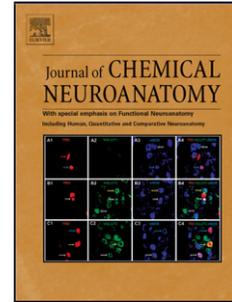


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Microwave frequency electromagnetic fields (EMFs) produce widespread neuropsychiatric effects including depression

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Abstract:

Non-thermal microwave/lower frequency electromagnetic fields (EMFs) act via voltage-gated calcium channel (VGCC) activation. Calcium channel blockers block EMF effects and several types of additional evidence confirm this mechanism. Low intensity microwave EMFs have been proposed to produce neuropsychiatric effects, sometimes called microwave syndrome, and the focus of this review is whether these are indeed well documented and consistent with the known mechanism(s) of action of such EMFs. VGCCs occur in very high densities throughout the nervous system and have near universal roles in release of neurotransmitters and neuroendocrine hormones. Soviet and Western literature shows that much of the impact of non-thermal microwave exposures in experimental animals occurs in the brain and peripheral nervous system, such that nervous system histology and function show diverse and substantial changes. These may be generated through roles of VGCC activation, producing excessive neurotransmitter/neuroendocrine release as well as oxidative/nitrosative stress and other responses. Excessive VGCC activity has been shown from genetic polymorphism studies to have roles in producing neuropsychiatric changes in humans. Two U.S. government reports from the 1970's-80's provide evidence for many neuropsychiatric effects of non-thermal microwave EMFs, based on occupational exposure studies. 18 more recent epidemiological studies, provide substantial evidence that microwave EMFs from cell/mobile phone base stations, excessive cell/mobile phone usage and from wireless smart meters can each produce similar patterns of neuropsychiatric effects, with several of these studies showing clear dose-response relationships. Lesser evidence from 6 additional studies suggests that short wave, radio station, occupational and digital TV antenna exposures may produce similar neuropsychiatric effects. Among the more commonly reported changes are sleep disturbance/insomnia, headache, depression/depressive symptoms, fatigue/tiredness, dysesthesia, concentration/attention dysfunction, memory changes, dizziness, irritability, loss of appetite/body weight, restlessness/anxiety, nausea, skin burning/tingling/dermographism and EEG changes. In summary, then, the mechanism of action of microwave EMFs, the role of the VGCCs in the brain, the impact of non-thermal EMFs on the brain, extensive epidemiological studies performed over the past 50 years, and five criteria testing for causality, all collectively show that various non-thermal microwave EMF exposures produce diverse neuropsychiatric effects.

Key Words: Excessive calcium effects; oxidative/nitrosative stress; low-intensity microwave electromagnetic fields

Chemicals having roles:

Calcium(2+)

Nitric oxide (NO)

Oxido nitrite (peroxynitrite)

Introduction:

Microwave syndrome (Hocking, 2001; Johnson Liakouris, 1998), a combination of various neuropsychiatric symptoms originally described in persons with occupational exposures to microwave frequency EMFs, has been disputed largely because of the lack of an apparent mechanism for generating these symptoms. It is reported to often include such symptoms as fatigue, headache, insomnia, dysesthesia (impaired sensation), irritability, lack of concentration and other symptoms (Hocking, 2001; Johnson Liakouris, 1998). Similar but more extensive combinations of symptoms have been reported following occupational exposures in two U.S. government reports from the 1970s/1980s (Naval Medical Research Institute Research Report, 1971; Raines, 1981) and following environmental exposures as described in two more recent reviews (Khurana et al, 2010; Levitt and Lai, 2010).

The goal here is not just to review the epidemiology, however, but more importantly to consider the issue of possible physiological mechanism(s). Hennekens and Buring (1989), on p. 40 in their textbook *Epidemiology in Medicine* state "The belief in the existence of a cause and effect relationship is enhanced if there is a known or postulated biologic mechanism by which the exposure might reasonably alter risk of developing disease." It is of critical importance therefore to assess possible biological mechanism before considering the epidemiological evidence.

Accordingly, this paper considers the mechanism by which low intensity microwave EMFs impact the cells of our bodies, how that mechanism may be predicted to impact the nervous system, evidence for such impact from experimental animal studies, genetic polymorphism evidence for that mechanism acting in humans to produce neuropsychiatric effects and finally, the epidemiological evidence for such effects in human populations with repeated low level microwave EMF exposure. Consideration of each of these types of evidence influences the overall interpretation presented in this paper.

Microwave/lower frequency EMFs act to activate voltage-gated calcium channels

In 24 different studies reviewed earlier (Pall, 2013) and two additional studies (Li et al, 2014; Lisi et al, 2006), microwave and lower frequency low intensity EMF effects were blocked or greatly lowered by calcium channel blockers, agents thought to be specific for blocking voltage-gated calcium channels (VGCCs). In these 26 studies, a total of 5

distinct types of channel blockers were used, with each type having a distinct structure and binding to a distinct site, such that it is essentially certain that these must be acting by blocking VGCCs, which is their only known common property. In each of these 26 studies, each of the responses studied, were blocked or greatly lowered by calcium channel blockers, showing that VGCC activation has roles in producing a wide variety of EMF effects. There is a large literature on changes in calcium fluxes and in calcium signaling following microwave EMF exposure (partially reviewed in Walleczek 1992; Adey 1993); each of these, including calcium efflux changes, can be explained as being due to VGCC activation, again suggesting a widespread role of VGCC activation in producing biological responses to EMFs. Pilla (2012) showed that pulsed microwave field exposure, produced an almost instantaneous increase in calcium/calmodulin-dependent nitric oxide (NO) signaling, providing strong evidence that these fields can produce an almost instantaneous VGCC activation. It is likely, that these EMFs act directly on the voltage sensor of the VGCCs to produce VGCC activation (Pall, 2015) with the voltage sensor being exquisitely sensitive to these EMFs because of its physical properties and location in the plasma membrane.

EMFs have been proposed to act to produce a wide variety of responses in the cell, via downstream effects of VGCC activation (Pall, 2013, 2014, 2015), including elevated intracellular calcium $[Ca^{2+}]_i$, excessive calcium and nitric oxide signaling and also excessive peroxynitrite, free radicals and oxidative stress.

VGCC activation has been shown to have a universal or near-universal role in the release of neurotransmitters in the brain and also in the release of hormones by neuroendocrine cells (Berridge, 1998; Dunlap et al, 1995; Wheeler et al, 1994), with such release being produced by calcium signaling. There are high densities of diverse VGCCs occurring in neurons throughout the nervous system. Both the high VGCC density and their function in neurotransmitter and neuroendocrine release throughout the nervous system suggests that the nervous system is likely to be highly sensitive to low intensity EMFs.

Genetic Polymorphism Studies

Genetic polymorphism studies are powerful tools for looking at the roles of specific proteins in human populations. In Table 1, a series of genetic polymorphism studies have been performed that show that an allele producing increased expression of the gene encoding the channel of the main L-type VGCC in the brain, produces diverse neuropsychiatric effects. These studies clearly show that excess L-type VGCC activity can cause neuropsychiatric effects. They also predict, therefore, that increased VGCC activity produced by microwave EMFs may be able to also produce widespread neuropsychiatric effects.

Table 1 Influence of Genetic Polymorphism of the CACNA1C in Producing Diverse Neuropsychiatric Effects

Citation	Genetic Polymorphism	Changes produced by allele of gene
Bhat et al,	Polymorphism	Review: The polymorphism Is associated with

2012	producing Increased expression of CACNA1C L-type VGCC subunit	increased susceptibility to bipolar disorder, “depression, schizophrenia, autism spectrum disorders, as well as changes in brain function and structure in control subjects who have no diagnosable psychiatric illness.”
Bigos et al, 2010	Polymorphism producing Increased expression of CACNA1C L-type VGCC subunit	Associated with increases in both bipolar disorder and schizophrenia
Krug et al, 2010	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Negatively influences language production on a semantic level
Krug et al, 2014	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Influences episodic memory and retrieval
Soeiro-de-Souza et al, 2012	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Produces impaired facial emotion recognition
Tesli, et al, 2013	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Produces increased activation of the amygdala during emotional processing
Thimm et al, 2011	Polymorphism producing increased expression of CACNA1C L-type VGCC subunit	Associated with attention deficits including alerting, orienting and executive control of attention

Histological and Functional Changes in Central Nervous System (CNS) and Peripheral Nervous System ((PNS) in Animals Exposed to Microwave EMFs

The most extensive literature on histological and functional changes in animals is from the Soviet literature from the 1950s/1960s with additional Western literature from the same time period. Both Soviet and non-Soviet literature were reviewed in an English language Publication by Tolgskaya and Gordon (1973). This publication is, therefore, the main focus of this section. That publication was divided into thermal and non-

thermal exposure studies, with the non-thermal studies which occupy the majority of the text (pp. 53-137) being of sole interest here.

Table 2 Histological and Functional Changes in Brain Function in Animals following Exposure to Non-Thermal Microwave EMFs

Observations including page numbers	Comment from Author
The majority of the histological changes seen following non-thermal exposures, occurred in the nervous system, despite its being only about 2% of the tissue mass in rodents; this suggests that the nervous system is highly sensitive to such exposures. Elsewhere (p.129,136), it is suggested that the nervous system is the most sensitive tissue, followed by the heart and the testis, among all of the tissues of the body. The most severe histological changes produced by these non-thermal EMF exposures occur in the nervous system (p. 136).	High CNS sensitivity to EMFs is predicted by the high density of VGCCs that occur in neurons throughout the nervous system, plus the VGCC role in neurotransmitter and neuroendocrine release.
Pulsed fields were more active than non-pulsed fields in producing histological changes (p. 71,97)	Pulsed fields have often been found to be more biologically active than are non-pulsed fields in many different studies from many countries (Pall, 2015, Panagopoulos et al, 2013; Belyaev, 2015)
Nervous system regions impacted by non-thermal microwave and lower frequency fields include: cortex, diencephalon including the hypothalamus and thalamus, hippocampus, autonomic ganglia, sensory fibers, pituitary gland including neurohypophysis	
Neuroendocrine changes seem to undergo change over increased time of exposure. Neurosecretion in the hypothalamus and in the pituitary each go through a complex sequence over time, where EMF exposure initially produces increased hormone secretion but where over time, the neurosecretory cells become “exhausted”, leading to lowered secretion and in some cases cell death (pp.77-96).	Elevated $[Ca^{2+}]_i$ stimulates hormone secretion. However when such elevated $[Ca^{2+}]_i$ occurs over extended time periods it is highly damaging to the cell, leading in some cases to apoptosis; thus this time course of action should not be surprising.
Histological changes include boutons/argyrophilia, smaller neurons, vacuole formation in neuroendocrine cells, bead-like thickening along dendrites (p.66,70,71,73,97,98,100,111,115-117,121-125). Spines near the ends of dendrites become deformed and with still more sessions of irradiation, disappeared	

<p>entirely (p.70). Sensory neurons, following exposures, developed changes characteristic of irritation, with “marked tortuosity of the nerve fibers.” Many histological changes are seen in the hypothalamic cells (p.87-92) as their neuroendocrine function becomes impacted. Histological changes were found even with exposures that produced no apparent functional changes.</p>	
<p>Many histological and functional changes are reported to initially be reversible, following cessation of exposure, but progressively become irreversible with longer exposure. (p.64,72,74). Paralleling the development of irreversibility, it is found that “Repeated exposure leads to gradual increase in severity of observed changes.” ... including “increasingly severe disturbance of conditioned reflex activity in the animals, changes in responses of animals particularly sensitive to acoustic stimulation... .” (p. 104)</p>	<p>If this is also true in humans, then claims that there cannot be non-thermal effects, claims which act to prolong exposures, may be causing irreversible damage to many humans.</p>
<p>EEG changes (p. 55,60,102), including seizure activity following sensory provocation</p>	<p>Lai, 1997 has an extensive review of EEG changes in animals following non-thermal microwave EMF exposures</p>
<p>Neurodegeneration is reported in a number of places in this review (p.72,83,117).</p>	
<p>Synaptic connections in regions of the brain are disrupted (p.65-74, 97,113,121,136), and at the extreme, some neurons are completely asynaptic (p.73).</p>	<p>Synaptic connections are known to be disrupted in autism; could this suggest that autism may be generated by EMF exposure? No doubt, we need much more evidence on this.</p>
<p>“after prolonged and repeated irradiation with low-intensity centimeter waves, with no elevation of the body temperature and when the animal’s condition remained satisfactory, changes were nevertheless found in the sensory fibers of the skin and viscera in the form of irritation phenomena. These findings concur with the view in the literature that the receptor system as a whole and, in particular its preterminal portions are highly sensitive.” P.76. This description is similar to what is reported to occur in electromagnetic hypersensitivity (EHS). Other such studies are described and include cumulative changes over time, that may also explain changes reported in EHS (p.75,99,100,104).</p>	<p>One wonders whether almost 60 years ago, the Soviet literature may have already described a possible animal model for EHS. None is known to exist today, and because of that, EHS studies are severely constrained. Clearly one needs to be skeptical about this interpretation, but it is of great importance that this be further studied.</p>

These were all derived from the Tolgskaya and Gordon, 1973 review and page numbers listed are page numbers from that document. All refer to changes produced by non-thermal exposures in the nervous system of experimental animals, with most being in rats.

This discussion scrolls down through Table 2.

The majority of the histological changes seen in these mostly rodent studies, are seen in the nervous system, despite its being less than 2% of the rodent cell mass. There are statements made that the nervous system, both central and peripheral, is the most highly sensitive tissue to these non-thermal microwave and lower frequency EMFs. Following the nervous system in sensitivity are the myocardium and the testis; myocardial cells are known to have very high densities of VGCCs with especially high densities in the pacemaker cells and the testis is known to have high densities specifically of the T-type VGCCs. Pulsed EMFs are more active in producing histological changes in the brain than are non-pulsed fields, in two studies reviewed; there is a much larger literature showing that in most cases pulsed fields are more biologically active (Pall, 2015, Panagopoulos et al, 2013, Belyaev, 2015).

A wide variety of brain and peripheral nervous system tissues show histological changes following non-thermal exposures. Among the important tissues impacted are the hypothalamus and pituitary gland, where both show similar patterns of changes in neuroendocrine activities. There is an initial increase in neuroendocrine activity (this may be produced directly by VGCC stimulation of secretion), followed over time by “exhaustion” of neuroendocrine activity (this may be produced by tissue damage produced from long term intracellular calcium $[Ca^{2+}]_i$ elevation).

There are widespread histological changes produced in neuronal and neuroendocrine tissues. These were repeatedly reported to be largely reversible on cessation of EMF exposure. They become, however, irreversible when exposure is extended in time. There are changes in EEG activity, which may be an easily measurable monitor of neurological damage.

In a summary statement, Tolgskaya and Gordon, 1973 state “This does not confirm the view, so widely held in the past among Soviet investigators and still maintained to a large extent even at the present time in the West, that the action of microwaves is entirely thermal.”

While there were many studies of brain impact of non-thermal EMFs performed in the 1950s/60s that make the information content of Tolgskaya and Gordon, 1973 quite high, there is also a substantial recent literature on brain effects of non-thermal microwave EMF exposures (see, for example: Ammari et al, 2008a; Ammari et al, 2008b; Bas et al, 2009; Brillaud et al, 2007; Carballo-Quintás, et al, 2011; Eberhardt et al, 2008; Dasdag et al, 2009 & 2012; Grafström et al, 2008; Kumlin et al, 2007; López-Martín, 2006; Mausset-Bonnefont et al, 2004; Odacia et al, 2008; Rağbetli, et al, 2010; Salford et al, 2003; Sonmez et al, 2010).

Older Epidemiological Reviews and Other Related Studies

Two U.S. Government reports each listed many apparent neuropsychiatric effects of microwave/radiofrequency EMFs and a third recognized the role of non-thermal effects on our bodies, but had only a little consideration of neuropsychiatric effects.

The earliest to these was a Naval Medical Research Institute (NMRI) Research Report (1971) which listed 40 apparent neuropsychiatric changes produced by non-thermal exposures:, including 5 central/peripheral nervous system (NS) changes, 9 CNS effects, 4 autonomic system effects, 17 psychological disorders, 4 behavioral changes and 2 misc. effects. This NMRI report also provided a supplementary document listing over 2300 citations documenting these and other effects of microwave exposures in humans and in animals.

The Raines (1981) NASA report reviewed extensive literature based on occupational exposures to non-thermal microwave EMFs, with that literature coming from U.S., Western European and Eastern European studies. There are no obvious differences in the literature coming from these different regions. Based on multiple studies, Raines (1981) reports 19 neuropsychiatric effects to be associated with occupational microwave/radiofrequency EMFs.

The Bolen (1994) report put out by the Rome Laboratory of the U.S. Air Force, acknowledged the role of non-thermal effects of microwave EMFs on humans. This report states in the Conclusion section that “Experimental evidence has shown that exposure to low intensity radiation can have a profound effect on biological processes. The nonthermal effects of RF/MW radiation exposure are becoming important measures of biological interaction of EM fields.” Clearly Bolen (1994) rejects the claim that only thermal effects occur. Bolen (1994) discusses a specific non-thermal neuropsychiatric effect, where anesthetized animals are awakened when the head is irradiated with microwave EMFs. This suggests a similar mechanism to that acting in humans where such EMFs produce insomnia (see below).

Specific Epidemiological Studies on Neuropsychiatric Effects of Microwave EMFs

There are 26 different epidemiological studies described in Table 3. Although 4 of these only studied a single neuropsychiatric effect, 22 of these each provide substantial evidence for the pattern described in the earlier U.S. reports, that a wide range of neuropsychiatric effects are produced by exposure to various non-thermal microwave frequency EMFs. Perhaps the most important of these 26 is the Santini et al, 2003 study of people living near cell phone base stations.

Table 3: Neuropsychiatric Symptoms Apparently Produced by Exposure to Various Electromagnetic Fields

<u>Citation</u>	<u>EMF exposure</u>	<u>Apparent neuropsychiatric symptoms</u>
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Abdel-Rassoul et al, 2007	Living near mobile phone base station	Significant increases in neuropsychiatric complaints included: headache, memory changes, dizziness, tremors, depressive symptoms, sleep disturbance; attributed to effects of EMFs on the human nervous system
Al-Khlaiwi & Meo, 2004	Mobile phone use	Higher prevalence of fatigue, headache, dizziness, tension and sleep disturbance; the authors conclude that mobile phone use is a risk factor for developing these symptoms
Altpeter et al, 2000	Short-wave broadcasting tower, ranging from 6.1 to 21.8 MHz	Sleep disruption shown to occur, correlated with exposures and apparent increase over time; short term suppression of melatonin shown, based on melatonin increases during a 3 day period when the tower was turned off.
Bortkiewicz A et al, 2004	Living near cell phone base station EMFs	Sleep disturbance, irritability, depression, blurred vision, concentration difficulties, nausea, lack of appetite, headache, vertigo
Bortkiewicz A et al, 2012	Living near mobile phone base stations	Dose response relationships for sleep disturbance, irritability, depression, blurred vision, concentration difficulties, nausea, lack of appetite,
Chu et al, 2011; Also Chia et al, 2000; Oftedal et al 2000	Mobile phone use	Headache during prolonged mobile phone use or within an hour following such use, with pain occurring on the ipsilateral side of the head; similar observations obtained in each of the 3 studies in column 1; see also Frey 1998
Conrad RH, 2013	Smart meter EMF exposure	14 common new symptoms (both severe and moderate) among those exposed and symptomatic, 13 apparent neuropsychiatric: Insomnia, tinnitus, pressure in the head, concentration difficulty, headaches, memory problems, agitation, dizziness, fatigue, skin tingling/burning, involuntary muscle contractions, eye/vision problems, numbness; These ranged in prevalence from 63% to 19% of those experiencing symptoms, such that most symptomatic people experienced multiple symptoms
Dasdag et al, 1992	People working in MW broadcasting or at a television transmitter station	These groups suffered from headache, fatigue, irritability, stress, sleepiness, loss of appetite, loss of hearing

Dwyer and Leeper, 1978	People working in radiofrequency EMFs	Headache, eyestrain, dizziness, disturbed sleep, daytime sleepiness, moodiness, mental depression, memory impairment, muscle and/or cardiac pain, breathing difficulties, increased perspiration, difficulty with sex life
Eger & Jahn, 2010	Living near mobile phone base station	Neuropsychiatric symptoms, with most showing dose-response relationships: depression; headache; cerebral symptoms; dizziness; disorders of optical and acoustic sensory systems; sleep disturbance; skin changes; with the exception of dizziness, all of these had $p < 0.001$
Johnson Liakouris AG, 1998	Study of personnel in U.S. embassy in Moscow exposed to microwave EMFs	Statistically significant increases in neurological (peripheral nerves and ganglia), dermatographism (skin responses), irritability, depression, loss of appetite, concentration difficulties, peripheral ganglia and nerve dysfunction
Khan MM, 2008	Excessive mobile phone use	Complaints of headache, fatigue, impaired concentration, memory disturbance, sleeplessness, hearing problems
Kolodinski & Kolodinska, 1996	Children living near a Radio Location Station, Latvia	Memory dysfunction, attention dysfunction, lowered motor function, slowed reaction time, lowered neuromuscular endurance
Lamech F, 2014	Exposure to wireless smart meter radiation in Victoria, Australia	The most frequent symptoms to develop after smart meter radiation exposure were insomnia, headache, tinnitus, fatigue, cognitive disturbances, dysesthesias (abnormal sensation), dizziness
Navarro et al, 2003	Living near cell phone base station	Statistically significant dose response relationships for fatigue, irritability, headache, nausea, loss of appetite, sleep disorder, depressive tendency, feeling of discomfort, difficulty of concentration, loss of memory, visual disorder & dizziness
Oberfeld et al, 2004	Living near cell phone base station	Statistically significant dose-response relationships for headache, fatigue, irritability, loss of appetite, visual disorder, nausea, sleeping disorders, dizziness, poor concentration, memory loss
Oto et al, 1994	Occupational exposure of 25 workers to either UHF television broadcasting (10) or to 1062 KHz medium	10 neuropsychiatric changes were assessed, all showing statistically significant changes compared with controls: Somatization*, obsessive compulsivity*, interpersonal sensitivity, depression, anxiety*, hostility*,

	wave broadcasting (15)	phobic anxiety*, paranoid ideation, psychoticism*, sleeping disturbance. *p<0.001
Sadcikova, 1974	Occupational exposure to microwave radiation, including at <.07 mW/cm ²	Heaviness in head*, fatigue*, irritability*, sleepiness, memory loss*, cardiac pain*, dermographism (skin sensitivity)*, hyperhidrosis* * significant increase with time of exposure
Salama et al, 2004	High cell (mobile) phone use	Most common effects were headache, ear ache, sense of fatigue, sleep disturbance, concentration difficulty, face burning sensation. The first three of these had very high statistical significance for correlation with extent of cell phone use.
Santini et al, 2003	Living near cell phone base stations	Each of the following neuropsychiatric symptoms showed statistical significant dose-response relationships: nausea, loss of appetite, visual disturbance, irritability, depressive tendencies, lowered libido, headache, sleep disturbance, feeling of discomfort, fatigue
Schüz et al, 2009	Mobile phone use	Found a small, statistically significant increase in migraine and vertigo. Also found an apparent lowered occurrence of Alzheimer's, other dementia, Parkinson's and epilepsy – these latter were interpreted as being due to perhaps early symptoms of the developing diseases lowering probability of acquiring a mobile phone
Söderqvist et al, 2008	Use of mobile phone among adolescents	Increased mobile phone use was associated with increases in tiredness, stress, headache, anxiety, concentration difficulties and sleep disturbances
Thomé et al, 2011	High mobile phone use	High mobile phone use was associated with statistically significant rises in stress and sleep disturbance, with somewhat weaker association with depression
Waldmann-Selsam C, et al. 2009	Digital TV signaling	Constant headaches, pressure in head, drowsiness, sleep problems, tightness in chest, shortness of breath, depressive mood, total apathy, loss of empathy, burning skin, inner burning, leg weakness, pain in limbs, stabbing pain in various organs, weight increase

There are three recent studies on the generation of headache during or shortly following long mobile phone calls (listed under Chu et al, 2011 in Table 3). The timing of development of these headaches and the finding that they occur on the ipsilateral side of the head, the side receiving much higher EMF exposure during the call, both argue strongly that these headaches are caused by the long mobile phone calls. Such causality was concluded earlier by Frey, 1998 based on earlier studies and is now still more strongly documented.

Criteria for Assessing Causality In Epidemiological Studies

It is important to consider the different criteria that allow one to judge whether a cause and effect relationship is justified by the studies listed in Table 3 and the individual studies cited in Raines, 1981. There are five such criteria that should be considered in making that judgment (See pp.39-43 in Hennington and Buring, 1987):

Strength of Association: Is there a strong correlation between exposure and the neuropsychiatric symptoms? There clearly is for several studies cited in Raines, 1981. One example is the Dwyer and Leeper, 1978 study (see Table 3) where there is a large increase in symptoms and where that increase is greater with longer occupational exposure. Another example is the Lerner, 1980 study of 1300 microwave workers, where workers with relatively low exposure levels had an approximate doubling of neurological complaints and where those with substantially higher exposure levels had an approximate tripling of neurological complaints over controls. Sadcikova, 1974 found that 7 of 8 neuropsychiatric symptoms studied, showed a statistically significant rise in prevalence with longer occupational exposure (see Table 3). Sadcikova, 1974, also found that microwave workers had increases of 3 to over 10-fold in: feeling of heaviness in the head; tiredness; irritability; sleepiness; partial loss of memory; and skin sensitivity. There is also a strong association where important new exposures occur – this is clearly the case with all of the studies of people living near cell/mobile phone base stations, listed in Table 3 and also with the two studies of people who become exposed to radiation from smart meters. The studies listed in Table 3 under Chu et al, 2011 (see also Chia et al, 2000; Oftedal et al 2000) are of a special type. Here people making very long (over 1 h.) cell/mobile phone calls develop headaches an hour or more following the initiation of the long call. So these occur within a specific time range following initiation of these long calls, such that headache would only occur very infrequently in that time frame by chance. So here again, there is a strong association. While there is no question that many of these studies show high strength of association, it is also clear that it is becoming progressively more difficult to do these studies. As exposures become almost universal in countries around the world, it is getting difficult if not impossible to find good negative controls. There may be a similar problem in doing animal studies, such that it may be necessary to raise animals in Faraday cages in order to avoid exposures that would otherwise occur as a consequence of our near ubiquitous EMFs.

Biological credibility is extremely strong here, with three aspects of the biology predicting that these low intensity fields cause widespread neuropsychiatric effects. This was discussed above and is reconsidered in the following section.

Consistency within the different epidemiological studies and with other types of studies: The epidemiological studies listed in Table 3 and also those showing neuropsychiatric effects that were cited in Raines, 1981 have been performed in many different countries with different cultures. They have been performed in multiple countries in Western Europe, Eastern Europe, the Middle East and in East Asia, as well as in the U.S. and Australia. They are, therefore, not limited to one or two cultural contexts. This is deemed, therefore, an important indicator of causality. We also have a surprising consistency of apparent neuropsychiatric effects of different fields, including various occupational exposures and exposures to cell/mobile phone base stations, exposure to the phones themselves, exposure to smart meter pulses, and other EMFs (see Table 3). Pulsation patterns, frequencies and exact intensities may produce various biological responses (Pall, 2015, Panagopoulos et al, 2013, Belyaev, 2015) so it is a bit surprising that we have as much consistency as we do have across different types of exposures. We also have consistency with the biology discussed in the previous section. Because elevated VGCC activity produced by genetic polymorphism (Table 1) produces diverse neuropsychiatric effects, it is not surprising that elevation of VGCC activity produced by microwave EMF exposure apparently also produces diverse neuropsychiatric effects. Similarly because non-thermal EMF exposures produce widespread changes in brain structure and function in animals (Tolgskaya and Gordon, 1973), it is not surprising that the neuropsychiatric symptoms, which are produced as a consequence of brain dysfunction are produced by such EMFs.

Time sequence: It is clear that all of these effects follow exposure in the various studies that have been published. In some studies, it is also clear that longer occupational exposure times produce increased symptom prevalence. These include Dwyer and Leeper, 1978 and Baranski and Edelwejn, 1975. These observations all support a causal relationship between exposure to EMF and the development of neuropsychiatric symptoms.

Dose-response relationship: It is assumed, here, that biological effects have a positive correlation with the intensity of the apparent causal stressor. This is not necessarily true of EMF effects, because it has been shown that there are “window effects” where specific intensities have larger biological effects, than *do either lower or higher intensities* (Pall, 2015, Panagopoulos et al, 2013, Belyaev, 2015). Nevertheless, where different intensities were studied in these epidemiological studies, they do show the dose-response relationship assumed here including Altpeter et al, 2000; Dwyer and Leeper, 1978; Eger and Jahn, 2003; Lerner, 1978; Navarro et al, 2003; Oberfeld et al, 2004; Salama et al, 2004; Santini et al, 2003; Thomée et al, 2011. Thus these data do fit well to the assumed dose-response relationship, found in most causal roles. The Altpeter et al, 2000 study showed a special type of evidence for causality: during a 3-day period when the broadcasting tower was turned off, the melatonin levels recovered to near-normal levels. The studies of headache occurrence on prolonged cell/mobile phone calls (typically well over one hour) listed under Chu et al, 2011 in Table 3 also suggest the assumed dose-response relationship (see also Chia et al, 2000; Oftedal et al 2000 and earlier citations listed in Frey, 1998). Because such headaches only occur with prolonged cell/mobile

phone calls, these studies also provide evidence for a dose-response relationship because low doses are ineffective. Furthermore these same studies provide evidence for such a dose-response relationship from another type of observation. Because the headaches occur predominantly on the ipsilateral side of the head which receives much higher EMF exposure intensity, rather than on the contralateral side of the head, which receives much lower intensities, this provides an additional type of evidence for the predicted dose-response relationship.

While the evidence is convincing that the various neuropsychiatric apparent consequences of microwave EMF exposure are in fact caused by such exposures, there may be somewhat more controversy about another EMF-neuropsychiatric linkage. Havas et al (2010) have reported a similar list of neuropsychiatric symptoms in electromagnetic hypersensitivity (EHS) patients. They found that each of the following symptoms were common in EHS: poor short term memory; difficulty of concentration; eye problems; sleep disorder; feeling unwell; headache; dizziness; tinnitus; chronic fatigue; tremors; body pain; difficulty speaking; tingling sensation in feet or hands; difficulty writing; difficulty walking; migraine. The similarity of these symptoms to the most commonly found symptoms following non-thermal microwave EMF exposures (Table 3), suggests that EHS is a genuine sensitivity to EMFs. In the bottom row in Table 2, sensitivities were found in rodent studies following non-thermal exposure, that suggest a possible animal model for the study of EHS. Each of these EHS-related issues needs to be followed up experimentally.

Discussion and Conclusions:

In the previous section, each of the five criteria for assessing whether an epidemiological association is causal were considered. Those five are (Hennekens and Buring, 1989): 1. Strength of association; 2. Biological credibility; 3. Consistency; 4. Time sequence; 5. Dose-response relationship. Each of these five provide strong support for causality such that the combination of all five provide compelling evidence for causality. Low-intensity microwave frequency EMFs do cause diverse neuropsychiatric symptoms. While each of these five is important here, the one that is most important is the criterion of biological credibility.

Three related sets of biological observations each predict that low-intensity microwave EMFs produce widespread neuropsychiatric effects:

1. Such EMFs act via activation of VGCCs, acting through the VGCC voltage sensor which is predicted to be exquisitely sensitive to these EMFs (Pall, 2015). VGCCs occur in high densities throughout the nervous system and have essential roles throughout the nervous system in releasing neurotransmitters and neuroendocrine hormones. These properties predict, therefore, that these low intensity non-thermal microwave EMFs cause widespread changes in the nervous system, causing, in turn, diverse neuropsychiatric effects.
2. Elevated VGCC activity, produced by an allele of the CACNA1C gene which encodes the channel of the main L-type VGCC in the brain, produces various

neuropsychiatric effects (Table 1). This predicts, that low intensity non-thermal microwave frequency EMFs which also produce elevated L-type and other VGCC activity, therefore produce widespread neuropsychiatric effects.

3. Studies reviewed in the Tolgskaya and Gordon, 1973 publication (Table 2) have shown that the cells of the mammalian nervous system show high sensitivity to various non-thermal microwave and lower frequency EMFs, being apparently more sensitive than any other organ in the body of rodents. These studies predict that the human nervous system is likely to be similarly sensitive to these EMFs, predicting, therefore, widespread neuropsychiatric effects in humans.

We not only have biological credibility but more importantly, each of these distinct but interrelated biological considerations predicts that low-intensity, non-thermal microwave EMFs produce widespread neuropsychiatric effects. That common prediction is verified by extensive data summarized in citations provided by the Naval Medical Research Institute Research Report, June 1971, data provided by The Raines, 1981 NASA report, and by 26 epidemiological studies summarized in Table 3.

The most commonly reported neuropsychiatric symptoms from these studies are summarized in Table. 4.

Table 4. Commonly Reported Neuropsychiatric Symptoms following Microwave EMF Exposure

Symptom(s)	Numbers of studies reporting
Sleep disturbance/insomnia	17
Headache	14
Fatigue/tiredness	11
Depression/depressive symptoms	10
Dysesthesia (vision/hearing/olfactory dysfunction)	10
Concentration/attention/cognitive dysfunction	10
Dizziness/vertigo	9
Memory changes	8
Restlessness/tension/anxiety/stress/agitation/feeling of discomfort	8
Irritability	7
Loss of appetite/body weight	6
Skin tingling/burning/inflammation/dermographism	6
Nausea	5

A total of 22 different studies described in Table 3 were used for data for this table, but not 4 others that only assessed a single neuropsychiatric end point. The Altpeter study which only assessed sleep disturbance/melatonin depletion and the three studies listed under Chu et al which only assessed headache occurrence following long cell phone calls, listed in Table 3 were *not* included. Because many of the studies only assessed from 3 to 7 specific symptoms, it is not surprising that the numbers of studies reporting a specific

symptom fall far below 22. Where several symptom descriptions were included under one heading, such as dysesthesia, if a study had more than one of these symptom descriptions, it was only counted once.

All the symptoms listed in Table 4 should be considered established parts of microwave syndrome (Hocking, 2001; Johnson Liakouris, 1998). Even if the statistical significance in each study was of the lowest statistical significance ($p < .05$) one would expect only 1 positive study to occur at random out of the 22 studies included here. Because many individual symptoms were not surveyed in many individual studies, the expectation is substantially lower than that. Each of these, having shown positive results in 5 or more studies, are highly unlikely, therefore, to have occurred by chance. Strong statistical significance is also seen for individual neuropsychiatric effects reported to have $p < 0.001$ in the Eger and Jahn, 2010 and Otto et al, 1994 studies (see Table 3).

EEG changes may well be part of microwave syndrome, as well. While none of the studies described in Table 3 measured EEGs, six studies of human occupational exposure cited in the Raines, 1981 showed EEG changes (Baranski and Edelwejn, 1975; Bise, 1978; Dumanskij and Shandala, 1974; Lerner, 1980; Hauf and Weisinger, 1973; Sheppard and Eisenbud, 1977). Murbach et al, 2014 cited 10 human studies in support of their statement that “The most consistently reported effects (of mobile phone use) in various studies conducted by different laboratories are changes in the electroencephalogram (EEG) power spectrum.” Three recent studies (Lustenberger et al, 2013; Schmid et al, 2012a,b) and several earlier studies cited in Wagner et al (1998) have each shown EEG changes in sleeping humans exposed to non-thermal pulsed microwave fields. Two recent studies showed EEG changes in persons exposed to Wi-Fi fields (Maganioti, 2010; Papageorgiou, 2011). Lai, 1997 described 8 animal studies showing changes in EEG patterns in animals exposed to non-thermal EMFs and three additional animal studies were described in Tolgskaya and Gordon, 1973. With the exception of the 6 studies cited in the second sentence in this paragraph, all of these are direct experimental studies which are not, therefore, susceptible to the questions of causality that can be raised about epidemiological studies. It is the author’s view that future studies should consider studying EEG changes as an objectively measurable assessment of brain physiology and that before and after increased exposure studies should be considered when a new EMF source is to be introduced into human populations. While such studies must be done carefully, given the complexity of EEGs, even very small numbers of individuals may produce highly statistically significant results in well designed studies analyzed with paired t-tests.

One of the citations from the previous paragraph, Bise, 1978 reviewed earlier studies of low level microwave frequency exposures in humans and concluded that such EMFs produced the following neuropsychiatric effects: headache, fatigue, irritability, dizziness, loss of appetite, sleepiness, sweating, difficulty of concentration, memory loss, depression, emotional instability, dermatographism, tremor, hallucinations and insomnia. The strong similarity of this list from 37 years ago and the list in Table 4 should be noted. The Bise, 1978 list is based on occupational exposure studies whereas the current list in Table 4 is based primarily on EMF exposures from cell/mobile phone base stations, from

heavy cell phone usage and from smart meters, *three types of exposures that did not exist in 1978*. The strong similarity between the Bise, 1978 list and the current one 37 years later alone produces a compelling argument that the 11 neuropsychiatric effects found on both lists are caused by exposure to multiple types of low-intensity microwave EMFs.

The pattern of evidence is compelling in support of the earlier statement of Levitt and Lai (2010) that “The primary questions now involve specific exposure parameters, not the reality of complaints or attempts to attribute such complaints to psychosomatic causes, malingering or beliefs in paranormal phenomena.”

We can barely imagine how the combinations of neuropsychiatric effects, including those in Table 4, will influence human behavior and social interactions, now that the majority of the human populations on earth are exposed to ever increasing intensities and diversity of microwave frequency EMFs. You may recall that three of the occupational exposure studies cited in (Raines, 1981 showed increasing prevalence of neuropsychiatric symptoms with years of exposure to consistent patterns of EMF exposure intensities (Dwyer and Leeper, 1978, Sadcikova, 1974 and Baranski and Edelwejn, 1975). With ever increasing exposures in human populations, we have no idea what the consequences of these ever increasing exposures will be.

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Highlights:

- Microwave EMFs activate voltage-gated Ca²⁺ channels (VGCCs) concentrated in the brain
- Animal studies show such low level MWV EMFs have diverse high impacts in the brain
- VGCC activity causes widespread neuropsychiatric effects in humans (genetic studies)
- 26 studies have EMFs assoc. with neuropsychiatric effects; 5 criteria show causality
- MWV EMFs cause at least 13 neuropsychiatric effects including depression in humans