THE RADIOLOGICALLY ISOLATED SYNDROME IS THE LAST LINK OF THE CHAIN FOR UNDERSTANDING THE ETIOLOGY OF MULTIPLE SCLEROSIS DISEASE

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Abstract

The increase in the dense and frequent use of the magnetic resonance imaging (MRI) device has led to incidental identification of abnormalities in the central nervous system (CNS). In the past five years, significant discussions have been made on the development of the radiologically isolated syndrome (RIS) which is highly suggestive of multiple sclerosis (MS) disease.In the authors' previous researches, the dielectrophoretic force has been found as the essential cause of MS disease by using seven different ways. This study aims to prove that radiologicallyisolated syndrome is the major clue to approve the authors' hypothesis on the etiology of MS disease and is also the very last link of the chain.The specific absorption rate concept (SAR) and Clausius-Mossotti equation for the myelin basic proteins(MBP) in the white, gray matter and the cerebrospinal fluid has been used to explain the cause of RIS.The RIS occurs due to dielectrophoretic force controlled electromagnetic fields of MRI scanners. MS occurs due to dielectrophoretic force by uncontrolled or controlled electromagnetic fields of weak or higher artificial and natural electromagnetic field sources.The RIS is not a syndrome suggestive of MS. In other words, RIS is the accelerated form of MS.

Keywords: Dielectrophoretic force, etiology, MRI, multiple sclerosis, RIS

Introduction

The increase in the dense and frequent use of the Magnetic Resonance Imaging device, which plays a significant role in the diagnosis of Multiple Sclerosis disease, has brought along new concerns. MRI symptoms which can anticipate multiple sclerosis disease in individuals who do not have typical multiple sclerosis symptoms and have normal neurologic symptoms are defined as radiologically isolated syndrome (RIS). According to radiological findings, there is a similarity between RIS and multiple sclerosis. This study investigates unaccountable syndromes which result in MRI tests imitating MS disease, named for the first time as RIS by (Okuda, 2009) and observed by other researchers (Lebrun 2011, Siva 2009, Stefano 2013).The peripheral nerve stimulation (PNS) is studied by some researchers (Liu, 2003) as a result of nerve stimulation by time-varying gradient electromagnetic fields during MRI scans.

For some researchers, RIS is a new and complex entity and there are some fundamental issues that need to be answered in order to clarify its association with MS. Some comprehensive epidemiological studies have been conducted in order to understand the reasons for these syndromes (Granberg, 2012).Several researchers have posed the following questions regarding these unclear cases in order to emphasize the complexity of the issue.Some researchers asked: “How much radiologically isolated syndrome suggestive of multiple sclerosis is multiple sclerosis?”(Lana, 2012). “The radiologically isolated syndrome: take action when the unexpected is uncovered?”(Sellner, 2010).“The radiologically isolated syndrome dilemma: just an incidental radiological finding or presymptomatic multiple sclerosis?”(Stefano, 2013). Many researchers have confirmed the recently developed concept of RIS patients who present features to similar MS patients. Naturally, occurring in the diagnosis of MS disease and having a complex and unclear etiology, these syndromes complicate the issue further and result in new syndrome names.

This study explains that the syndrome named as RIS, which occurs following the applications of MRI and imitates MS disease, results from a dielectrophoretic force which I stated in my previous researches to be the main cause of MS disease (Canbay 2010, Canbay 2013). Furthermore, RIS is a major clue to approve my hypothesis about the etiology of MS and the last issue to be resolved in order to prove this hypothesis.

Methods

This study proves that syndromes following MRI examinations and are defined as Radiologically Isolated Syndrome (RIS) and have MS-like symptoms, arise from a dielectrophoretic force. Using various methods and approaches,I have proven that this is the main cause of MS disease. Although scientific evidence completely supports the issue, this last evaluation made regarding the RIS-MS relationships can be regarded, without any doubt, as the last stage in the etiology of MS disease. I have shown in my previous researches that dielectrophoretic force is the maincause of MS disease and this fact can be proven through various approaches. To contribute to a better understanding of this issue, these approaches can be summarized as follows:

1-The effect of the dielectrophoretic force on Myelin Basic Protein (MBP) was determined in white matter, grey matter and cerebrospinal fluid (CSF) by use of Clausius-Mossoti equation as shown in Figure1,Figure 2.Since the MBP, has a molecular weight of 18.5 kDa, a radius of 1.525 nm and an adhesion force of 0.05 mN/m between MBP and the nerve cell, the dielectrophoretic force at some frequencies and under long term exposure conditions, pulls off the MBP from the nerve cell (Canbay, 2010).

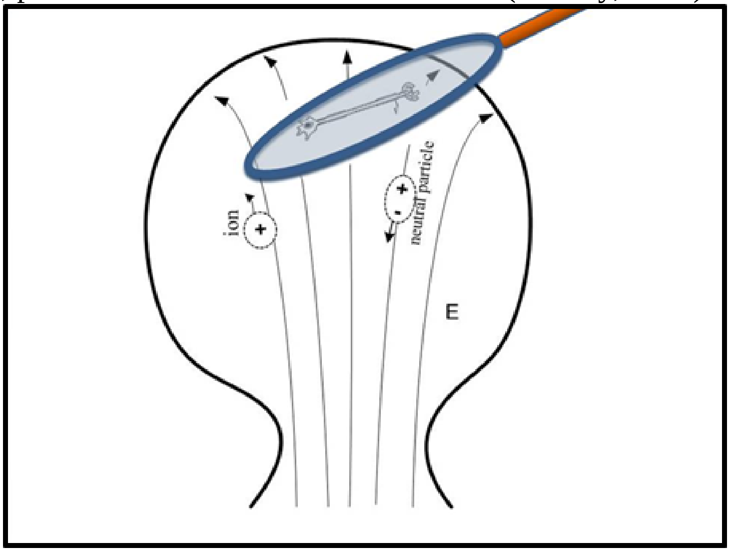


Figure 1. Dielectrophoretic field affecting an ion and a dielectric particle in schematic representation of human head.

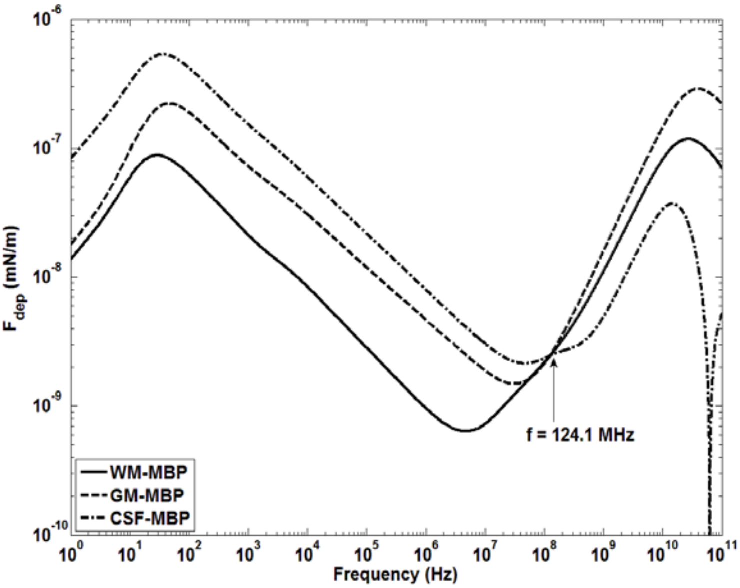
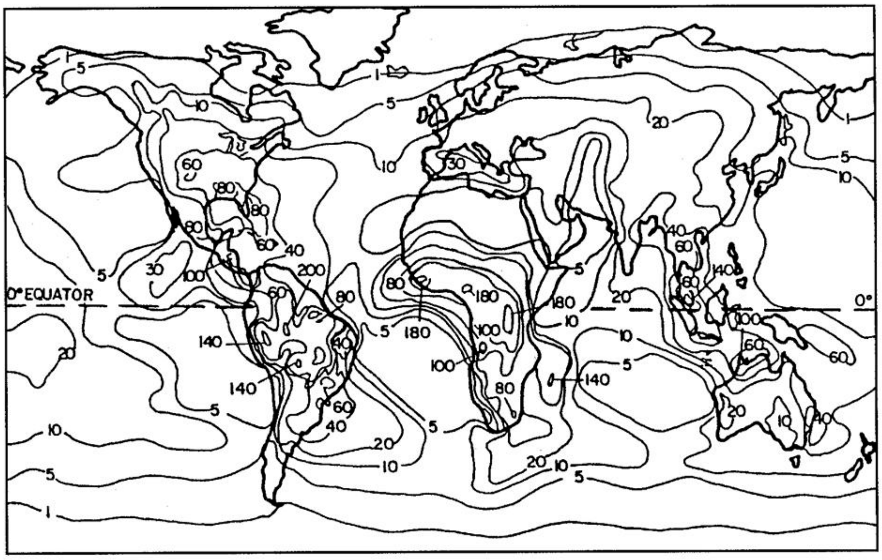


Figure 2. Variations of dielectrophoretic force, affecting MBP in white matter, gray matter and CSF with respect to frequency, $(10^0\text{-}10^{11})$ Hz.

2-Electromagnetic field distribution, which results from natural electromagnetic field resources, even when there is no artificial electromagnetic field resource, induces an electromagnetic field in the human body. It can be said that lightnings, which form the final structure of electrosphere, lead to an electromagnetic field distribution released at Schuman frequencies in the electrosphere. The Schumann Resonance is a set of spectrum peaks in the ELF portion of the Earth's electromagnetic field spectrum. The nominal average the Schumann Resonance frequencies are observed 7.8, 14, 20, 26, 33, 39, and 45 Hz with slight diurnal variations. The maximum dielectrophoretic force in the human brain occurs at around of the Schumann Resonance frequencies. When the Schumann Resonance frequencies are compared with the results of Clausius-Mossotti equation as shown in Figure 2, it is clear that the history of MS disease is as old as the history of humanity(Canbay 2010, Canbay 2013).

3-After a lightning, the local electric field intensity approaches the fair air electric field intensity level. As a result of this, a relaxed medium occurs. The fair air conditions provide minimum electric field intensity in our environment. On thecontrary, cloudy weather conditions provide higher electric field intensity in the medium.

In the comparative study between keraunic map of the world prepared by IEEE and the common report of the WHO (World Health Organization) with MSIF (Multiple Sclerosis International Federation) dated 2013 (MS Atlas WHO-MSIF, 2008 and 2013), we can find some clues in answering the question "why some places have higher risk with respect to other places in terms of prevalence of Multiple Sclerosis disease". Figure 3 and Figure4 show that Multiple Sclerosis inversely proportional to the number of annual lightning. Generally, we don't need to investigate the prevalence of MS disease in South America and Africa. According to my hypothesis, most of countries in these continents have to be painted in blue and dark blue colors.The comparison of the keraunic map in Figure 4 with the epidemiological map in Figure 5 and the consideration of the aforementioned data support my hypothesis. Sardinia, Orkney and Faroeaislands can be assumed as risky places in terms of multiple sclerosis disease (Canbay, 2014).



Source: World distribution of thunderstorm days, Part II,
published by World Meteorological Organization (1956)

Figure 3. The keraunic map (Canbay, 2010).

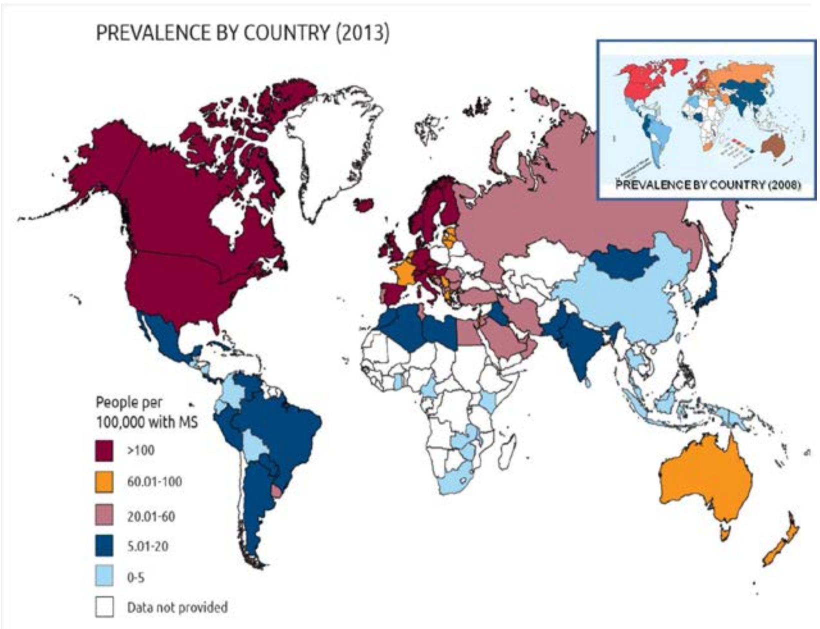


Figure 4. The distribution of MS in the world2013 (MS Atlas WHO-MSIF, 2008 and 2013).

4-The dielectrophoretic force is capable of separating lipids of proteins from the nerve cell and accumulating the separated protein particles at places where the gradients of square of electric field reach their maximum values in the human body. MS symptoms also can be observedin the same places (Canbay, 2013). Since the gradients of square of electric field in the brain of animals with four legs or without legs is approximately equal to zero (Figure 5). MS disease is not observed in these animals. MS is a disease of human`s disease and will remain so in the future as well. There will not be any advantage and requirement of laboratory studies concerning animals in terms of understanding the etiology of MS disease (Chen, 1986). The mice cannot be used in the MS disease-related experiments.

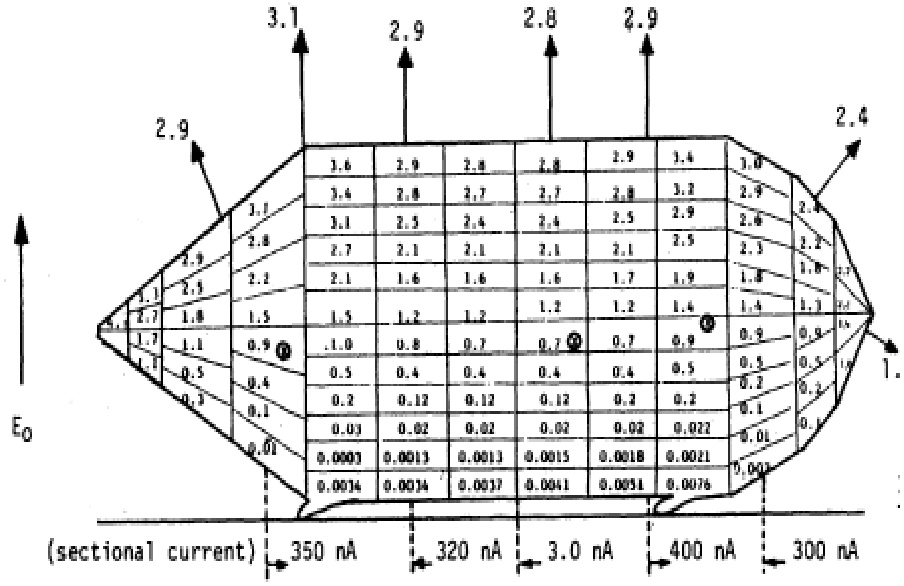


Figure 5. Distribution of induced current density (nA/cm^2) in a rat (Chen, 1986).

5-The connection between electromagnetic pollution and asthma, diabetes, multiple sclerosis, chronic fatigue, fibromyalgia has been investigated in the study (Havas, 2006). In this study, GS(Graham/Stetzer) filters, microsurge meters operating at ELF and RF frequencies were used to reduce and monitor the dirty electricity inside the building where the patient lived. The observation results show that the symptoms of these disorders were reduced.

6-The interaction between the neurons and electromagnetic fields can be investigated by in vitro experiments. For example, as shown in Figure 6 and Figure 7, the fetal cortical rat neurons were trapped in the center of an electrode arrangement operating at different amplitudes and frequency ranges (Heida, 2001).

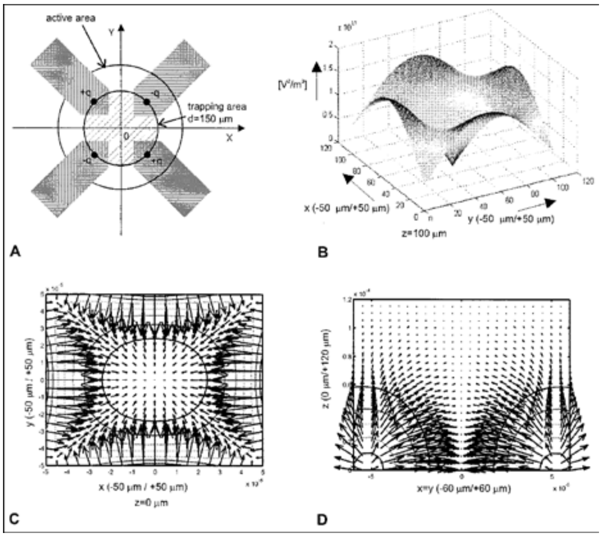


Figure 6. (A) The electrode structure represented by four point charges. The point charges are located at 100 μm from the center and are given such a value that the potential at a distance R = 50 μm (a distance equal to the "diameter" of the electrode tips) from these points is 5 V (or -5 V). (B) The relative dielectrophoretic force in the xy plane at z = 100 μm. The square of the electric field (the solid lines, contours, give the iso-electric field lines) and the gradient of this field (arrows) in (C) the xy plane at z = 0 μm, and (D) the (x = y)z plane at z = 0 μm (Heida, 2001).

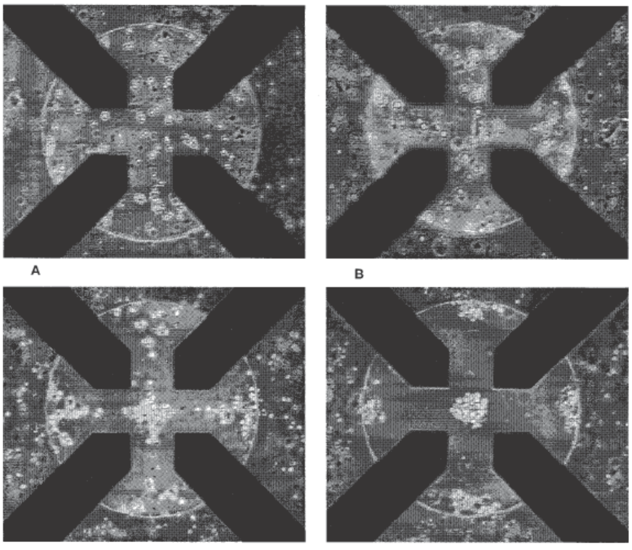


Figure 7. Image nr.180 of several experiments using different amplitudes (i.e., the situation after 30 min. of field application). (A) No input signal (reference experiment), (B) 1 V/12 MHz, (C) 3 V/12 MHz, and (D) 5 V/12 MHz(Heida, 2001).

7-A volcano in Iceland erupted in March of 2010. The lavas, volcanic ash plumes and the highest concentration of aerosols (tiny airborne particles, sulphur dioxide) in the ash plume spread into the atmosphere. As shown in Figure 8, the sulphur dioxide plumes located at higher altitudes are less affected by winds and concentrate on a strip over the Faroe and Oerkney Islands. The reason for higher concentration of aerosols on this strip over the Faroe and Oerkney Islands is the dielectrophoretic force over this region, just as in the brain, as conceptually expected to be by the author (www.ssd.noaa.gov/VAAC, 2011).

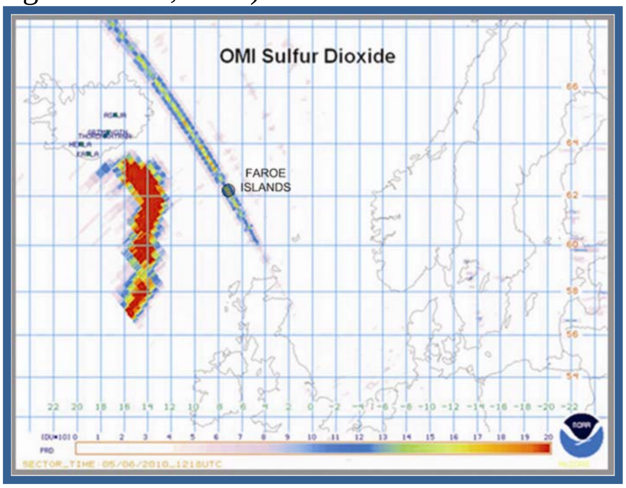


Figure 8. Distribution of the sulphur dioxide plumes in the electrosphere (www.ssd.noaa.gov/VAAC, 2011)

SAR ratios (SARR) and dielectrophoretic force in an MRI scanner

The result obtained from these summarized evaluations supports the very clear relationship between MS disease and dielectrophoretic force. In magnetic resonance, time varying gradient magnetic fields may stimulate nerves by inducing gradient electric fields in human body. The movement ofthe dielectric particle within the liquid in any gradient electrical field depends on the particle diameter, the dielectric permittivity of the liquid and the particle, andthe electric field intensity. The Clausius-Mossoti equation can be used to find the force that acts on adielectric particle.

$$\mathbf{F}_{DEP} = 2\,\pi\, r_p^3\ \varepsilon_0\, \varepsilon_m\, \mathrm{Re}\big[K(\omega)\big]\,\nabla\,(\mathbf{E}\cdot\mathbf{E})\ \ (\mathrm{N}) \qquad (1)$$

wherer_p is the particle radius, ε_0 is the permittivity of free space, ε_m is the real part of the permittivity of the suspending medium, and E isthe electric field intensity.

In MRI applications, it is very important to minimize the dielectrophoretic force for MS disease. The Clausius-Mossoti factor $K(\omega)$ depends on the complex permittivity of both the particle and the medium and is a measure of the effective polarizibility of the particle. The real part of the Clausius-Mossoti factor gives us information about the frequency dependence and the direction of the DEP force(Figure 9**)**. When $\mathrm{Re}[K(\omega)] >$

0, particles are attracted to regions of stronger electric field when their permittivity exceeds that of the suspension medium. This is called positive dielectrophoresis (p-DEP). When permittivity of the suspendingmedium is greater than that of the particles, this results in motion of particles to lesser electric field (Re $[K(\omega)] < 0$), as observed in Figure 6C. This is called negative dielectrophoresis (n-DEP). The programs Mathcad, Matlab and Sigma-Plot were utilized to plot the expressions of interest.

CSF: Cerebrospinal Fluid, SC: Spinal Cord, GM: Grey Matter, WM: White matter: Re(K): Real part of the Clausius-Mossoti factor.

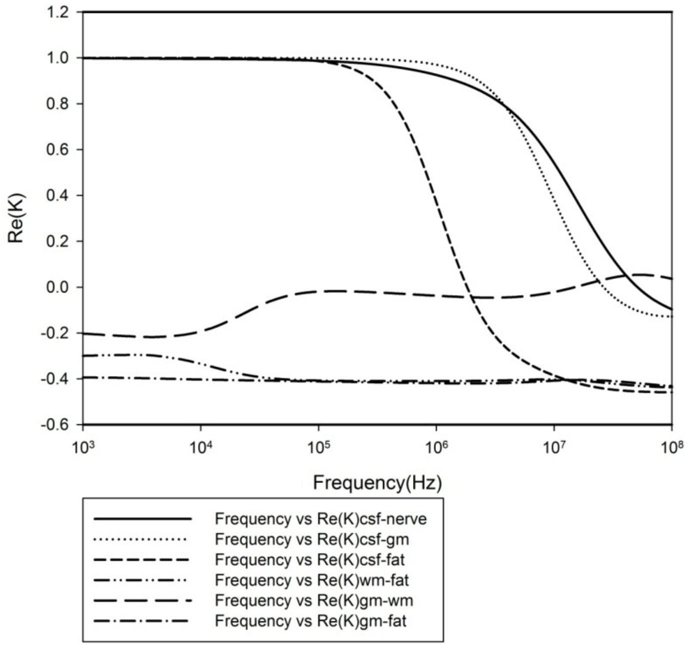


Figure 9. Variation of the Re(K) versus frequency, (10^3-10^8) Hz.

The general concept of the gradient system in MRI scanners is used to provide the image of a biological slice. Although the peripheral nerve stimulation has been known as a reality, the main cause of the peripheral nerve stimulation in MRI scanners has not been fully understood. In order to reduce the effect of nerve stimulation due to time varying electromagnetic fields of the MRI scanners with gradient coil, new types of gradient coils creating multiple, approximately linear gradient regions that oscillate in gradient polarity have been developed(Liu 2003, Parker 2006).

The gradient electrical fields occur as a result of discontinuity along the interface between two biologic tissues and also as result of the gradient effect based on the electrical field polarization generated by the gradient and the radio frequency(RF) coils. These effects cause a change in the Clausius-

Mossoti force which acts on the dielectric particle within the medium. As shown in the equation (1), this force is correlated with the gradient of the squared electrical field. In other words, the Clausius-Mossoti force is proportional to the gradient of the Specific Absorption Rate (SAR). The SAR can be written as

$$SAR = \int \frac{(\sigma_{LF}(r) + \omega \varepsilon_0 \varepsilon_r^{''})}{\rho(r)} (\mathbf{E} \cdot \mathbf{E}^*)\, dV \text{ (Watts/Kg)} \qquad (2)$$

where σ_{LF} is the conductivity of the medium at low frequencies, ω is the angular frequency, ε_0 isthe absolute dielectric permittivity of vacuum, ε''_r is the imaginary part of the dispersive relative dielectric permittivity of the medium, ρ is the density of the medium, and E* is the complex conjugate of the electric field intensity.

The Clausius-Mossoti force affects and polarizes MBP in the media such as CSF, GM and WM within the human head. This force also separates MBP from nerve cells under appropriate conditions and gets MBP collected in certain fields as in approach no. 1. The region no. 1, in Figure 10 can be considered as a layered-sphere (brain) with GM, WM and surrounded by CSF. The region no. 2 in Figure 10 can be considered as a layered, long and cylindrical structure, through the center of which nerve fibers pass. The ratio of squared electrical fields or the ratio of SARs (SARR) between two media in cases which spherical and cylindrical diameters are smaller compared to wavelength of electromagnetic wave incident upon the sphere and cylinder are given (Joines, 1984). Consider the electromagnetic (EM) wave propagating within each tissue with the electric field vector parallel to the interface between two tissues. Thus, the direction of propagation can be either parallel or perpendicular to the common interface. The case of the electric field polarization vector parallel to the surface of intersection is very effective when compared to other cases.

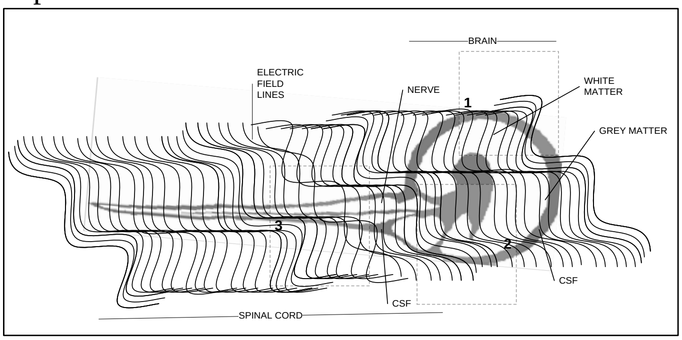


Figure 10. Schematic representation of the brain and the spinal cord in the gradient electromagnetic fields of an MRI scanner.

The results, as shown in Figure 11 and Figure 12, can be found if SAR ratios are calculated considering the dispersive properties of two media.

In case of SARR=1, there will not be any gradient electric field because of the nature of biological tissues.

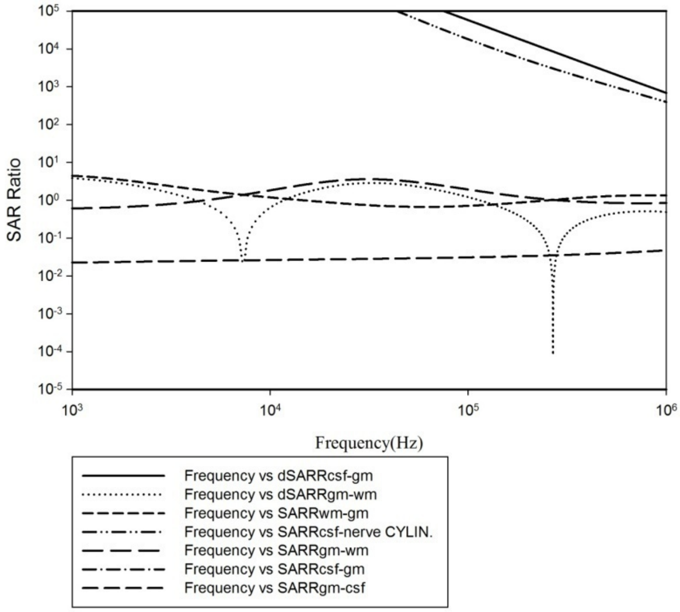


Figure 11. Variation of the SARR versus frequency, (10^3-10^6) Hz.

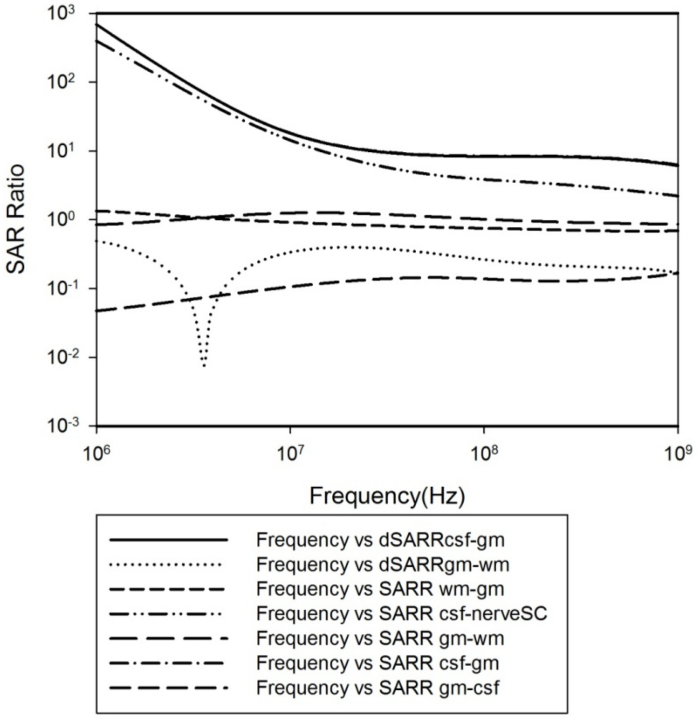


Figure 12. Variation of the SARR versus frequency, (10^6-10^9) Hz.

When compared the SAR ratios, it is seen that in the CSF-GM and GM-WM transition directions has a more effective power flow. This explanation is valid only in case of the electrical field changes as sinusoidal. However, the pulse modulation results can be easily estimated using the results of the sinusoidal variations. As shown in Figure 11 andin Figure 12, the ratio between power fluxes on CSF-GM boundary decreases swiftly with increase in frequency. As $Re[K(\omega)] > 0$ up to f=27.2 MHz in CSF-GM transition zone and within GM, MBP orientation and mobilization is proportional to the direction in which electromagnetic field intensity increases and the exposure time. In this condition, higher MBP levels in the CSF should be expected (positive dielectrophoresis). As $Re[K(\omega)] < 0$ in applications with higher than f=27.2 MHz, the dielectrophoretic force is prevailing in CSF-GM and CSF-NERVE(Spinal Cord) transition direction and MBP orientation and accumulation should be expected in the same direction. As a difference between the SAR ratios is minimum at 14.96 MHz and 196 MHz ($Re[K(\omega)] = 0$) in GM-WM and WM-GM transition directions where nerve cells are densely found, these frequencies and surroundings should be used in MRI examinations. As shown in Figure 11, there will be a MBP orientation and accumulation that is proportional to GM-WM and the difference in the reverse direction. The real part of the Clausius-Mossoti factor within the spinal cord and between 10^3-10^9 frequencies will be zero at f=51.6 MHz. $Re[K(\omega)]$ takes higher and positive values up to f=51.6 MHz, as f>51.6 MHz frequencies, it becomes $Re[K(\omega)] < 0$ and the value is around -0.15. In addition, the dielectrophoretic force resulting from electromagnetic fields with gradient which are formed by the coils will play a significant role in determining on MBP the orientation and the accumulation zones. According to Figure1 and Figure 11, taking into account the skin depth problem, the brain MRI scanners has to be operated at the suitable frequencies.

The electric field distribution formed by MRI radio frequency and gradient coils, as shown in Figure 13d (Liu, 2003)can be calculated by using the Maxwell equations.The gradient electric field in the laboratory experiment (Figure 6) and (Figure 7) (Heida, 2001) and the MRI examinations has a very intensive effect on MBP. MBPs (like nerve cells polarized and collected within half an hour in the laboratory conditions(Heida, 2001)) will accumulatein the direction where the gradient of square of the electrical field is at its maximum. When the brain and spinal cord are located in the natural or artificial electromagnetic fields,(Figure 13), as explained in the approach1, in the laboratory experiment (Figure 6) and (Figure 7) and in the MRI radio frequency coils (Figure 13), they can be understood to be under similar conditions in terms of the occurrence of dielectrophoretic force.

The electric field intensity in the brain and spinal cord under normal conditions is lower when compared to the electrical field intensity under the brain and spinal cord in the gradient and radio frequency coils of MRI scanners. Ifsuitable conditions occur for developing of MS disease, the accumulation of MBP will also occur over the years.

Considering the results mentioned with the sixth approach, it will be easy to understand that the force that acts on the nerve cells of the brain within the gradient electric field and RF coils environment is the dielectrophoretic force in the first approach. Furthermore, the anatomicalnarrowing of CSF towards the back of the brain results in a rapid change in the gradient of square ofthe electrical field in the CSF-GM-WM transition zone. The narrowing of CSF towards that field makesthe region more sensitive to MBP motion. This region, which is related to the vision function of the brain, is where the gradient of the electrical field induced in the human body as a result of external electrical field is at its maximum.

The idea of RIS that emerged as a result of MRI practices is neither a new symptom imitating MS nor an anticipated one. Clearly, RIS can be accepted as the laboratory results of the dielectrophoretic force. In this test, as the Clausius-Mossoti factor was Re(K)<0, nerve cells were collected in the direction of decreasing electric field; in other words, in the center of the electrode array. Figure 6 presents the electric field distribution and illustrates where nerves collect and shows the number of nerves based on the exposure time of the electrical field (Heida, 2001).

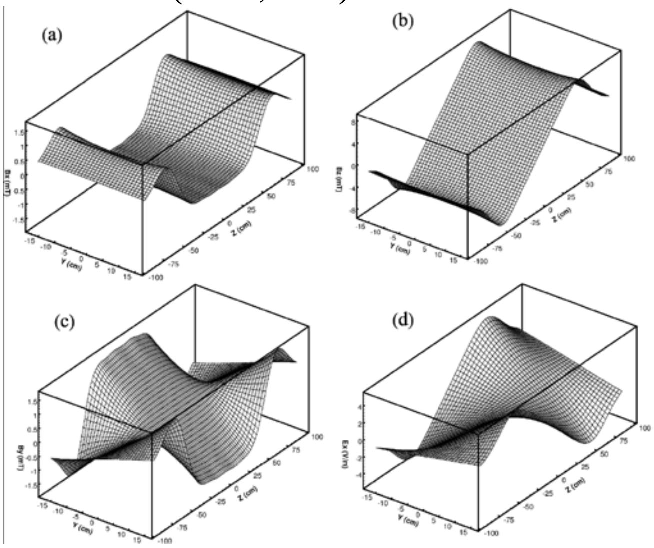


Figure 13. The contour of the induced electromagnetic fields produced by cylindrical Z-coils. (a)–(c) Magnetic fields in the X = 0:1 m plane. (d) Electric field (E) in the X = 0 plane (Liu, 2003).

Similarly,considering that the brain and the spinal cord are placed within the electrical field of the gradient and RF coils of MRI, as shown schematically in Figure 13, an aggregation of MBPs within the cerebellum and spinal cord based on the gradient of the squared electric field will be ensured.The force which creates MS over several years in direction of CSF-GM-WM, is the same dielectrophoretic force that also creates RIS. However, the electric field intensity and the gradient of the squared electric field in an MRI scannerare more powerful. Therefore in the laboratory, the collection or orientation of the MBPs within half an hour, where the gradient of the squared electric field is at its maximum occurred because of the same dielectrophoretic force.

Whereas, within a human brain that is under the effect of weak dielectrophoretic force, the collection of MBPs occurs very slowly due to the same reasons, and the observation of symptoms of MS take 20-30 years. No one can ever expect to prove such a long-term process by observation. As demonstrated, RIS and PNS concepts are very important as they contribute to the revelation of the fact.

Conclusion

The main cause of Multiple Sclerosis disease is the dielectrophoretic force in the brain depending on the electromagnetic environmental factors. The other causal factors such as genetic, immunologic factors have secondary importance. Every symptom in MS disease can be explained by this hypothesis. The RIS is not a syndrome suggestive of MS. The RIS occurs due to dielectrophoretic force controlled electromagnetic fields of MRI scanners. MS occurs due to dielectrophoretic force by uncontrolled or controlled electromagnetic fields of weak or higher artificial and natural electromagnetic field sources. In other words, RIS is the accelerated form of MS. Therefore, the brain MRI should not be applied without requirement. The choice of the frequency and homogeneity in the gradient and RF coils in MRI scanners is very important. Although it is known that the reason for MS is dielectrophoretic force, successful ways and methods of treatment and methods should still be applied in treatment of MS. I will elaborate on this issue in my further studies. I would like to underline once more that multiple sclerosis disease is not a modern day disease, in fact it is as old as mankind itself.

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