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Could Myelin Damage From Radiofrequency Electromagnetic Field Exposure Help Explain the Functional Impairment Electrohypersensitivity? A Review of the Evidence

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COULD MYELIN DAMAGE FROM RADIOFREQUENCY ELECTROMAGNETIC FIELD EXPOSURE HELP EXPLAIN THE FUNCTIONAL IMPAIRMENT ELECTROHYPERSENSITIVITY? A REVIEW OF THE EVIDENCE

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Myelin provides the electrical insulation for the central and peripheral nervous system and develops rapidly in the first years of life, but continues into mid-life or later. Myelin integrity is vital to healthy nervous system development and functioning. This review outlines the development of myelin through life, and then considers the evidence for an association between myelin integrity and exposure to low-intensity radiofrequency electromagnetic fields (RF-EMFs) typical in the modern world. In RF-EMF peer-reviewed literature examining relevant impacts such as myelin sheath, multiple sclerosis, and other myelin-related diseases, cellular examination was included. There are surprisingly little data available in each area, but considered together a picture begins to emerge in RF-EMF-exposed cases: (1) significant morphological lesions in the myelin sheath of rats; (2) a greater risk of multiple sclerosis in a study subgroup; (3) effects in proteins related to myelin production; and (4) physical symptoms in individuals with functional impairment electrohypersensitivity, many of which are the same as if myelin were affected by RF-EMF exposure, giving rise to symptoms of demyelination. In the latter, there are exceptions; headache is common only in electrohypersensitivity, while ataxia is typical of demyelination but infrequently found in the former group. Overall, evidence from in vivo and in vitro and epidemiological studies suggests an association between RF-EMF exposure and either myelin deterioration or a direct impact on neuronal conduction, which may account for many electrohypersensitivity symptoms. The most vulnerable are likely to be those in utero through to at least mid-teen years, as well as ill and elderly individuals.

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A recent report by the Health Council of the Netherlands highlighted the importance of myelination because of its role in providing electrical insulation to the nerve fibers (Health Council of the Netherlands, 2011). The council raised an important question: Can exposure to external electromagnetic fields, which create an electrical field in the brain, affect natural development and pruning of synapses during human development? This conservative advisory body stated that it is of "great importance to gather more information on this" (20). The council refers to both radiofrequency and extremely low-frequency electromagnetic field (RF-EMF and ELF-EMF) exposures at intensities too low to produce thermal damage. These are omnipresent, both environmentally (such as from mobile phone base stations and WiFi routers) and individually (such as from mobile phones, tablets, laptops, and iPods). The council's question is relevant and particularly important in the unborn and very young. The

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brain develops rapidly in utero, and at critical stages of development from infancy through adolescence and early adulthood, when axons and dendrites undergo pruning and synapses are formed. The process occurs under the influence of the brain's internally generated electrical activity in concert with an intricate chemical crosstalk using growth and differentiating factors as well as modulators and co-modulators (Fuxe et al., 1986).

Individuals claiming to suffer from exposure to electromagnetic fields (EMF) have been reported. In Sweden, electrohypersensitivity (EHS) is an officially fully recognized functional impairment (i.e., it is not regarded as a disease). Those who are electrosensitive commonly indicate having particular sources of exposures to which they are sensitive, which vary among those with the condition (Röösli et al., 2004). A rudimentary analysis comparing reported symptoms of those having EHS with those in a Swiss Health Survey showed significantly increased incidence of sleep disorders and severe headaches, and a reduced incidence of asthma in those with EHS (Röösli et al., 2004). With repeated exposures, response time reduces and reaction tends to grow more severe than when symptoms from the same source were first experienced, unless there has been an unexposed period of months, after which recurrence of symptoms may take a day or more (personal communication, Rob Hutchins, spokesperson for ElectroSensitivity New Zealand, April 2014).

Different sources may elicit different responses in any one person. Röösli et al. (2004) noted a trend toward more headaches in those using (cathode ray) display terminals, concentration problems and tinnitus with use of communication devices (RF), and nervousness or distress from ELF exposures. This is in agreement with the findings of Gordon et al. (1963), who suggested that "with low-intensity irradiations [1 mW/cm^2], the degree and sometimes even the nature of the functional and morphological changes depended on the wavelength." It may also explain why double-blind exposure studies with electrohypersensitives and a control group have not generally or consistently found a significant relationship (Rubin et al., 2005), as responses appear not to be uniform (Havas, 2013) and depend upon the stage of EHS and the time since the last exposure.

In Sweden, the prevalence of EHS was first estimated at 1.5% of the population in a survey undertaken in 1997 (Hillert et al., 2002), and a newer estimate is 2.6–3.2% (Johansson, 2006). In Austria the prevalence was estimated to be less than 2% in 1994 but rose to 3.5% in 2001 (Schrottner and Leitgeb, 2008). In California, the prevalence of self-reported sensitivity to electromagnetic fields was 3.2%, with 24.4% of those surveyed also reporting sensitivity to chemicals (Levallois et al., 2002). In Switzerland, 5% of the population was estimated to suffer from EHS in a survey undertaken in 2004 (Schreier et al., 2006). Finally, the Canadian Human Rights Commission noted that approximately 3% of Canadians have been diagnosed with environmental sensitivities, including to chemicals and EMF in their environment (Sears, 2007). In the report, Sears (2007) recommended improving the environmental quality at workplaces.

In yet unpublished studies by Johansson et al. (personal communication), the epidermal nerve fibers of electrohypersensitive persons were markedly reduced in length and number of nerve terminals, indicating apparent damage. The question is whether this occurred due to myelin sheath destruction or functional axonal conduction disruption. In neuroscience it is a well-established fact that reduction of the number of nerve fibers and concomitantly axonal terminals leads to an elevation in sensitivity, the so-called supersensitivity phenomenon (Gerfen, 2003). Can these also be underlying mechanisms for electrohypersensitivity?

This review focuses on effects attributed to RF-EMF. Extremely low-frequency (ELF) effects are also important to explore with relation to myelin, as there have been studies conducted regarding the use of ELF for therapeutic purposes (Sherafat et al., 2012; Baptista et al., 2009; Protasoni et al., 2009; Aydin et al., 2006; Mert et al., 2006). Perhaps the most important observation regarding these is that they present vital evidence that biological effects are

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frequency dependent: that is, responses may be positive, neutral, or negative, depending upon the frequency of the exposure. However, the associations of ELF and myelin integrity were not examined.

It is also pertinent to ask whether nonmyelinated nerves are more susceptible to direct interference from RF EMF, but this also lies outside the scope of this article. Briefly, there are studies that demonstrated redistribution of transmembrane sodium channels after exposure to pulsed RF EMF (Schneider and Pekker, 2013), and changes in neuronal firing rate and plasma membrane properties after extremely low, brief exposures of neonatal rat cerebral cortical tissue (Pikov et al., 2010).

In this review, we examined whether there may be a connection between symptoms reported after exposure to RF-EMF (chronic and acute nonthermal exposures) and compromised myelin integrity. Is there any evidence to suggest it, and is the hypothesis reasonable? These are important questions because loss of myelin is critical in several diseases, including multiple sclerosis (MS).

The aim of this review is to outline what myelin is and its normal course of development over the life span. Animal studies examining effects of RF-EMF on myelin sheathing and epidemiological research examining multiple sclerosis with relation to RF-EMF exposure are presented.

METHODOLOGY

Published information was collected on myelin and myelin damage, related diseases such as multiple sclerosis, relevant cellular changes, and the functional impairment electrohypersensitivity, by using conventional scientific literature databases, such as biomedical literature from PubMed, Medline, life science journals, EMF-Portal, and online books, available on the Internet.

MYELIN AND ITS DEVELOPMENT

Myelin is a fatty membrane that provides insulation that enables rapid propagation of electrical impulses along nerves. Myelin is produced by two types of glial cell, oligodendrocytes and Schwann cells, and is primarily composed of water, lipids, and protein. Within the myelin, there are interlinked hydrocarbon chains of sphingomyelin, which provides a strengthening framework (Mandal, 2014). Sphingolipids also play important roles in signal transduction (Healy, 2008). Disorders in sphingomyelin result in lack of sphingomyelin phosphodiesterase (SMase). SMase is a hydrolase enzyme whose role is to degrade sphingolmyelin in phosphocholine and ceremide. This prevents buildup of sphingomyelin in the brain, bone marrow, and liver, which would otherwise result in impaired motor skills, muscle strength, vision and hearing problems, and ultimately death (Healy, 2008).

Myelin develops spirally around neuronal axons, creating a sheath that increases in effectiveness as it thickens. Oligodendrocyte cells are found only in the central nervous system (CNS), and each cell myelinates the axons of several neurons, while Schwann cells are responsible for myelinating the peripheral nervous system (PNS), there being one cell for each axon (Bear et al., 2007). There are small gaps in the myelin sheath at the axon hillock and at locations called the nodes of Ranvier. At these points, ions cross the axon to create action potential, thus boosting the signal along the axon.

If myelin is damaged, the impulses traveling along the nerves slow down. Apart from crush injuries, initiation and mechanism for myelin damage are not understood but are considered to be related to environmental or genetic factors. If myelin is not repaired, this results in a variety of symptoms and diseases. The most common of these is the autoimmune condition multiple sclerosis, which affects the CNS (Table 1). Conditions that affect the PNS include Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). CIDP is thought to be an autoimmune condition and is generally characterized by fatigue and increasing weakness, tingling, and pain in the limbs, beginning at the toes and fingers (National Institute of Neurological

TABLE 1. Symptoms Reported by People After Exposure (or Presumed Exposure) to RF-EMFs With Symptoms of Demyelination

	Symptoms of electrohypersensitivity	Symptoms of demyelination
Vision	Difficulty in seeing, smarting, pain	Blurred vision Progressive vision loss/blurring (children), pain, light flashes (children)
Motor	Trunk/limb/joints aches, pain Numbness Weakness	Trunk/limb weakness Numbness Weakness and fatigue Balance problems
Sensory	Tickling, prickling, burning sensations (ie numbness, paraesthesia)	Numbness, paresthesia (i.e., tickling, prickling, burning sensations)
Cerebellar	Tremor Faintness Dizziness Sleep problems Headaches Abnormally tired/sleep problems	Tremor Ataxia (reduced muscle control, incoordination) Seizures (children) Balance problems (children) Lethargy (children)
Cognitive/neuropsychiatric/ emotional	Short and long term memory impairment Lack of concentration Difficulty learning new things Irritability Anxiety Stress (feeling of lack of control) Mood changes (including anger) Depression	Memory impairment Concentration impairment Irritability Anxiety Confusion (children)

Note. Sources: ESUK (2014); Mar (2014); National Multiple Sclerosis Society (2014).

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Disorders and Stroke, 2014). It is most common in young men.

Humans are born with scant electrical insulation of their nervous system. During development, a sheath of fatty myelin begins developing, first around axons in the CNS, then also sheathing peripheral and increasingly thinner axons (Wheeler, 2009). Once developed, it acts as electrical insulation and prevents the electrical signaling along the neuron from leaking out through the walls of the neuron. Its purpose is to enable efficient, speedy conduction of electrical nerve impulses. The major development of CNS sheathing occurs during the fourth and fifth months of gestation, continuing from the wk 25 of gestation until the age of 2 yr (Rathus, 2010), but age-related changes to axon thickness and white matter density visible in magnetic resonance imaging (MRI) scans indicate that it continues throughout childhood and adolescence (Paus et al., 1999). Myelination begins in the brainstem and cerebellar regions, progressing through to the frontal lobes during adolescence (Yakovlev and Lecours, 1967), and thereafter repeating in cycles. Wheeler (2009) suggested that myelination development, repair, and replacement continue throughout the CNS and PNS until late middle age, coating smaller and smaller diameter axons in increasingly thinner layers. The myelination of the splenium (located at the posterior end of the corpus callosum) is central to the efficiency of interhemispheric synchronization; this occurs over a protracted period (Knyazeva, 2013). Bartzokis (2011) proposed a theory that optimal brain function relies on finely tuned action potential synchronization, which myelin enables, but that in the presence of oxidative and environmental abnormalities and stressors, epigenetic changes result, leading to developmental and degenerative diseases. Being fatty, myelin does not contain free ions. Keshvari et al. (2006) postulated that this indicates that as the myelin sheath develops there is also a reduction in electrical conductivity of brain tissue. The reverse side of this coin is

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that there is a higher overall electrical conductivity in the fetus, infant, and young child brain, as well as in those whose myelin has begun degenerating. Myelin deposition is delayed in malnourished children (Rodier, 2004), thereby possibly leaving some of lower socioeconomic status more vulnerable.

Excessive production of synaptic connections during fetal development is followed by heavy perinatal pruning; a second round, in the prefrontal cortex, occurs later with a marked rise in synapses at the onset of puberty (Huttenlocher, 1979), followed by pruning and reorganization during adolescence (Blakemore and Choudhury, 2006). This process is not complete until early adulthood. Rodier (2004) suggested that because prenatal CNS and myelination developmental processes are highly vulnerable to damage by environmental agents, it is reasonable to expect that brain development during childhood and adolescence also faces particular risks.

RF-EMF RESEARCH

The most relevant studies available were undertaken in the 1970s. In considering chronic effects, Switzer and Mitchell (1977) exposed 6-wk-old rats (5 h/d, 5 d/wk for 22 wk) to continuous-wave 2450-MHz RF-EMR (SAR 2.3 W/kg). There was a gap of 6 wk after exposure before analysis. Analysis using an electron microscope indicated a significant elevation in the number of myelin figures protruding into the cortical dendrites of the radiated, compared to control, subjects. No other striking structural changes were apparent. Baranski (1972) exposed guinea pigs and rabbits. Different guinea pig groups had exposures of 3.5 mW/cm^2 or 25 mW/cm^2, each being either continuous or pulse modulated. Exposure was at 3000 MHz, for 3 h daily for 3 mo, or the same frequency for a single 3-h session. The rabbits experienced 3 mo of chronic exposure at 5 mW/cm^2. Resulting damage was the same with both types of irradiation, but lesions were more marked and extensive from pulsed transmissions. Baranski (1972) found spherical metachromatic bodies in the myelin with large spheres in nervous tracts and glial cells, and smaller ones near the third ventricle and reticular formation structures, particularly around blood vessels within the myelin. These spheres were attributed to metabolic disturbances in the myelin sheath and particularly in the oligodendrocytes. Demyelination was indicated by a Marchi's reaction test. Some hyperchromatic cell bodies in the white matter had spirally twisted neurites typical of "chronic Nissl's disease." It should be noted that exposure at 25 mW/cm^2 produced thermal damage, and that 3.5 mW/cm^2 exceeds the public exposure reference levels, although falling within occupational exposures. Further, 2.3 W/kg is higher than permitted under International Commission on Non-Ionizing Radiation Protection (ICNIRP) or Institute of Electrical and Electronics Engineers (IEEE) standards. However, no temperature increases were evident at 3.5 mW/cm^2 or 2.3 W/kg. The greater impact of pulse-modulated exposures reported by Baranski (1972) is of great importance, since all present-day digital microwave radiation types are pulsed. This occurrence is explained by the ion forced-vibration theory (Panagopoulos et al., 2002), supported theoretically more recently by Halgamuge and Abeyranthe (2011).

OTHER RESEARCH RELEVANT TO MYELIN LOSS AND RELATED SYMPTOMS

A national Danish cohort study compared the country's MS register against private mobile phone subscription holders and nonholders prior to 1996 (Poulson et al., 2012). Despite the most basic estimate of exposure (phone ownership or not), there was one subgroup of account holders with significant elevated incidence, namely, women with >10 yr of mobile phone subscription (RR 2.08, 95%CI: 1.08-4.01; $n = 9$). A few MS onset symptoms were also significantly related, although different for men and women. Women had an increased incidence of fatigue (RR 3.02, CI: 3.02–6.28),

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while men experienced an elevated frequency of optic neuritis (RR 1.38 CI: 1.03–1.86). Diplopia (blurred vision) was not significant in either group separately, but together the incidence risk rate was 1.38 (CI: 1.02–1.86). Finally, there was an elevated risk of death in MS patients with subscriptions 7–9 yr after MS diagnosis compared to those without subscriptions (RR, 2.44; 95% CI: 1.20–4.98; $n = 8$); however, it should be noted that the number in this category was small. The study excluded corporate subscriptions, which are likely to have been the highest users at that time. Since these are also likely to have been predominantly accounts for use by men, this may explain the significant MS results being in a subgroup of women.

Schüz et al. (2007) investigated a possible link between cellular telephone use and risks for various CNS diseases. In their large nationwide cohort study of 420,095 persons in Denmark, no marked associations for amyotrophic lateral sclerosis, multiple sclerosis, or epilepsy (in women) were observed, but there was an excess of migraine and vertigo connected to the mobile phone use. Elsewhere, rats were exposed to both 1.5 W/kg and 6 W/kg (GSM [global system for mobile communications] pulsed modulation) (Anane et al., 2003). There was a significant rise in amplitude of induced experimental allergic encephalomyelitis crisis between sham and real exposure at 1.5 W/kg (which is a permitted exposure in the ICNIRP and IEEE guidelines) but not at 6 W/kg, despite no marked difference in onset, duration, or termination. This condition is an inflammatory demyelinating disease of the CNS. The abstract does not mention this increase.

A small study published in 2007 found no gross effects on measured human cortical parameters in either healthy participants ($n = 10$) or MS participants ($n = 2$) (Inomata-Terada et al. 2007). Subjects were exposed to an 800-MHz pulsed signal for 30 min at the maximum permitted power output, using an adapted hand-held phone. For those with MS, exposure was before and after a hot bath, which generally brought on MS-related weakness. These data were unable to be analyzed statistically and were assessed individually by observation.

Symptoms of myelin loss include numbness and paraesthesia. An explanation is that alterations of myelin as well as Schwann cells of the sensory nerves may lead to functional alterations, slowing down of nerve signal conductance, and changes of nerve terminal sensitivity, which would lead to sensations of numbness and paresthesia, with the latter forming conscious thoughts via the spinal cord, thalamus, and primary as well as associative sensory brain cortex.

The skin is the organ most exposed to RF-EMF. Effects of EMF exposure on the skin were published in the 1960s. In experiments with rats, low-intensity exposure ($\leq$1 mW/cm^2) reduced nucleoprotein content of various cells and tissues. Thereafter, marked morphological changes were observed in the receptor and interoceptor apparatuses for skin after exposures of 1 mW/cm^2, with slight changes noted elsewhere, including intestinal wall, the wall of the bladder, and aorta (Gordon et al., 1963). This study also found slight morphological changes in the axon-soma and axon-dendrite interneuron connections of the cerebral cortex. These effects were reversible, disappearing after 3 to 4 wk. Some reactions were only seen with frequencies below 3GHz, suggesting that the degree of functional and morphological changes depended on the wavelength.

There are also studies indicating involvement of cells or proteins related to production of myelin. Peinnequin et al. (2000) found that 2.45-GHz nonthermal exposure of Jurkat T cells over 48 h initiated Fas-induced apoptosis. When considered with other results, there was the potential that exposure affected either membrane proteins through the Fas receptor or SMase activation, or the Fas pathway between receptor and caspase-3 activation. In a study exposing human bone-marrow mesenchymal stem cells to a 1-mT 50-Hz field for 12 d, oligodendrocyte protein O4 was induced (Cho et al., 2012). Data indicated that in toto ELF might induce neural differentiation in these

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cells. Hardell et al. (2010) determined the risk of oligodendroglioma and mobile or cordless phone exposure in deceased cases from certain areas of Sweden who were diagnosed with this tumor between 1997 and 2003. Results revealed a high odds ratio (OR) for those with >10 yr of phone use (OR = 10, 95% confidence interval [CI] = 1.1–89), but this was based on only 2 cases in this category, out of 9 who died from this tumor.

The presence of intraepidermal nerve fibers was investigated in normal human skin from healthy volunteers using the new marker PGP 9.5 (Wang et al., 1990). The intraepidermal nerve fibers are found as close as 20–40 μm from the surface, which makes it highly possible that weak EMF may affect them. In facial skin samples of electrohypersensitive persons, the most common finding was a marked rise of mast cells (Johansson and Liu, 1995). From these studies, it is clear that the number of mast cells in the upper dermis is increased in the EHS group. A different pattern of mast cell distribution also occurred in the EHS group, namely, the normally empty zone between the dermo-epidermal junction and mid- to-upper dermis disappeared in the EHS group and, instead, this zone had a high density of mast-cell infiltration. These cells also seemed to have a tendency to migrate toward the epidermis (= epidermiotrophism), and many of them emptied their granular content (= degranulation) in the dermal papillary layer. Further, more degranulated mast cells could be seen in the dermal reticular layer in the EHS group, especially in those cases that had the mast-cell epidermiotrophism phenomenon just described. Finally, in the EHS group, the cytoplasmic granules were more densely distributed and more strongly stained than control, and generally, the size of the infiltrating mast cells was noted to be larger in the EHS group. It is noteworthy that increases of a similar nature were demonstrated at a later experimental study employing normal healthy volunteers in front of cathode ray tube (CRT) monitors, including ordinary household television sets (Johansson et al., 2001).

A COMPARISON OF SYMPTOMS OF ELECTROHYPERSENSITIVITY AND DEMYELINATION

If myelin sheathing were compromised by repeated or chronic exposures to RF-EMF, one might expect to see an elevation in typical symptoms of demyelination. Specific symptoms depend upon the particular disease, which are diverse and include blurred vision, trunk/limb weakness, numbness, paresthesia, tremor or reduced coordination, memory impairment, reduced concentration or processing speed, depression, irritability, and anxiety (National Multiple Sclerosis Society, 2014). MS is unusual in children; however, symptoms they encounter include confusion, alteration of consciousness, lethargy, and visual symptoms including pain and flashes of light (Mar, 2014).

These symptoms have also been described as symptoms of EHS, although generally in lay language such as tickling/prickling sensations as opposed to paresthesia (Table 1).

Onset of any of these symptoms in these circumstances has come to be called electrohypersensitivity, although any one person may have a different set of symptoms from another. It should be noted that in a systematic review of both short-term exposure and epidemiological studies to investigate such claims, the overall evidence to support them was thin (17 out of 117 potentially eligible papers were included after checking the qualifying criteria set by the research group) (Röösli et al., 2010). Johansson (2006, pp. 245–246) recorded early symptoms of electrohypersensitivity as "itch, smarting, pain, heat sensation, redness, papules, pustules . . . [and] frequently [symptoms related to] internal organ systems, such as the heart and the central nervous system, are also encountered." According to Sweden's National Board of Health and Welfare, the most commonly reported symptoms of electrohypersensitivity are fatigue, difficulty in concentrating, dizziness, nausea, palpitations and digestive disturbances (Socialstyrelsen (The National Board of Health and Welfare) 2014).

The British organization ElectroSensitivity United Kingdom (ESUK) describes symptoms

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such as those itemized in the left column of Table 1 (ESUK, 2014). There have been reports of cardiovascular problems such as tachycardia and arrhythmia, although these are relatively rare. Havas (2013) demonstrated these symptoms in double-blind, sham-controlled circumstances.

DISCUSSION

Despite early indications of damage to myelin sheathing in animals exposed to RF-EMF in the 1970s, there has been remarkably little research follow-up. There is still a lack of basic experimental evidence for a clear association between myelin damage and electrohypersensitivity, but given the preceding hypothesis it would be of great interest to investigate this in more detail using classical immunohistochemical markers for healthy and degenerated myelin, respectively, and for Schwann cells in general. Since myelin is the main electrical insulation that ensures efficient electrical functioning of the CNS, its integrity is vital to this, and healthy development of the neuronal system may also be. Therefore, it is important to know whether or not it is damaged by exogenous RF-EMF exposures.

What evidence is there that it may be? There do not appear to be national registers for MS, but the UK Multiple Sclerosis Trust reports that prevalence in women is increasing (Multiple Sclerosis Trust 2014). Race and latitude have been identified as influential in risk, but that incidence may be modified by the environment (Rosati 2001). When a child uses a wireless phone against the head (held at the usual angle), the most exposed area in that child's brain is the cerebellum (Christ et al. 2010); this is one of the first areas myelinated. As the head size nears adulthood, and depending upon head geometry, the most exposed area becomes the temporal lobes. This suggests that during adolescence the temporal lobes may be more susceptible to RF-EMF interference, not only because this region is not yet fully myelinated at that age, but because of enhanced vulnerability during active synaptic rearrangement and pruning in progress at that age.

Demyelination and electrohypersensitivity have many symptoms in common. This latter condition is frequently regarded as psychosomatic, with the symptoms being claimed to be subjective, nonspecific, and hard to test objectively. However, these symptoms clearly point to a common, highly specific, biological and behavioral avoidance reaction and most can easily be objectively studied and quantified. For instance, the subjective sensations of tingling in the skin, itching, and heat may all be explained by changes in biochemical markers, especially histamine of the mast cells, observed by Johansson (2006).

A review of provocation studies of electrohypersensitives investigations generally did not show a significant response compared with control groups (van Rongen et al., 2009); however, it was acknowledged that such studies are often disadvantaged by short exposure durations.

The symptoms of the two conditions, demyelination and electrohypersensitivity, are not entirely matched. Reduced muscle control (ataxia) is an important symptom of demyelination, as are seizures and balance problems in children, but infrequently reported as a symptom of RF-EMF exposure, although the more minor cerebellar conditions of tremors and dizziness are. On the other hand, there are a few symptoms such as headache, tinnitus, heart arrhythmia, and skin problems that are commonly reported from RF-EMF exposure but are not symptoms of demyelination.

An increased heart rate, altered heart-rate variation, and changes in the sympathetic and parasympathetic control of the autonomic nervous system have been objectively tested and demonstrated as associated with RF-EMR exposure in more than one study (Havas and Marrongelle 2013). Headaches have been associated with exposure in several epidemiological studies. In a review by Augner et al. (2012), there were in total 737 participants in 8 studies who evaluated headaches with relation to RF-EMF exposure and demonstrated an overall marginal association of headaches

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with RF-EMFs. Such a link was also found by Redmayne et al. (2013). It is possible that these or other non-myelin-related conditions are a result of stress due to worry regarding exposures. It is also possible that there is another as yet unidentified mechanism responsible.

It is risky to identify a cause by linking it backwards to symptoms such as discussed in this review because these symptoms are also intrinsic to other diseases. Therefore, this review began by asking, is there any evidence to support the hypothesis that RF-EMF exposure symptoms are related to demyelination, and is the hypothesis reasonable? It appears that the hypothesis is reasonable and that the evidence from in vivo, in vitro, and epidemiological studies is sufficiently strong to warrant urging that RF-EMF exposure from prebirth through to at least mid teens should be minimized until this issue is clarified. Overall, evidence suggests an association between RF-EMF exposure and either myelin deterioration or a direct impact on neuronal conduction, which may account for many electrohypersensitivity symptoms.

If myelin integrity is compromised by RF-EMF exposure, the greatest impact for humans would most likely be at each end of the life span. The CNS of the fetus, infant, child, and adolescent, whose myelination is incomplete, especially peripherally, and whose neural connections are rapidly forming and being pruned may be most susceptible, as may that of older people whose myelin protection is already degenerating, notably those with MS or other diseases in which loss of myelin is instrumental. It is not clear whether myelin deterioration from repeated RF exposure may initiate MS or whether it might exacerbate an existing condition. It may also be that before myelin sheath has developed or after it has begun deteriorating, functional axonal conduction may be disrupted directly, but this needs exploring. The similarities of demyelination and electrohypersensitivity cannot be taken as any proof of cause and effect, but it is believed they, and other evidence provided here, highlight the necessity for research in this area. Knowing whether myelin integrity or the natural development and pruning of synapses during human development are affected by RF-EMF is of great importance because of the serious consequences it implies for personal and public health if that is the case.

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