13	.87	0.060
TLG10	323	17	0.053	–0.12	0.55	0.86	.20	–0.029
TLG11	180	49	0.27	0.48	0.32	0.17	.43	0.068
TLG12	182	17	0.094	0.79	0.22	2.80	.0064	0.187
TLG13	320	101	0.32	1.81	0.037	0.44	.33	0.178
TLG14	724	133	0.18	–2.08	0.98	–2.41	.99	–0.179
TLG15	2360	768	0.33	0.61	0.27	–0.62	.73	0.022
TLG16	166	71	0.43	0.93	0.18	0.40	.35	0.11
TLG17	185	12	0.065	–0.93	0.81	–0.02	.51	0.257
RR1	111	36	0.32	1.48	0.074	2.13	.020	0.241
NE1	87	167	1.9	–0.22	0.59	–0.28	.61	–0.017
NE2	5164	109	0.021	–1.15	0.87	–1.74	.96	–0.11
NE3	563	281	0.50	1.45	0.074	3.29	.00057	0.086
WO1	62	276	4.5	2.89	0.0021	3.64	.00016	0.172

[a] Epoch –1 refers to comparisons between the day of the seizures and previous days.
[b] Epoch –2 refers to comparisons with the day 2 days before the seizure day.