August 28, 2018

mr. Jeremy V. Farrell
mr. Paul Shane Miller
Attorneys for Duquesne Light Co.
Tucker/Arensberg Attorneys
1500 One PPG Place
Pittsburgh, PA 15222

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SECRETARY'S BUREAU

CC: Rosemary Chiavetta, Seceretary
PA Utility Commission
Keystone Bldg. 2nd floor-W
400 N. St.
Harrisburg, PA 17120

RE: Kathrine E. Hubel v. Duquesne Light Co.
Docket No. C-2018-30002620

Response to Motion for a Prehearing Conference

I have no objections to a prehearing conference providing I have 2 months or more from the dispositive motion to prepare.

Respectfully Submitted,

Kathrine E. Hubel

Kathrine E. Hubel 611 Edgewood Rd. Pitts, PA 15221

August 28, 2018

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Mr. Paul Shane Miller
Attorneys for Duquesne Light Co.
Tucker/Arensberg Attorneys
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CC: Rosemary Chiavetta, Secretary
Pennsylvania Public Utility Commission
Keystone Bldg. 2nd floor W
400 N. St.
Harrisburg, PA 17120

RE: Kathrine E. Hubel v. Duquesne Light Company
Docket No. C-2018-3002620

Response to First set of Discovery Requests

1. a. multitudes of scientists, researchers, doctors, & veterinarians have reported on the biological harm of the pulsed microwave radiation emitted by smart meters as well as the dirty electricity

that is generated by them. I have enclosed some of these articles & letters. There are additional ones on the enclosed memory stick.

b. multitudes of people (like myself) experience immediate adverse symptoms with exposure to the pulsed microwave radiation emitted by smart meters and/or the dirty electricity they generate. Symptoms occur at exposures far below any limits set by government agencies. This condition is known as Electromagnetic Hypersensitivity.

c. The Academy of Environmental Medicine recommends that those who suffer from the condition minimize their exposures to all forms of "Electrosmog" (magnetic fields, electric fields, microwave radiation, & dirty electricity) to minimize symptoms & prevent worsening of the condition. Exposures in the home are considered the most important, especially the bedroom.

A report from The American Academy of Environmental medicine entitled "American Academy of Environmental medicine Recommendations Regarding Electromagnetic and RadioFrequency Exposure" recommends that patients with certain medical conditions be accommodated to protect their health by not having a smart meter on Their home & by not having collection meters placed near Their home. This would include me. A copy of this document is on The enclosed memory stick.

d. My doctor has written a letter to DuQuesne Light requesting That a smart meter not be installed on my home due to This condition. A copy of The letter is enclosed.

e. A large number of individuals have reported significant changes in Their health & well being related to The installation of wireless smart meters on their homes. This has led to community activism against the meters, with websites and appeals to decision makers & politicians.

f. An increasing number of physicians are becoming convinced of the harmfulness of the radiation emitted by smart meters. Dr. Joseph Mercola and Dr. Dietrich Klinghardt are 2 internationally knowned physicians that have been very vocal about the issue, but there are so many more. Dr. Thomas Rau, medical Director of the world-renowned Paracelsus Clinic in Switzerland, has stated he has become convinced that "electro magnetic loads can lead to cancer, Parkinson's, ADD, arrhythmia, back pain, insomnia, concentration problems, tinnitus, & migrains. At Paracelsus, cancer patients are now routinely educated in electromagnetic field remediation strategies with inspectors from the Geopathological Institute of Switzerland sent to patients' homes to assess their exposures. At Dietrich Klinghardt's clinic, The Sophia Health Institute, people are told up front that mitigating exposures to things such as radiation from smart meters, are a pre-condition to being accepted as a patient there.

g. The BioInitiative Report which can be found online & is many hundreds of pages, contains a lot of research as well on the harmful biological effects of the radiation emitted by smart meters. I was not able to download it due to a corruption issue, but I plan to use pieces of it to, also, support my case.

h. Although there are no lab tests for Electromagnetic Hypersensitivity, my friends & family members can vouch for my adverse symptoms. Additionally, I have been on the State's Chemical Sensitivity Registry for many years & have spent a lot of money on my home to reduce my exposures.

2. Scientific articles and other documents that support my contention that the radiation from smart meters is harmful & in particular to someone who suffers from Electromagnetic Hypersensitivity are either enclosed with this response or can be found on the enclosed memory stick. This is only a very small percentage of the material available. I plan to continue adding to it until closer to my hearing. I am also waiting for some research results that have not yet been published & will forward them as soon as I receive them.

3. These concerns were addressed in #1.

4. same as above

5. Electromagnetic Hypersensitivity

6. A copy of the original letter my doctor wrote to Duquesne Light Co. stating my sensitivity is enclosed.

7. These documents have been included in my response to #1.

8. The letter is enclosed.

9. I am a college graduate who received a bachelor of science in electrical engineering from Duke University. I, also, spent 6 months studying electrical engineering at The City University in London, England. Additionally, I did post-graduate coursework at the University of Vermont in human development, physiology, anatomy, and health education.

10. My resume was destroyed in flooding of our previous home. I have not had need of one since then, as I have not been employed. All the employment information you would have any interest in is listed in # 9, 11, 12, 13, and 14.

11. Yes

12.
a, b, c. I worked for Duke University Sept. 1976-May 1978 as a research assistant on studies on aging. I

performed data collection & analysis of cognitive data on older patients.

I worked for Digital Equipment corporation as an electrical engineer from august 1979 - Jan. 1982. I wrote inspection procedures for certain components of large frame CPU's that were manufactured by the company. Additionally, I was responsible for solving manufacturing problems as they arose & in plant preparations for new products & contracts with other Digital vendors.

I worked for the University of Vermont School of Medicine and Given comprehensive medical center from Jan. 1982 - June 1986 as clinic research coordinator. I worked on studies involving blood sugar control of diabetics, smoking cessation, and medical records sharing. I provided smoking cessation counseling, conducted patient interviews, generated questionnaires, & did data collection and statistical analysis.

13. NO

14. N/A

15. All relevant documents are listed in my response to #1.

16. I own a cell phone that is rarely used. I only use it to make important calls when I am away from home. Otherwise, it is off & non-operational. my husband, also, owns a cell phone. He only uses it at work. At home, he uses our land-line phone. These 2 phones are an LGI LG-VX 5400 (my phone) and an Apple iPhone 7 (my husband's phone).

17. Copies of the last 6 bills from verizon for our cell phones are enclosed. my son's cell phone is included on our bill (Nathaniel Huber), but he does not live with us.

These bills encompass our cell phone usage from Jan. 29, 2018 Thru July 28, 2018.

18. The user manuals to my cell phone & my husband's is on The enclosed memory stick.

19. This has been covered in response to #1.

20. same as above

21. As stated previously, I am continuing to accumalate research findings & other documents to support my claims & will continue to share These as we move to a hearing.

22. At This point in time, I am not expecting to call anyone to testify.

23. N/A
24. N/A
25. N/A

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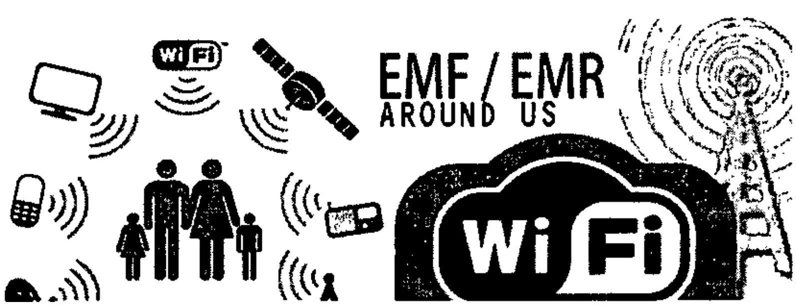
Dramatic Visual Medical Proof Of EMF Electromagnetic Hypersensitivity In EHS Patients

TOPICS: Catherine Frompovich EHS EMF Smart Meters WiFi

DECEMBER 6, 2017



erine J. Frompovich

agnetic hypersensitivity (EHS), or y known as idiopathic environmental intolerance (IEI) by the World Health Organization [1], is described as haracterized by a variety of non-specific nptoms, which afflicted individuals aribute to exposure to EMF. The symptoms st commonly experienced include matological symptoms (redness, tingling, l burning sensations) as well as neurasthenic and vegetative symptoms (fatigue, tiredness, concentration difficulties, dizziness, nausea, heart palpitation, and digestive disturbances). The collection of symptoms is not part of any recognized syndrome.

EHS resembles multiple chemical sensitivities (MCS), another disorder associated with low-level environmental exposures to chemicals. Both EHS and MCS are characterized by a range of non-specific symptoms that lack apparent toxicological or physiological basis or independent verification. A more general term for sensitivity to environmental factors is Idiopathic Environmental Intolerance (IEI), which originated from a workshop convened by the International Program on Chemical Safety (IPCS) of the WHO in 1996 in Berlin. IEI is a descriptor without any implication of chemical etiology, immunological sensitivity or EMF susceptibility. IEI incorporates a number of disorders sharing similar non-specific medically unexplained symptoms that adversely affect people. However since the term EHS is in common usage it will continue to be used here.

One of the most frustrating, and truly unfortunate aspects of EHS, is that everyone in the industries which generate EMFs/RFs which cause the problem, [...] ly the professional association ICNIRP, [...] ly denies it exists, and those who suffer [...] re "psych jobs"! Well, that's got to end now, [...] are graphic studies proving visual differences in the brains of EHS sufferers compared [...] se folks who do not experience EHS or IEI.

Below are two lateral X-rays showing the differences between the brain of an EHS/IEI patient on the left and the brain of a non-EHS-compromised individual on the right.

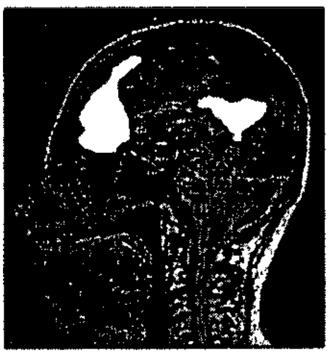


Figure 5. Lateral view of case no. 5.

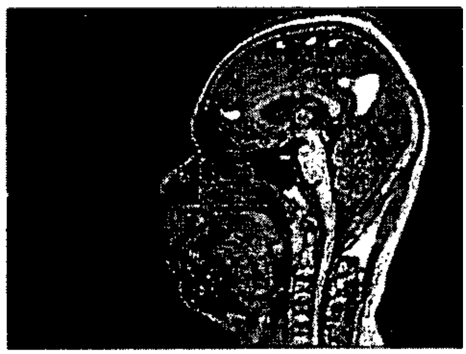


Figure 11. Lateral view of a normal brain. Note absence of abnormal white areas seen in the patient group

In a preliminary Press Release dated December 5, 2017, the results of brain fMRIs (functional magnetic resonance imaging) from a pilot study have been released in anticipation of a **Tele-Press Conference to be held Thursday, December 7, 2015, in Los Angeles, California.**

e Peoples Initiative Foundation will be lding a tele-press conference to take uestions from the media Thurs. Dec. 7th @ noon PST. The study's principle author, Gunnar Heuser* [MD, PhD] *will be on the l to take questions about the study, as well as Liz Barris, study organizer and one of the EHS cases in the study to take questions about EHS.

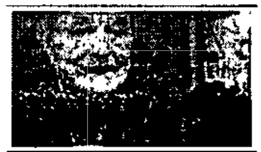
Please call 515-739-1219 access code 283521#

Emergency backup # *only in case above # has problem*: 605-472-5616 access code 106520#

The results of Dr. Gunnar Heuser and Sylvia A. Heuser's study were published in Volume 32 (September 2017) of De Gruyter's ***Reviews on Environmental Health*** as the paper "**Functional brain MRI in patients complaining of electrohypersensitivity after long term exposure to electromagnetic fields.**"

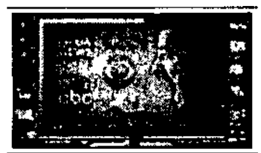
Problem With...

AUGUST 26, 2018



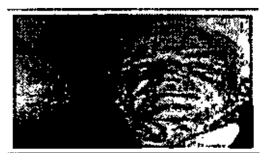
Soros' Role in Social Media Censorship Revealed in...

AUGUST 26, 2018



The 10 Primary Directives of Mainstream Media

AUGUST 24, 2018



The Un-American Hero: The Crimes of John McCain

FEBRUARY 2, 2015

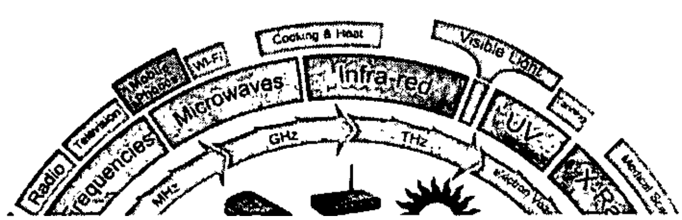
5G Explained By Researcher Arthur Firstenberg: Be Forewarned

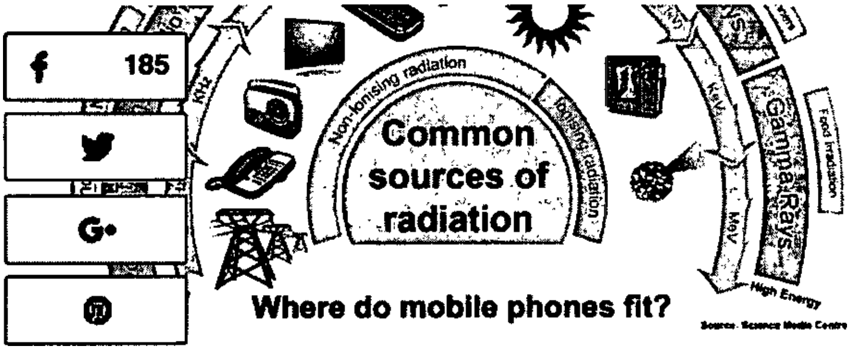
AUGUST 27, 2018

The online published paper includes X-rays of all patients in the study, which indicate the severity of EHS/IEI and shows graphically how it physically affects brain tissue.

Electromagnetic fields are emitted by the following high-tech, aka 'smart' products, appliances and services:

- Any service or device that sends and/or receives voice, data or graphics/pictures using microwave wireless technology, e.g., cell phones, iPhones, smart phones, etc.
- AMI Smart Meters being retrofitted by electric, natural gas and water utilities
- Monitoring devices, e.g., baby monitors and wearable devices that track and record body data
- Wi-Fi in homes, schools, work places, cafés, or other public places providing it, such as doctors' offices
- Routers





Source

Source

For all those EHS patients, who refuse AMI Smart Meters claiming EHS and have *pro se* lawsuits before their respective state Public Utility Commission agency's Administrative Law Courts, this 2017 study ought to refute the utilities medical and EMF/RF experts, who still believe in the 'flat earth society' theory when it comes to EMFs/RFs/ELFs and microwave-produced, non-thermal radiation waves adverse health effects that cause EHS/IEI.

References:

[1] http://www.who.int/peh-emf/publications

One-time charges

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Plan and account

Late fee for amount due February 20	**$5.00**

Kathy Hubel 412.977.2870

Usage while in the US

1 call to 411	**$1.99**

$6.99

The new Verizon Plan Large 8 GB

8 GB Shared Data, Carryover Data, Unlimited Talk and Text
+ 1.723 GB extra

Monthly charges (Mar 1 - Mar 28)	**$70.00**

$70.00

Shared data usage

	Used/Allowance
	6.198 of 9.723 GB
Nathaniel Hubel 412.862.0757	**4.262 GB**
Carl Hubel 412.952.6307	**1.938 GB**
Kathy Hubel 412.977.2870	**0.001 GB**

The new Verizon Plan Large 8 GB

8 GB Shared Data, Carryover Data, Unlimited Talk and Text
+ 1.801 GB extra

Monthly charges (Mar 29 - Apr 28) **$70.00**

$70.00

Shared data usage

	Used/Allowance
	5.400 of 9.801 GB
Nathaniel Hubel 412.862.0757	**3.350 GB**
Carl Hubel 412.952.6307	**2.051 GB**
Kathy Hubel 412.977.2870	**0.001 GB**

Types of data you used

	Used/Allowance
The new Verizon Plan Large 8 GB	**5.400 / 8 GB**
Carryover from last month (Mar 01 - Mar 28)	**0 / 1.801 GB**

2.600 GB of unused data will carry over to next month (Mar 29 - Apr 28)

Unused Carryover data from last month expired March 28.

Estimated top activities*

Web & Apps 43%

Social 21%

Video 20%

*Top activities are estimated for general information purposes only.

Usage history

Mar 1 - Mar 28	**5.400 / 9.801 GB**
Jan 29 - Feb 28	**6.198 / 9.723 GB**
Dec 29 - Jan 28	**7.276 / 10.638 GB**

Shared data usage

	Used/Allowance
	5.468 of 10.599 GB
Nathaniel Hubel 412.862.0757	**2.802 GB**
Carl Hubel 412.952.6307	**2.668 GB**
Kathy Hubel 412.977.2870	**0.001 GB**

Types of data you used

	Used/Allowance
The new Verizon Plan Large 8 GB	**5.468 / 8 GB**
Carryover from last month(Mar 29 - Apr 28)	**0 / 2.599 GB**

2.532 GB of unused data will carry over to next month (Apr 29 - May 28)

Unused Carryover data from last month expired April 28.

Estimated top activities*

Web & Apps 40%

Social 23%

Gaming 12%

*Top activities are estimated for general information purposes only.

Usage history

Mar 29 - Apr 28	**5.468 / 10.599 GB**
Mar 1 - Mar 28	**5.400 / 9.801 GB**
Jan 29 - Feb 28	**6.198 / 9.723 GB**

One-time charges

Carl Hubel 412.952.6307

Usage while in the US

Long Distance - Verizon Wireless	**$0.49**

Usage while outside the US

Travelpass - Canada (May 16)	**$5.00**

Kathy Hubel 412.977.2870

Usage while in the US

2 calls to 411	**$3.98**

$9.47

The new Verizon Plan Large 8 GB

8 GB Shared Data, Carryover Data, Unlimited Talk and Text
+ 2.531 GB extra

Monthly charges (May 29 - Jun 28)	**$70.00**

$70.00

Shared data usage

	Used/Allowance
	6.464 of 10.531 GB
Nathaniel Hubel 412.862.0757	**4.415 GB**
Carl Hubel 412.952.6307	**2.051 GB**
Kathy Hubel 412.977.2870	**0.001 GB**

The new Verizon Plan Large 8 GB

8 GB Shared Data, Carryover Data, Unlimited Talk and Text
+ 1.535 GB extra

Monthly charges (Jun 29 - Jul 28)	$70.00

$70.00

Shared data usage

	Used/Allowance
	7.742 of 9.535 GB
Nathaniel Hubel 412.862.0757	5.761 GB
Carl Hubel 412.952.6307	1.982 GB
Kathy Hubel 412.977.2870	0.001 GB

Types of data you used

	Used/Allowance
The new Verizon Plan Large 8 GB	7.742 / 8 GB
Carryover from last month(May 29 - Jun 28)	0 / 1.535 GB

0.258 GB of unused data will carry over to next month (Jun 29 - Jul 28)

Unused Carryover data from last month expired June 28.

Estimated top activities*

Web & Apps 49%

Social 20%

Audio 9%

*Top activities are estimated for general information purposes only.

Usage history

May 29 - Jun 28	7.742 / 9.535 GB
Apr 29 - May 28	6.464 / 10.531 GB
Mar 29 - Apr 28	5.468 / 10.599 GB

One-time charges

Carl Hubel 412.952.6307

Usage while in the US

Long Distance - Verizon Wireless	**$29.40**

Kathy Hubel 412.977.2870

Usage while in the US

1 call to 411	**$1.99**

$31.39

The new Verizon Plan Large 8 GB

8 GB Shared Data, Carryover Data, Unlimited Talk and Text
+ 0.257 GB extra

Monthly charges (Jul 29 - Aug 28)	**$70.00**

$70.00

Shared data usage

	Used/Allowance
	7.024 of 8.257 GB
Nathaniel Hubel 412.862.0757 [redacted]	**4.820 GB**
Carl Hubel 412.952.6307 [redacted]	**2.205 GB**
Kathy Hubel 412.977.2870	**0.001 GB**

The Hormone center

Phone: 412.432.7909
Fax: 412.202.2304

2100 Wharton Street
Suite 315
Pittsburgh, PA 15120

Diamond Physical Therapy
4623 State Route 136
Greensburg, PA 15601

One Landmark North Bldg
20399 Route 19, Suite 120
Cranberry Twp., PA 16066

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June 16, 2016

To Whom It May Concern:

It has been brought to my attention that you intend to install smart meters on all of your customers' homes and businesses in the very near future. I am writing to request that you do not install one on the home of Kathrine Hubel at 611 Edgewood Rd., Pittsburgh, PA (Forest Hills) 15221 for medical reasons. As her physician, I am aware of her sensitivity to strong electromagnetic fields, dirty electricity, and especially pulsed radio frequency which is emitted by smart meters.

She has a long history of health problems associated with such exposure and has taken steps to limit her exposure, especially in the home. This has been very beneficial and will help to prevent worsening of the sensitivity. She has been diagnosed with chronic lyme disease and this sensitivity to radiation is well known to Lyme disease specialists among their patients with chronic lyme. My hope is that you will do everything in your power to accommodate this request for someone who's life is already hard enough.

Yours truly:

Lauren Loya, M.D.

DE GRUYTER Rev Environ Health 2015; 30(2): 99–116

Open Access

Martin L. Pall*

Scientific evidence contradicts findings and assumptions of Canadian Safety Panel 6: microwaves act through voltage-gated calcium channel activation to induce biological impacts at non-thermal levels, supporting a paradigm shift for microwave/lower frequency electromagnetic field action

Abstract: This review considers a paradigm shift on microwave electromagnetic field (EMF) action from only thermal effects to action via voltage-gated calcium channel (VGCC) activation. Microwave/lower frequency EMFs were shown in two dozen studies to act via VGCC activation because all effects studied were blocked by calcium channel blockers. This mode of action was further supported by hundreds of studies showing microwave changes in calcium fluxes and intracellular calcium [Ca2+]i signaling. The biophysical properties of VGCCs/similar channels make them particularly sensitive to low intensity, non-thermal EMF exposures. Non-thermal studies have shown that in most cases pulsed fields are more active than are non-pulsed fields and that exposures within certain intensity windows have much large biological effects than do either lower or higher intensity exposures; these are both consistent with a VGCC role but inconsistent with only a heating/thermal role. Downstream effects of VGCC activation include calcium signaling, elevated nitric oxide (NO), NO signaling, peroxynitrite, free radical formation, and oxidative stress. Downstream effects explain repeatedly reported biological responses to non-thermal exposures: oxidative stress; single and double strand breaks in cellular DNA; cancer; male and female infertility; lowered melatonin/sleep disruption; cardiac changes including tachycardia, arrhythmia, and sudden cardiac death; diverse neuropsychiatric effects including depression; and therapeutic effects. Non-VGCC non-thermal mechanisms may occur, but none have been shown to have effects in mammals. Biologically relevant safety standards can be developed through studies of cell lines/cell cultures with high levels of different VGCCs, measuring their responses to different EMF exposures. The 2014 Canadian Report by a panel of experts only recognizes thermal effects regarding safety standards for non-ionizing radiation exposures. Its position is therefore contradicted by each of the observations above. The Report is assessed here in several ways including through Karl Popper's assessment of strength of evidence. Popper argues that the strongest type of evidence is evidence that falsifies a theory; second strongest is a test of "risky prediction"; the weakest confirms a prediction that the theory could be correct but in no way rules out alternative theories. All of the evidence supporting the Report's conclusion that only thermal effects need be considered are of the weakest type, confirming prediction but not ruling out alternatives. In contrast, there are thousands of studies apparently falsifying their position. The Report argues that there are no biophysically viable mechanisms for non-thermal effects (shown to be false, see above). It claims that there are many "inconsistencies" in the literature causing them to throw out large numbers of studies; however, the one area where it apparently documents this claim, that of genotoxicity, shows no inconsistencies; rather it shows that various cell types, fields and end points produce different responses, as should be expected. The Report claims that cataract formation is produced by thermal effects but ignores studies falsifying this claim and also studies showing [Ca2+]i and VGCC roles. It is time for a paradigm shift away from only thermal effects toward VGCC activation and consequent downstream effects.

***Corresponding author: Martin L. Pall,** Washington State University, 638 NE 41st Ave., Portland, OR 97232-3312, USA,
E-mail: martin_pall@wsu.edu

Keywords: calcium and nitric oxide signaling; calcium channel blockers; low level microwave/radiofrequency radiation; oxidative and nitrosative stress; peroxynitrite.

DOI 10.1515/reveh-2015-0001
Received January 8, 2015; accepted March 10, 2015; previously published online April 16, 2015

Introduction

There has been a literature reporting various non-thermal effects of microwave/radiofrequency radiation exposures starting with the Soviet literature in the 1950s. Subsequently, there have been thousands of international published studies reporting non-thermal or what are sometimes called micro-thermal effects producing therapeutic responses, changes in calcium fluxes and signaling, increased oxidative stress, and a wide variety other health-related responses in humans and animal models.

Nevertheless, there has been a series of medical reports, arguing that only thermal effects need be considered when setting guidelines or safety standards for microwave electromagnetic field (EMF) exposures. These have been based mainly on two types of arguments:

- That there cannot be any biophysically viable mechanism for any such non-thermal effects and therefore that reports of such effects should be viewed with great skepticism.
- That there are many "conflicts" or "inconsistencies" in the literature which according to these reports, justify rejection of the various thousands of publications showing apparent non-thermal effects.

The focus of this review is to consider whether it is time for a "paradigm shift" away from strictly thermal effects toward non-thermal effects. Specifically, it is focused on the recent finding that most, possibly all non-thermal effects can be produced by microwave activation of voltage-gated calcium channels (VGCCs). It is also focused on the 2014 Report of the Canadian Panel of Experts on Safety Code 6 as the most recent and therefore up-to-date summary of the evidence supporting the strictly thermal point of view.

EMFs act via stimulation of voltage-gated calcium channels (VGCCs)

Calcium provides an essential role in cell function, being normally maintained at very low, circa 10^{-7} M intracellular levels, but also with transient intracellular calcium ([Ca2+]i) increases being used for widespread and important regulatory signaling. A recent review (1), noted that in two dozen studies, calcium channel blocking drugs block a wide range of electromagnetic field (EMF) effects on cells and organisms by blocking voltage-gated calcium channels (VGCCs which are also known as voltage-operated, voltage-dependent or voltage-regulated calcium channels). In most but not all cases, L-type VGCCs were studied, but T-type, N-type and P/Q-type channels can also have roles, as shown by channel blockers specific for these other channels (1). In each of these studies, calcium channel blockers blocked or greatly lowered each of the responses studied, showing that VGCC activation is required for low intensity fields to produce a wide range of responses (1). Each of these channel blockers is thought to be highly specific, such that with two different types of L-type blockers being used that act at different sites on the L-type VGCCs and also one each of the T-type, N-type and P/Q type blockers being used, with each showing activity in blocking or greatly lowering EMF responses, it is highly unlikely that a non-VGCC mechanism is involved here.

VGCC activation is thought to act mainly by increasing [Ca2+]i. Other considerations also support VGCCs as a major EMF target, accounting for numerous biological impacts of microwave exposures (1–3) at levels not producing substantial changes in temperature.

Pilla published a very important paper, suggesting in retrospect that these low-level fields directly activate the VGCCs (4, see also 1–3). He showed that cells in culture when exposed to a low intensity pulsed microwave field, produce an almost instantaneous Ca^{2+}/calmodulin-dependent increase in nitric oxide (NO), occurring in <5 s. The NO increase is produced by the [Ca2+]i activating the two Ca^{2+}/calmodulin-dependent NO synthases, which can occur almost instantaneously. These results show that the [Ca2+]i increases must also occur almost instantaneously, providing strong evidence that the VGCCs are directly activated by the low intensity field in this study. The known properties of the VGCCs are discussed below, properties that are expected to make them particularly susceptible to activation by such low intensity fields.

In addition to calcium channel blocker studies, the important role of VGCC activation for the biological effects of microwave radiation at levels that do not produce measured changes in temperature is also supported by a large number of studies, some of which were reviewed earlier (5, 6), showing that low level microwave EMF exposures lead to measured changes in calcium signaling and/or calcium fluxes consistent with VGCC activation. There are also hundreds of studies of oxidative stress responses to low intensity field exposures, which can also be produced by downstream effects of increased [Ca2+]i (1–3). The mode of microwave action via VGCC activation also confirms earlier predictions of Panagopoulos et al. (7, 8) that EMFs may act via voltage-gated ion channel activation. The whole issue of the biophysics of VGCCs and other voltage-gated ion channels is discussed in some detail below.

Various frequencies, intensities and pulse patterns of EMFs act via VGCC activation (1), including extremely low frequency fields of 50 or 60 Hz electrical wiring, microwave frequency EMFs also referred to as radiofrequency (RF), very short "nanosecond" pulses, and even static electric or magnetic fields. Given recent global increases in exposures to microwave/RF EMFs, the findings for microwave EMFs create the most concerns for both human and environmental health.

We are therefore in a situation where the paradigm of EMF action focused solely on heating (9–13), should be replaced by one based on VGCC activation of microwave and other EMFs (1–3).

In addition to impacts of EMFs directly involving VGCCs, there are a number of other related mechanisms which should be explored. For instance, Pilla reviewed 2 studies in which microwave EMFs increased apparent calmodulin activation (14). Calmodulin is regulated by [Ca2+]i such that calmodulin activation may act along with VGCC activation in two related pathways of action discussed below.

Three other types of observations that contradict the assumptions of current safety standards

Current safety standards are based on the assumption that all important biological effects of microwave and lower frequency EMFs are due to tissue heating (thermal effects) and that specific absorption rates (SARs) of EMFs are therefore a measure of their ability to produce all important biological effects. While the VGCC studies, discussed above clearly invalidate that assumption, there are three other distinct types of observations that also contradict that assumption. As discussed below, an extensive scientific literature reports biological microwave EMF effects at exposure levels well within safety standards and that therefore should not occur according to current safety standards. Two other types of falsifying evidence are the findings that pulsed fields are often much more biologically active than non-pulsed fields and that certain intensity windows of exposure are more biologically active than are exposures of both lower and higher intensities. These two are each discussed in some detail immediately below.

It has been known for well over 30 years that pulsed microwave fields are often much more biologically active than are continuous non-pulsed fields. This was shown, for example, by Seaman and Wachtel in studies of microwave exposures of Aplysia pacemaker cells (15). Pacemaker cells have a very high density of VGCCs, suggesting that the pulsed microwave exposures may in this study act via VGCC activation. This was shown by Bassett et al. (16) and by Pilla (17) both in 1974 studies of augmentation of bone repair, that pulsed field microwaves were much more active than continuous field microwave exposures. Both Baranski (18) and Czerski (19) showed that microwave pulsed field exposures were more active than non-pulsed fields in terms of their impact on blood forming cells. Micro pulsed field exposures were also more effective than non-pulsed continuous wave (CW) fields in producing a breakdown of the blood-brain barrier (20). Adey's review (21) stated that "There is evidence of interactions with radio and microwave fields pulse-modulated at higher frequencies from 500 to 1500 Hz and an absence of similar effects with CW fields of the same average power density at the same carrier frequency." Several other studies are cited in the Adey (21) review documenting higher biological activity of pulsed fields than non-pulsed CW fields at identical power levels. A recent study showing that pulsed microwave EMFs acted via activation of L-type VGCCs (22) suggests that all these inconsistencies of the pulsed field findings with any heating mechanism may be due to their action in VGCC activation.

More than four decades ago, the biological impact of non-thermal levels of pulsed fields was sufficiently well documented that it became the basis for a number of therapeutic applications of microwave pulses. Therapies currently employed include a wide range of bone growth and orthopedic rehabilitation regimens as well as some applications to enhance the uptake of chemotherapeutic agents (14). These numerous therapeutic effects are well established to be non-thermal and operate through increased levels of [Ca2+]i and nitric oxide (NO) signaling (2, 14). The medical use of these pulsed fields provides therefore prima facie evidence that such fields are often more active in VGCC activation than are non-pulsed fields.

The greater biological activity of pulsed field exposures were sufficiently well documented 30–48 years ago, such that it influenced safety standards of the 1960s and 1970s. For example, the Canadian Standards Association 48 years ago in 1966, adopted lower standards [see Table 2 in ref. (23)] for occupational exposure to pulsed field exposures (1 $mWhr/cm^2$, limited to 6 min exposure) in contrast to those for continuous, that is non-pulsed exposures

(10 mW/cm^2, for which there was no time limitation). In 1974, in the United States, the American National Standards Institute (ANSI) adopted essentially identical standards as had Canada for occupational pulsed field and non-pulsed field exposure (23). In 1970, the Czechoslovakian government adopted more stringent occupational and general public standards for pulsed field exposures vs non-pulsed field exposures (23). Pulsed fields are, of course, produced by any type of wireless communication device since it is the pattern of pulsations that conveys the information. Different devices often use different types of pulsation patterns. However, we do not know how biologically active the different pulsation patterns are, because this has not been systematically studied. As a result, we cannot rationally compare the dangers of one device vs another.

Furthermore, Barrie Trower, a retired military intelligence expert from the United Kingdom, has stated that classified research indicates that different wavelengths vary in their biological activities as well. He reports that the specific details about the biological impacts of variations in pulsed electromagnetic fields are classified by multiple countries because of "national security". Thus much of what research appears to have been done in this field remains unavailable to decision makers charged with setting standards on such devices that emit pulsed electromagnetic fields.

It has been shown that there can be intensity "windows" where biological activity is greater than at intensities both higher and lower than the window intensity (24–32). This again argues against a heating mechanism as there are no known thermal dose-response curves with similar windows. In addition, these window effects are also found at levels where there is extremely low heating. For example, Blackman et al. (28) state that "Because of the extremely small increments of temperature associated with positive findings [less that $4\times10(-4)$ degrees C], and the existence of more than one productive absorption rate ("window"), a solely thermal explanation appears extremely unlikely". It is (31) stated that "Since there was no detectable temperature increase during exposures, the recorded effects are considered non-thermal". The suggested mechanism (31) may involve a role of voltage-gated ion channels such that "the action of external EMF on cells is dependent on irregular gating of membrane electrosensitive ion channels whenever a force on the channel sensors exceeds the force exerted on them by a change in the membrane potential of about 30 mV which is necessary to gate the channel normally. If in some kind of cells there is an upper limit for this value of membrane potential change, then the channel would be gated whenever the force exerted on its sensors is within this 'window'". Five of these studies show effects on $[Ca2+]$ i fluxes (24–28), consistent with possible roles of VGCCs. These studies provide strong evidence that these window effects occur at levels where there is either no measured change in temperature or extremely low heating.

Perhaps the strongest evidence for non-thermal effects of EMFs comes from studies on animal female and human male reproduction. This literature indicates that sperm exposed to microwave radiation emitted by approved mobile phones die three times faster and develop significantly more damage to their mitochondrial DNA (33). Studies of pregnant mice, rats and rabbits report that prenatally exposed offspring develop significantly more damage to their eyes, skin and liver (33) with hippocampus and pyramidal cell formation are impaired as well.

In summary, four distinct types of evidence provide contradictory information about the basic assumption underlying current US, Canadian and International Commission on Non-Ionizing Radiation Protection (ICNIRP) safety standards that non-thermal effects do not exist: Microwave and other lower frequency EMFs act via VGCC activation rather than by heating; there are numerous papers in the scientific literature reporting biological effects with exposures well within safety standards where substantial heating cannot occur. Moreover, pulsed fields are, in most cases, more biologically active than non-pulsed fields that produce equal heating; windows of exposure intensities occur which are more active than both higher and lower exposures of the same fields. While, in general, lower intensities are safer than higher intensities, this "window" effect shows that there are some major, biologically and medically important exceptions to this pattern. The pulsed field effects and the window effects make it impossible to currently predict biological activity without doing actual measurements of biological activity of specific devices at specific exposure intensities. The question of how to best approach and evaluate such biological effects is discussed below.

The properties of VGCCs and other voltage-gated ion channels may make them uniquely susceptible to low intensity MF activation

There has been an argument repeatedly put forth that there cannot be a biophysically viable mechanism for low intensity, apparently non-thermal effects. This claim is argued as follows [see Sheppard et al., ref. (34)]: While they acknowledge that EMFs can exert forces on charged groups, they argue that weak EMFs produce only weak forces that are less than are exerted by thermal motion produced at normal body temperature. They argue therefore that the only effects that can be produced by weak EMFs would be dwarfed by a high background noise created by random thermal motion. One of the problems with the Sheppard argument comes from a consideration of the structure of the voltage-gated ion channels and how these channels detect electrical changes, which may lead to opening the channel. The structure of the alpha-1 subunit containing the channel has been modeled and discussed (35–38).

What can be seen is that there are four similar domains in this protein, with each domain containing six transmembrane alpha helixes in it. These four domains are thought to have been produced evolutionarily by two tandem duplications, starting with a gene encoding a protein with one such domain. The fourth helix in each domain contains five positively charged amino acid side chains which collectively make up the voltage sensor (37, 38). It is thought that 20 (4×5) charges make up the voltage sensor, each of which must be pushed in approximately the same direction (and the right direction) at the same time in order for the channel to open. Changes in the membrane potential across the plasma membrane can do this, as can EMFs, because the fields will produce forces on these different charged groups in the same direction at a particular time. Random thermal motion, in contrast, is random in three dimensions and will only extraordinarily rarely produce forces on 20 groups in approximately the same direction at the same time. So you can see the thermal motion argument is clearly at best highly questionable when it is applied to voltage-gated ion channels including VGCCs.

There are other issues that come into play, both influencing the effects of fields on the VGCC voltage sensor. One is that the plasma membrane has high electrical resistance whereas both the aqueous extracellular fluid and the aqueous cytoplasm, with their dissolve salts are good electrical conductors. EMFs only traverse plasma membranes with great difficulty (39, 40). Therefore, fields will produce rapid movement of charges in the intracellular and extracellular aqueous phases which will be blocked by the plasma membrane such that voltage sensor will be influenced by greatly amplified electrical forces, in a direction perpendicular to the plain of the plasma membrane. That circa 3000-fold amplification is recognized by Sheppard et al. (34) immediately before their Conclusion section. The only example of an integral membrane that may be influenced in this way, that they give (34) is that of bacteriorhodopsin, where light exposure leads to the pumping of a proton across the plasma membrane. They attempt to estimate the effects of voltages on the proton pumping, by looking a the effects of voltages on the absorption changes that occur in bacteriorhodopsin (34); however, the cycling of bacteriorhodopsin is a complex process (41) where the proton pumping is not rate-limiting and therefore these studies give little insight into the actual effects on proton pumping.

Bacteriorhodopsin differs from the voltage-sensor in the VGCCs in several important ways:

- The voltage sensor has evolved to respond to voltage changes across the plasma membrane, whereas bacteriorhodopsin has evolved to respond to light exposure.
- There are 20 charged groups in the VGCC voltage sensor (37, 38), whereas there is one charge involved in the bacteriorhodopsin mechanism.
- Whereas the bacteriorhodopsin has considerable water in the center of its structure, water seems to be excluded near the helix 4 structures that constitute the voltage sensor.

The third way, above, is important because the force on charged groups, as shown by Coulomb's law, is inversely proportional to the dielectric constant of the surrounding material. The charged groups of the voltage sensor are found in the lipid region of the plasma membrane. The dielectric constant of the lipid section of the membrane is similar to the dielectric constant of hydrocarbon solvents (41), whereas the water dielectric constant is about 40 times higher than that of hydrocarbon solvents (41). The dielectric constant of the extracellular fluid is 2.5–3.5 times that of water, because of the dissolved salts (42, 43) and the measured dielectric constant of cytoplasm is quite similar to the dielectric constant of extracellular fluid. It follows from this that the aqueous phase where most charges exist in cells has about 120 times the dielectric constant of the membrane where the voltage sensor resides. Therefore, the forces on the voltage sensor charges are on the order of 120 times higher than the forces on most charges in the cell.

It follows from this that if one wants to compare the forces on the voltage sensor with that produced by EMFs on most other charged groups in the cell, the voltage sensor forces are approximately 3000×120×20=7.2 million times greater. [Please note again that the 3000 figure is recognized by Sheppard et al. (34); 120 is the effect of the dielectric constant and 20, the number of charges in the voltage sensor.]

The above considerations in this section, clearly show that Sheppard et al. (34) provide no evidence arguing for biophysical implausibility of the VGCC voltage sensor as a target of low-intensity EMFs, such that when we have compelling empirical evidence that it is the main target, that evidence should be taken at face value. Furthermore, the VGCC voltage sensor is likely to be many orders of magnitude more sensitive to EMF effects than are any non-plasma membrane localized target. Because heating is produced by the joggling of charged/partially charged groups almost all of which are outside the plasma membrane, the much greater forces on the VGCC voltage sensors show that fields 6–7 orders of magnitude lower than produce heating may activate the VGCC voltage sensors.

Have others been influenced by somewhat similar considerations? I believe it is likely that W.R. Adey was influenced by the plasma membrane properties when in the 1980s he proposed that a plasma membrane protein was the likely target of weak EMFs. Panagopoulos et al. (7, 8) may have been influenced by these plasma membrane and voltage sensor considerations when they decided to do biophysical modeling on voltage gated ion channels. The two reviewers of this paper each had some criticisms of the Panagopoulos et al. (7, 8) modeling, and some of the things in their papers go beyond my biophysics understanding, so I am unable to judge. What I would say is that the modeling studies came to three important predictions: That voltage-gated ion channels may be targets of low-intensity EMFs, that the VGCCs may be particularly activated because of the mechanism of the actual calcium flux through the channel and that pulsed fields may be more active than non-pulsed fields. Biophysical modeling of such complex membrane proteins as the voltage-gated ion channels is, at best a work in progress, given their complexity.

At this point, there is much evidence implicating VGCC activation but no apparent evidence implicating other voltage-gated ion channels in low intensity EMF responses (1–3). Possible reasons for this should be assessed elsewhere.

What is most needed at this point is not more biophysical modeling, although that would be useful, but extensive detailed information on the effects of various fields on VGCC activation. Such information can be obtained via the types of studies advocated below for biologically-based safety standards.

Canadian Royal Society Expert Panel Report on radiofrequency fields

This Royal Society Expert Panel was charged with reviewing Safety Code 6 (2013) safety limits for exposure to radiofrequency (primarily microwave frequency) fields, following the charge to "advance knowledge, encourage integrated interdisciplinary understanding and address issues that are critical to Canadians". The Expert Panel Report (44) can be judged based on these charges and also the requirements that apply to authors of all purportedly scientific documents:

- The need to provide documentation that it has given as objective an assessment of the science as possible;
- The need for clarity of thought and clarity of expression, such that it will be clear to the reader what the Report is trying to say;
- The need to provide the reader of the Report with sufficient information in the Report and in the citations provided in the Report such that the reader can make an independent assessment of the quality of the science;
- And perhaps most importantly, the need to follow widely accepted principles for assessing scientific evidence.

This paper considers both the charges to the panel and these more generally applicable scientific principles to judge the scientific merit of the Report.

What is in the report?

The Report is, in the author's view, stronger on opinion than on evidence (44). Let us consider some specifics.

The Report states that "The Panel considered an 'established adverse health effect' as an adverse effect that is observed consistently in several studies with strong methodology. With this definition in mind, the Panel reviewed the evidence for a wide variety of negative health impacts from exposure to RF energy, including cancer, cognitive and neurologic effects, male and female reproductive effects, developmental effects, cardiac function and heart rate variability, electromagnetic hypersensitivity, and adverse health effects in susceptible regions of the eye." Despite this claim to have reviewed a broad array of biological impacts, in fact the Report does not provide a comprehensive review. Rather it engages, as documented below, in what can be referred to as "cherry-picking" – selecting studies consistent with its assumptions. Moreover, it often ignores studies that are not consistent with its assumption that there are no biological effects excepting those that, in their view, may be tied to heating. Thus the Report completely excludes many different studies on prenatally exposed animals and those on spermatogenesis, on oxidative stress, changes of calcium fluxes and thousands of studies on therapeutic effects, all at nonthermal levels of exposure.

The Report uses the existence of what it calls "inconsistent," and others have called "conflicting" studies to argue that conflict *per se* indicates a lack of established health impact. This paper considers below whether there are any genuine "inconsistencies" in this literature. Henry Lai and Devra Davis have documented that "conflicting" scientific evidence in the field of bioelectromagnetics relating to mobile phones has been carefully cultivated (45), an inference that may also explain the data of Huss et al. (46). Huss et al. stated "We found that the studies funded exclusively by industry were indeed substantially less likely to report statistically significant effects on a range of end points that may be relevant to health. Our findings add to the existing evidence that single-source sponsorship is associated with outcomes that favor sponsors' products." The panel ignores these findings and considers that conflicting evidence about effects of exposure to RF energy on cancer or other end points means that effects are possible but are not 'established' in accordance with its definition of 'established health effects'. Similarly, while the Report notes that effects of exposure to RF energy on aspects of male reproductive function have been found, it concludes that "the evidence has not been established to indicate that these translate into fertility or health effects" even when such aspects are used clinically to assess male fertility.

The Panel reviewed "inconsistent" evidence about effects of exposure to RF energy on cancer, concluding that effects are possible but are not 'established in accordance with its definition of 'established health effects'. The Report states that the Panel's conclusion on cancer is in agreement with a recent report from the International Agency for Research on Cancer (47). In fact, the Report's characterization of the IARC (47) position does not agree with the IARC actual position. IARC states that "In the text, the Working Group provides comments on those findings that are of greatest relevance to the evaluation, e.g., risk in the overall exposed group, patterns of change in risk with increasing exposure (such as a monotonic increase in risk with increasing exposure), and changes in risk with duration of exposure or latency." Furthermore, the Report ignores the fact that WHO considers microwave radiation to be a Class 2B carcinogen, and the Report also ignores the fact that four prominent reviews on this topic (48–51) all come to the conclusion that microwave exposures can cause cancer. It is apparent therefore that the Panel of Experts on Safety Code 6 has allowed its assumptions to greatly influence its assessment here, rather than providing an objective assessment of the literature.

There are complexities here that the Expert Panel fails to consider. For example, oxidative stress produced by microwave EMF exposure is likely to have a role in causation of cancer. For decades, it has been established that low level oxidative stress can lower oxidative stress markers below initial, pre-stress levels and protect the body from subsequent higher level oxidative stress, a phenomenon known as hormesis that has been recently shown to act by raising the activity of a transcriptional regulator, Nrf2; it has been suggested that this may explain some observations that low level cell phone use may lower cancer incidence via this mechanism, whereas higher level, long-term cell phone use may produce major elevation of cancer incidence. However, the Expert Panel apparently considers these studies to be conflicting, when to the contrary, these studies may raise the issue of biological complexity and a possible U- or J-shaped dose-response curve.

Another even clearer example where inferences of "inconsistencies" or "conflicts" in the literature have been misconstrued regarding the induction of single strand breaks in cellular DNA, measured by what are known as alkaline comet assays, a well-documented method for such studies (1). This literature was reviewed by the author (1), who found 19 different studies where greatly elevated levels of such single strand breaks were found following exposure as well as eight studies where they were not found. However, in examining these studies in detail, it is clear that the differences can be easily explained. For instance, regarding in vitro studies of DNA damage, some of the studies have used different cell types and studied different microwave source EMFs. Thus adult lymphocytes appear relatively resistant to EMF, while neural stem cells are much more susceptible. Different cell types differ from one another in how many and what types of VGCCs may be present and they may differ as well in how the VGCCs are regulated and so may be expected to differ widely in terms of response. All of these studies were done using exposures that were well within current safety standards. Consequently, each of these 19 positive findings contradict the assumptions behind the current safety standards, assumptions that are being defended by the Expert Panel Report, but the Report ignores all of these studies. Moreover, in two of the 19 positive studies, results were positive in some cell types but not others (1), clearly showing that in measurements using identical methodologies, the properties of the cells being studied are critical in determining the biological response found.

Thus the Panel has failed to take into account important nuances regarding scientific research in this field. It has limited considerations to what the Panel calls "established health effects" defined in terms of consistent responses of various cell and tissue types (44). Where apparent conflict exists, the Panel uses its existence as proof that an effect is not established. In doing so, the Panel fails to take into account scientific details that account for many "inconsistent" results. Such details are likely to include, in addition to the factors discussed above in this section, such factors as the role of different pulsation patterns in different types of exposures, the presence of "window effects" providing very complex dose-response relationships and the role of field frequencies in determining biological response. In effect, the panel dismisses science that does not comport with their underlying assumptions that only thermal effects are relevant.

Genotoxicity of non-thermal microwave exposures: examples of inconsistency?

This inconsistency issue is central to the Report's consideration of genotoxicity of non-thermal microwave exposures. This is one of the two areas (pp. 80–82) where the Report cites substantial numbers of primary citations (22 in this case). It lists 13 citations where studies found genotoxicity following exposure levels, well within safety standards. It also lists nine citations where the Report states that no genotoxic effect was found. The Report only cites a small fraction of the overall literature on genotoxicity. For example, it only cites one of the 19 studies reviewed earlier by the author (1) on induction of single strand DNA breaks in microwave frequency exposed cells [that of Kesari et al. (52)]. In overall outline, the literature cited in the Report on this topic reflects fairly well this overall much larger literature. There are, however, a number of ways in which the Report is problematic in dealing with this subject. The author has looked up all 22 of these studies to determine from the original papers what the original authors stated.

Scientists often look at genotoxicity because of its importance in carcinogenesis and this section of the Report is part of a larger section on carcinogenesis. However, the Panel of Experts nowhere considers that many of the authors of these studies discuss their own work as strengthening the case that such fields are carcinogenic. A second connection, to male infertility, is also hidden in the report. Two of the positive studies (53, 54) are falsely stated in the Report as being on blood formation but what was actually being studied in both of these studies was testicular sperm formation. The positive study Liu et al. (55) which shows genotoxicity in a spermatocyte cell line may also have implications regarding male infertility, because of the cell type being studied. There is also a connection with male infertility of one of the negative studies (56). This study of effects of mobile phones, found no genotoxic effects on human sperm, but the same group published two earlier studies showing that other EMFs had substantial effects that suggested lowered fertility as a consequence of exposure. The Report cited the Falzone et al. (56) study but not the two earlier studies. Perhaps this is an overreaction, but the Report seems to be hiding studies providing substantial support for the view that these EMFs can substantially impact male fertility and also hiding the implications of many of these studies on carcinogenesis.

There are other aspects of this section that are problematic. The Report listed the Franzellitti et al. (57) study as a negative one but it is not; it reports increased single strand DNA breaks as measured by alkaline comet assays following exposure. The Report accurately lists the Bourthoumieu et al. (58) study as being negative, but that study cites other studies by the same research group using other cell types as being positive; these positive studies are not cited or discussed in the Report. Similarly, the Report correctly lists two studies by Zeni, Sannino and their colleagues as being negative for apparent genotoxicity; however, this same research group published 6 additional studies, with three showing positive effects, depending on the cell type being studied. The Xu et al. (59) study found genotoxicity in two cell types but not in four other cell types. These studies clearly show that different types of cells respond differently to low level microwave exposures, but for some reason, the Panel of Experts seems unable to draw this very important conclusion. The cell type differences are discussed above in relation to the role of VGCCs in producing single strand breaks in cellular DNA (1). Another problematic aspect of this part of the Report, is that it lists seven of the 13 positive studies as studies providing evidence for "genotoxic or epigenetic" changes but none of those seven have anything to do with epigenetics.

We have here 13 (14 actually when the Franzellitti study is added) studies each of which provide clear evidence for genotoxic activity of non-thermal microwave fields and each of which therefore falsify the heating/thermal hypothesis underlying the Report and also falsify current safety standards. Therefore, based on widely accepted scientific standards, the heating/thermal hypothesis and the safety standards should be rejected.

What conclusion does the Panel draw? It concludes that "Extensive in vitro studies have generated inconsistent evidence that RF energy has genotoxic or epigenetic potential". There is, however, no inconsistent evidence whatsoever. When one studies different cell types, different fields with different pulsation patterns, and different end points, even an elementary understanding of biology argues that different results are likely to be obtained. This section of the Report makes very clear on what basis the Panel is inferring "inconsistency". The authors of the Report are simply looking at superficial similarities of studies and falsely inferring that differences should be interpreted as "inconsistencies" or "conflicts", when they are not inconsistent or conflicting at all. The only type of studies that can produce clear evidence of inconsistency are identical studies that produce different results. Neither the Report nor, to my knowledge, its predecessors have provided any examples of such identical studies. Because this inconsistency argument underlies so much of the Report, one can see that this argument and the Report and also the current safety standards are each deeply flawed.

Karl popper and how to assess scientific evidence

What is the responsibility of the Expert Panel as a group of scientists attempting to produce a scientifically defensible Report? Probably the most influential work on this topic comes from the famous philosopher of science Karl Popper. In his work, *Conjectures and refutations*, Popper argues that scientific hypotheses cannot be proven, but they can be falsified (60). Thus science is to be regarded as tentative information that can always be advanced through further research. Falsifying information, information that apparently falsifies a theory, is the most important type of scientific information and needs therefore to be considered very carefully. The next more important type of evidence is what he calls "risky predictions" where one makes a prediction based on a hypothesis, a prediction that is not likely to be made based on any other unrelated hypothesis. Confirmation of such a risky prediction provides substantial support whereas lack of confirmation can again lead to falsifying the hypothesis. Finally, there are confirmatory evidence studies where multiple hypotheses may explain any confirmation and consequently such confirmation is of low scientific significance.

When considered against the Popperian framework, all of the evidence supporting the heating/thermal hypothesis, favored by the Expert Panel (44) is of the third type. It is widely established therefore that a scientific assessment of this area needs to consider in detail each apparently falsifying study and unless each of them can clearly be shown to be deeply flawed, the inference that should be drawn is that the heating hypothesis should be rejected. This rejection is the one aspect of this that may need to be modified in biology, given the inherent complexity of biology. It is possible that rather than rejection, the hypothesis needs instead to be modified in such a way that the information no longer falsifies the new hypothesis. However, in this situation where perhaps thousands of such modifications may be needed because of thousands of apparent falsifying studies, the difference in practice from outright falsification by each study may be trivial. It is clear, in any case that the Expert Panel has completely avoided doing its scientific duty here, failing to assess each of the thousands of apparent falsifying studies, and opting instead, as seen above, to make specious arguments. That is tragic, in my view, failing to protect the health of many Canadians, and indeed others around the world.

Some other aspects

Most of the Report is focused on their heating/thermal interpretation of microwave radiofrequency effects (44). That is, perhaps, not surprising. What is however very surprising, is that having made such a fetish out of the "inconsistencies" in dealing with various topics, nowhere does the Expert Panel consider in this very large section of the Report, the thousands of findings that clearly conflict with their own favorite hypothesis. What sections of data should be thrown out that may be relevant to this section? The Panel of Experts seem to be completely oblivious that if in its view "inconsistencies" are sufficient to throw out many studies in one area, it should have at least a little consistency in dealing with "inconsistencies" in the heart of their own Report.

In the first paragraph in the conclusion section, the Panel of Experts state that (44) "No viable biophysical mechanism has been proposed for carcinogenic effects for exposure below the levels of SC6 that are supported by results in experimental systems," citing three earlier studies but neglecting to consider the VGCC mechanism of microwave EMF action. The VGCC mechanism is clearly a viable biophysical mechanism, because of the properties of the voltage sensor located in the plasma membrane. VGCC activation produces downstream effects including $[Ca2+]i$ elevation, NO elevation and peroxynitrite/oxidative stress/

free radical elevation (1–3), see Figure 1. It has been shown that NO and peroxynitrite/oxidative stress/free radical elevation are central to the mechanism of inflammatory carcinogenesis (61–64), the type of carcinogenesis that occurs in chronically inflamed tissues and therefore causes cancer in such tissues. It follows that it is biophysically and physiologically plausible, that microwave caused VGCC activation may cause cancer via the same mechanisms shown to cause cancer in inflammatory carcinogenesis. It has also been shown that free radicals formed through Compton scattering by ionizing radiation have essential roles in ionizing radiation carcinogenesis (65–67), providing probable mechanistic similarities between microwave EMF carcinogenesis and ionizing radiation carcinogenesis, as well. There have been many arguments made by the advocates of the heating/thermal mechanism of action, emphasizing the correct fact that the individual microwave photons have insufficient energy to perturb the chemistry of our bodies and they infer from this that these photons cannot cause cancer or many other pathophysiological responses. But what the Panel of Experts and others fail to realize is that the microwave fields as a whole, acting through downstream effects of VGCC activation, lead to high densities of intracellular free radicals (Figure 1) and can produce therefore similar effects on the body to those produced by ionizing radiation exposure. In any case, it follows from this paragraph, that the statement, in the Report, that there is

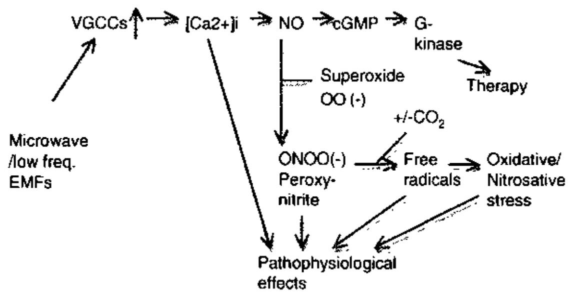

Figure 1: Mechanisms of action for microwave EMFs leading to diverse pathophysiological responses and therapeutic responses. Microwave/lower frequency electromagnetic fields (EMFs) act to stimulate voltage-gated calcium channels (VGCCs), increasing levels of intracellular calcium [Ca2+]i. Elevated [Ca2+]i increases nitric oxide (NO) synthesis which can act along two pathways. The NO signaling pathway, raises cyclic GMP (cGMP) levels and G-kinase activity, producing therapeutic effects. In the other pathway of action of NO reacts with superoxide to form peroxynitrite [ONOO(0)], which either before or after reaction with carbon dioxide (CO_2) can break down to form free radicals, producing oxidative/nitrosative stress. The excessive calcium signaling produced by [Ca2+]i and the peroxynitrite/free radical/oxidative stress pathway each contribute to pathophysiological responses.

no viable biophysical mechanism for low level microwave exposure to cause cancer or other diseases is false, with that falsehood apparently based on the failure of the Panel of Experts to consider the information provided to the panel by the author (Refs. 1 and 3).

This issue of biophysical plausibility of a mechanism for such low intensity exposures is a terribly important one. In the Report, there is a quote from a 2009 Health Canada document, which authors of the Report essentially adopt as their own [p. 78, ref. (44)]; "At present, there is no scientific basis for the occurrence of acute, chronic and/or cumulative adverse health risks from RF field exposure at levels below the limits outlined in Safety Code 6. The hypothesis of other proposed health effects occurring at levels below the exposure limits in Safety Code 6 suffer from lack of evidence of causality, biological plausibility and reproducibility and do not provide a credible foundation for making science-based recommendations for limiting human exposures to lower-intensity RF fields (Safety Code 6)." Whether or not this was a defensible position in 2009, it clearly is not defensible in 2014. This issue of biological/biophysical plausibility is a key one in considering various types of epidemiological evidence, such as were considered in the Report, whenever the role of such stressors in initiating disease is being considered based on studies of groups of people. Hennekens and Buring (68), 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." Consequently, all of the epidemiological evidence considered in the Report and elsewhere needs to be reconsidered in the light of the biophysical and physiological plausibility of the VGCC mechanism and downstream effects produced by VGGC activation.

Cataract formation as claimed effects of microwave-caused heating

The Report presents a fairly extensive specific case, arguing that microwave exposure produced cataract formation is produced by their heating/thermal mechanism (44). Unlike most other areas of the Report, the Panel considers substantial amounts of the primary literature on this topic. The studies discussed, provide evidence for the third and weakest test, according to Karl Popper's analysis

(60), namely that the exposures studied are mostly within the range that produce substantial tissue heating and may therefore produce both cataracts and lens opacification via heating. This type of evidence is considered to be the weakest of the three types of evidence in Popper's schema, because alternative mechanisms are not in any way ruled out.

What is interesting is that there are three published studies which argue strongly against a heating mechanism for cataract formation by microwave exposures. One of these, a study by Cleary and Mills (69), showed that in comparison with other treatments raising lens temperatures, microwave radiation "appears to exert a unique component of thermal stress in the induction of opacification in the mammalian lens," arguing against a strictly thermal mechanism. Two studies have been published testing in effect the "risky prediction" that microwave-induced cataracts are produced by heating. One of these showed that neither eye-localized or whole-body hyperthermia to 42° produced any cataract-like opacity in the rabbit (70). The other showed that localized eye heating in the rabbit, producing the same temperature for the same duration as cataractogenic microwave exposures, produced no opacity in the rabbit eye (71). Both of these "risky predictions" failed to confirm the prediction and strongly suggest falsification of the hypothesis that microwave-induced cataracts are produced through heating. What is particularly disturbing about the Report is that it fails to cite any of these three studies (44) despite the fact that each of them has been cited by others in this context, according to the Google Scholar database. Clearly, the literature the Expert Panel cites regarding cataract formation, which includes the second most extensive primary literature in the Report, does not provide an objective assessment of the scientific literature in this area.

In contrast to studies discussed in the previous paragraph, the equally "risky prediction" that VGCCs and excessive [Ca2+]i have roles in such cataract formation have produced validation of the hypothesis that microwave-induced VGCC activation causes cataracts. Walsh and Patterson (72) demonstrated that elevated [Ca2+]i in the lens of the frog eye has a central role in cataract formation and that calcium channel blockers, which of course block VGCC activation, can block cataract formation. In a recent review, it was shown that excessive [Ca2+]i in the lens of the human and mammalian eye plays a major role in the opacification process producing cataracts and that VGCCs can have a substantial role in this process (73). While these studies do not directly relate to microwave exposures, they clearly show that excessive [Ca2+]i in the lens of the eye has essential roles in cataract formation and that excessive VGCC activity causes cataract formation in experimental animals. Much of the action of [Ca2+] i in cataract formation has been shown to occur through the action of several calcium receptors that act independently of NO. However, there is also an established role of oxidative stress in cataract formation, and it is thought that peroxynitrite also has a role because of the elevation of a marker for peroxynitrite, 3-nitrotyrosine in cataracts (74). It is likely therefore that microwaves act to produce cataracts via calcium signaling as well as via downstream effects involving peroxynitrite and oxidative stress (see Figure 1). The difference in confirmation of these "risky predictions" clearly shows that the VGCC/[Ca2+]i role in producing cataracts is far better documented than any possible heating role.

It can be seen from the above, that although the Canadian Panel of Experts seems to argue that cataract formation is the strongest example of a strictly thermal EMF response (44), the case for such a thermal mechanism is to the contrary extremely weak. Their case is totally dependent on ignoring both evidence that falsifies their view and also evidence that confirms "risky predictions" of the VGCC mechanism that is ignoring the two strongest types of evidence. Thus the claimed role for heating being the cause of cataract formation following microwave exposure, advocated by the Expert Panel, has now been apparently debunked.

Summary of the report

In summary, then each of the following failures in the Report can be seen to be important in our rejecting its conclusions:

- It fails to individually assess the thousands of studies that provide evidence apparently falsifying their heating/thermal paradigm. By failing to assess studies containing this most important type of evidence, as shown by Popper (60), this failure provides more than sufficient reason to reject the conclusions of the Report.
- The Report fails to provide any "risky prediction" type evidence (the second most important type of evidence) in favor of the heating/thermal hypothesis, but such risky predictions are available supporting the VGCC mechanism of action.
- The Report bases its conclusion on the weakest type of evidence, evidence that some responses could be generated by heating but does not rule out other types of mechanisms. A close examination of what the Expert Panel considers to be the strongest case for heating,

that of cataract formation, shows that this is another example of a probable VGCC mechanism, not heating.
- The Report repeatedly fails to provide an objective assessment of the scientific literature. Because omitted citations consistently have the effect of weakening their position, it seems unlikely that these omissions are just coincidental.
- The Report claims that there is no biophysically viable alternative to the heating/thermal paradigm, a claim clearly shown here to be false.
- The Report claims extensive inconsistencies (what others have called conflicts) occur in the literature, where what it considers "similar" studies produced different results and it uses these claims of "inconsistencies" to throw out large amounts of the literature. However, these "similar" studies are in fact, dissimilar, differing in cell type being studied, the properties of the fields being studied and/or the end point being studied, with each of these having demonstrated roles in determining outcome. It follows that the Report provides no evidence for any such "inconsistencies." Any claims of such "inconsistencies" are at best undocumented.
- The Report fails to use its own inconsistency argument (6 above) in the heart of the report, the part that argues for a heating/thermal mechanism, thus failing to be consistent in its own treatment of this issue.
- The Report fails to give the reader enough information in the Report itself or in the citations provided to allow the reader to assess its scientific merit.

The author is aware that similar flaws to those described immediately above occur in earlier studies arguing for the heating/thermal/SARs mechanism (9–13). But that only emphasizes the fact that this whole point of view has been on extraordinarily weak ground all along. That makes it crucially important that safety standards on which the health of most Canadians and indeed, most people around the world are dependent, be examined in scientifically defensible ways.

It is perhaps surprising that the case developed by the Panel of Experts is so weak. That is especially so because industry-funded research has been skewed in support of the heating/thermal interpretation (45, 46), so one would think that with a lot of industry-supported research, the Expert Panel would have come up with some stronger evidence.

Let me say that it is my opinion that the Panel of Experts may not have been corrupted by industry influence, but rather it may have fallen victim to a common affliction, that of groupthink. Groups of people each carrying misconceptions in common, act to encourage their common misconceptions in other members of the group. What was apparently lacking in the Panel of Experts was someone who could challenge those misconceptions, rather than encourage them. However the "logic" presented in the Report provides industry with a strategy to indefinitely prevent any true scientific standards from being used to assess safety. Industry need only fund research that ends up making "inconsistent" conclusions, thus allowing all independently funded studies to be thrown out because of these "inconsistencies" and thus indefinitely preventing adoption of safety standards based on genuine, independent science. It is my hope and expectation that this was not the goal of the Expert Panel, but it is nevertheless an apparent consequence of their Report, if it is viewed as being scientific.

Still, it can be argued, that the Panel of Experts has perhaps unwittingly fulfilled a very valuable function. By clearly showing how weak their case is in 2014, the Panel has shown that none of the more recent evidence has substantially strengthened their case. It is still based on a false premise (biophysical implausibility of alternative mechanisms) and circular reasoning, it is still based on the failure to consider large numbers of apparent falsifying studies, it is still based on ignoring large amounts of the relevant literature and it is still based on the failure to provide the most well supported types of evidence needed to establish biological mechanisms in medicine, just as was true earlier (9–13). Of course, the weakness of the Panel's case means that the current safety standards are based on quicksand.

How VGCC activation by microwave/RF exposure can produce a variety of important biological responses

Table 1 summarizes how VGCC activation may plausibly produce a wide range of reported responses to microwave and, in some cases, lower frequency EMF exposures. It can be seen that a wide range of reported responses to low level microwave exposures can apparently all be understood as being a consequence of VGCC activation and downstream effects of such activation that were outlined in Figure 1. These can all be seen as "risky predictions" of the VGCC activation mechanism produced by EMF exposures. While these mechanisms support the inference that all of these effects seem to be produced by VGCC activation, that inference must be viewed as being surprising. After all,

Table 1: Apparent mechanisms of action for microwave exposures producing diverse biological effects (see Figure 1).

Reported biologic response	Apparent mechanism(s)	Citation(s)/Comments
Oxidative stress	Peroxynitrite and consequent free radical formation	(1–3); detected via a large number of oxidative stress markers
Single strand breaks in cellular DNA	Free radical attack on DNA	(1, 3)
Double strand breaks in cellular DNA	Same as above	Same as above; detected from micronuclei and other chromosomal changes
Cancer	Single and double strand breaks, 8-nitroguanine and other pro-mutagenic changes in cellular DNA; produced by elevated NO, peroxynitrite	This paper and (3)
Breakdown of blood-brain barrier	Peroxynitrite activation of matrix metalloproteinases leading to proteolysis of tight junction proteins	(3)
Male and female infertility	Induction of double strand DNA breaks; other oxidative stress mechanisms; [Ca2+]i mitochondrial effects causing apoptosis; in males, breakdown of blood-testis barrier	(3)
Therapeutic effects	Increases in $[Ca]_i$ and NO/NO signaling	(1–3; 13)
Depression; diverse neuropsychiatric symptoms	VGCC activation of neurotransmitter release; other effects? possible role of excess epinephrine/norepinephrine (75)	These were reported in occupational exposures (22); also reported in people living near cell phone towers
Melatonin depletion; sleep disruption	VGCCs, elevated $[Ca]_i$ leading to disruption of circadian rhythm entrainment as well as melatonin synthesis	(3)
Cataract formation	VGCC activation and $[Ca]_i$ elevation; calcium signaling and also peroxynitrite/oxidative stress	This paper
Tachycardia, arrhythmia, sometimes leading to sudden cardiac death	Very high VGCC activities found in cardiac (sinoatrial node) pacemaker cells; excessive VGCC activity and [Ca2+]i levels produces these electrical changes in the heart	(3)

although low level EMF activation of VGCCs is now well-documented, other possible direct targets of EMFs cannot be ruled out, targets that may produce changes that cannot be easily explained as being caused by VGCC activation and downstream effects of such activation. When the apparent mechanisms summarized in Table 1 are put together with the calcium channel blocker studies and other studies on widespread changes in calcium fluxes and calcium signaling following microwave EMF exposures, we are left without any alternative, non-VGCC target of EMF action that currently can be studied for its role in producing biological effects in humans.

Biologically-based EMF safety standards

Hardell and Sage (76), the Scientific Panel on Electromagnetic Health Risks (77) and the author (3) have called for biologically-based EMF safety standards that are based on genuine biologically relevant responses to low-level microwave and other EMFs, rather than SARs. The only approaches we have available for this based on a known biological end point, as shown in the previous section, are approaches based on VGCC activation. There are experimental whole animal approaches based on VGCC activation (3), but my feeling is that initial studies should focus on using cells in culture, cells that have high levels of some VGCCs. Some such studies would use cell lines with such high VGCC levels, such as neuroblastoma cell lines or perhaps cell lines derived from endocrine cells with relatively high VGCC levels. Among these cell lines should be the neuroblastoma cell lines previously studied by Dutta et al. (78) and shown to produce changes in calcium fluxes in response to very low level EMF exposures. PC12 cells, a commonly used chromaffin cell line should also be considered for such studies. In addition, it may useful to use cardiac pacemaker cells which have very high activities of VGCCs (35) and can be derived from stem cells (79).

Two approaches suggest themselves for measuring responses of such cells to EMF exposure: Cells in culture could be monitored for NO production using an NO electrode in the gas phase over the culture, both before and following EMF exposure. This approach was used by Pilla in studying effects of pulsed microwave fields (4) in trying to understand the mechanism of microwave therapy. Pilla found that the NO increase in such cultures on EMF field exposure was almost instantaneous, using a NO electrode in the gas phase (4). With this sort of approach, many different fields can be quickly and easily studied for their ability to produce NO increases, including different frequencies, pulsation patterns and possibly intensities, with the last of these needed to analyze window effects. Different cordless communication devices can be compared for activity using several cell types. Continuous measurements from an NO electrode can be recorded and easily quantified, allowing accumulation of very large amounts of data in very short time periods. Therefore, issues such as reproducibility should be quickly resolved. One might even be able to determine whether previous exposures produce increased sensitivity to exposure, possibly developing a cell culture model of electromagnetic hypersensitivity.

Another approach to such studies involves using calcium-sensitive fluorescent probes that concentrate into the cytoplasm of cells, allowing assessments of [Ca]i levels with a fluorescence microscope. This may allow one of obtain information of different types than described in the previous paragraph. One can get information on heterogeneity of responses at the cellular level and also how raised [Ca]i levels may propagate over time from one part of the cell to another. However, a limitation to this approach may occur if the fields generated by the microscope perturb the [Ca]i levels and cannot be well shielded using a small Faraday cage that does not cage exposures that are to be studied. It is also true that the NO electrode studies are easier to quantify than such fluorescent probe studies. So these two approaches are distinct from one another and whether they will complement each other as they develop is uncertain. It is my view that both of these should be investigated if only to explore their strong points and weak points but that the NO electrode approach may be a very good place to start because it has already been used to assess EMF effects (4) and because it allows easy quantification.

Brief overview

Havas' recent review (80) discusses 14 different documents prepared by international scientists (dated 2002 through 2012) expressing deep concern about various non-thermal effects of microwave radiation exposures and other studies have expressed similar views. W.R. Adey's papers (6, 21) reviewed much of the then current evidence for many non-thermal effects of microwave radiation. But his prescience is most clearly shown by his statement that "Collective evidence points to cell membrane receptors as the probable site of first tissue interactions with both extremely low frequency and microwave fields for many neurotransmitters, hormones, growth-regulating enzyme expression, and cancer-promoting chemicals. *In none of these studies does tissue heating appear to be involved causally in the responses*" [italics added, from a talk at the Royal Society of Physicians, London May 16–17, 2002, quoted in ref. (81)]. The recent Herbert and Sage review (81) discusses "the emergence of ever larger bodies of evidence supporting a large array of non-thermal but profound pathophysiological impacts of EMF/RFR in transforming our understanding of the nature of EMF/RFR impacts on the organism." In a second paper (82), Herbert and Sage state that "Our EMF/RFR standards are also based on an outdated assumption that it is only heating (thermal injury) which can do harm. These thermal safety limits do not address low-intensity (non-thermal) effects. The evidence is now overwhelming that limiting exposure to those causing thermal injury alone does not address the much broader array of risks and harm now clearly evident with chronic exposure to low-intensity (non-thermal) effects." The Khurana et al. review (83) states: "The authors reviewed more than 2000 scientific studies and reviews, and have concluded that: (1) the existing public safety limits are inadequate to protect public health; (2) from a public health policy standpoint, new public safety limits on further deployment of risky technologies are warranted based on the total weight of evidence. A precautionary limit of 1 mW/m^2 was suggested ...." The Scientific Panel on Electromagnetic Field Health Risks listed four well-documented central conclusions at the beginning of their publication (77):

- Low-intensity (non-thermal) bioeffects and adverse health effects are demonstrated at levels significantly below existing exposure standards.
- ICNIRP and IEEE/FCC public safety limits are inadequate and obsolete with respect to prolonged, low-intensity exposures.
- New biologically-based public exposure standards are urgently needed to protect public health worldwide.
- It is not in the public interest to wait.

Canadian Panel of Experts do not cite these papers or others providing clear and focused views that contradict the views advocated in the Report, showing again that the Report fails to provide an objective assessment of the scientific literature. The current paper adds a number of specific considerations to the needed debate:

- VGCC activation produces most, possibly even all microwave and lower frequency EMF health-related

responses. Each of the studies on VGCC activation or on changes in calcium fluxes and signaling following low level exposure clearly falsifies the thermal/heating paradigm.
- This VGCC activation mechanism by low level microwave and lower frequency fields, rather than individual photons, is biophysically plausible based on the special properties of the voltage sensor and its localization to lipid region of the plasma membrane.
- Downstream effects of VGCC activation (Figure 1) can generate each of 13 different health effects repeatedly found to be produced by microwave exposure (Table 1).
- Studies document roles of pulsation in influencing biological responses to microwave exposures, influences that are incompatible with these being produced by heating.
- "Window" effects occur, where specific intensities of microwave EMF exposure produce higher biological effects than those produced by both lower and higher intensities, observations incompatible with heating effects.
- Thousands of studies have reported biological effects at intensities well within safety standards, each of which appear to falsify the heating/thermal paradigm, none of which have been considered in this light by the Panel of Experts, despite the scientific requirement to do so under well-accepted scientific principles.
- The claims in the Report that microwave induction of cataracts is produced by heating has been tested in three studies, each contradicting this claim; two of them produce clear falsification, but none of these three studies are cited in the Report. Because VGCC activation can cause cataracts and elevated [Ca2+]i has essential roles in producing cataracts, a VGCC mechanism for microwave-induced cataracts is much more strongly supported than is the claimed heating mechanism.
- The claim in the Report of widespread "inconsistency" in the literature is tested here through examination of the literature cited on genotoxic effects. No inconsistencies were found in this literature despite the Report claiming such. Furthermore, no identical studies are cited anywhere in the Report showing inconsistency of results, these being the only types of studies that can clearly show inconsistency. Claims of widespread "inconsistency" or "conflict" in the literature must be viewed as, at best, undocumented.
- Each of the 8 considerations listed immediately above clearly show that the Report fails to provide anything resembling an objective assessment of the evidence on biological effects of microwave EMF exposures and provides therefore no scientifically valid support for Safety Code 6, ICNIRP or other current safety standards.
- Development of biologically-based safety standards has been called for and approaches to using cell culture-based tests that may be used to develop such safety standards are discussed.

It has been clear for a long time that the heating paradigm is indefensible and that a new paradigm is much needed. We now have that with VGCC activation, and while VGCC activation may not be the entire story behind the biological actions of such EMFs in humans and other mammals, it clearly is most of the story. It is time therefore for a paradigm shift away from strictly thermal effects and toward a central role for VGCC activation in the cellular response to microwave and lower frequency EMFs.

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A Prospective Cohort Study of Adolescents' Memory Performance and Individual Brain Dose of Microwave Radiation from Wireless Communication

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Background: The potential impact of microwave radiofrequency electromagnetic fields (RF-EMF) emitted by wireless communication devices on neurocognitive functions of adolescents is controversial. In a previous analysis, we found changes in figural memory scores associated with a higher cumulative RF-EMF brain dose in adolescents.

Objective: We aimed to follow-up our previous results using a new study population, dose estimation, and approach to controlling for confounding from media usage itself.

Methods: RF-EMF brain dose for each participant was modeled. Multivariable linear regression models were fitted on verbal and figural memory score changes over 1 y and on estimated cumulative brain dose and RF-EMF related and unrelated media usage ($n = 669$–676). Because of the hemispheric lateralization of memory, we conducted a laterality analysis for phone call ear preference. To control for the confounding of media use behaviors, a stratified analysis for different media usage groups was also conducted.

Results: We found decreased figural memory scores in association with an interquartile range (IQR) increase in estimated cumulative RF-EMF brain dose scores: −0.22 (95% CI: −0.47, 0.03; IQR: 953 mJ/kg per day) in the whole sample, −0.39 (95% CI: −0.67, −0.10; IQR: 953 mJ/kg per day) in right-side users ($n = 532$), and −0.26 (95% CI: −0.42, −0.10; IQR: 341 mJ/kg per day) when recorded network operator data were used for RF-EMF dose estimation ($n = 274$). Media usage unrelated to RF-EMF did not show significant associations or consistent patterns, with the exception of consistent (nonsignificant) positive associations between data traffic duration and verbal memory.

Conclusions: Our findings for a cohort of Swiss adolescents require confirmation in other populations but suggest a potential adverse effect of RF-EMF brain dose on cognitive functions that involve brain regions mostly exposed during mobile phone use. https://doi.org/10.1289/EHP2427

Introduction

The rapid evolution of information and communication technologies (ICTs) during the past 20 y has caused an increase in man-made exposure to radiofrequency electromagnetic fields (RF-EMFs). However, the health effects of RF-EMFs are still unknown. Neurological functions are of special concern given that the brain is heavily exposed while calling with a mobile or cordless phone (Joseph et al. 2010). Present-day adolescents will likely have higher cumulative lifetime exposure to RF-EMF, and the developing brain might be particularly susceptible to RF-EMF–induced alterations up to 15 y of age (Kheifets et al. 2005; Luciana et al. 2005; Schüz 2005). In this age group, memory functions are particularly important because proper encoding, processing, and retrieval of information are required for learning. However, to date studies addressing this topic have produced inconsistent results.

Controlled-exposure studies in animals and humans have found limited evidence for both positive and negative effects of RF-EMF on memory performance and related neural processes (Bouji et al. 2012; Deshmukh et al. 2015; Hao et al. 2013; Jeong et al. 2015; Klose et al. 2014; Son et al. 2016). Among the few epidemio-logical studies, the Australian Mobile Radiofrequency Phone Exposed Users' Study (MoRPhEUS) cohort of 317 adolescents with a median age of 13 y observed faster but less accurate responses in working memory and associative learning tasks for frequent mobile phone users (Abramson et al. 2009). The same result was observed in relation to the number of text messages (SMS), which involve only marginal RF-EMF exposure. This may suggest that aspects other than RF-EMFs are the underlying cause of this association. A longitudinal analysis of the MoRPhEUS data indicated associations between mobile phone use and changes in response times for some cognitive tasks over a 1-y period, but the authors proposed regression to the mean as a potential explanation because associations were inconsistent and increase in exposure was mainly seen in those who had fewer calls and SMS at baseline (Thomas et al. 2010).

In the following Examination of Psychological Outcomes in Students using Radiofrequency dEvices (ExPOSURE) study by the same research group as MoRPhEUS, 617 primary school children were investigated and little evidence for cognitive effects due to RF-EMF was found (Redmayne et al. 2013). However, the number of calls was generally very low in these young children (8–11 y of age): a median of 2.5 and 2 calls per week for mobile phones and cordless phones, respectively, among those children using these devices.

In both studies, the RF-EMF exposure was assessed via self-reported number of calls, which usually yields an overestimation of the actual use by adolescents (Aydin et al. 2011). Further, personal exposure to RF-EMF is dependent on other factors such as the call duration, the distance of the device from the body (Joseph et al. 2010; Kühn and Kuster 2013), and the network used for calling. For instance, the global system for mobile communications standard (GSM) produces about 100–500 times higher exposure than the universal mobile telecommunication system (UMTS) (Gati et al. 2009; Persson et al. 2012). Furthermore, using mobile phone calls as a proxy for RF-EMF exposure ignores confounding by the media-related lifestyle impacting individuals' cognition, behavior, and emotion (Kuss et al. 2014; Kuss and Griffiths 2011, 2012; Roser et al. 2016). The present Health Effects Related to Mobile phone usE in adolescentS (HERMES) cohort was the first study in

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adolescents that used individually modeled RF-EMF doses and operator-recorded mobile phone use to investigate potential effects of RF-EMF exposure on cognitive functions (Roser et al. 2015). With this approach, cumulative RF-EMF brain dose was associated with a significant decrease in figural memory performance over a 1-y period (Schoeni et al. 2015), with a stronger decrease observed in right-side users.

The present study aims to follow-up our previous results using an approximate doubling of sample size. Further, we have updated the individual RF-EMF dose model using more recent information on adolescents' brain specific absorption rates (SARs) for different exposure scenarios and by calibrating self-reported call duration on objective operator-recorded call duration. In addition, the present study applies a new approach to control for confounding due to device usage in epidemiological RF-EMF studies.

Materials and Methods

Data of the prospective HERMES cohort study were collected in two independent sampling waves. The first wave of baseline investigations commenced in June 2012 among a cohort of seventh-through ninth-grade students from 24 secondary schools in Central Switzerland. A second wave commenced in April 2014 that included a new group of seventh- through ninth-grade students from 22 secondary schools. Of the 22 schools, 2 had already taken part in the first wave, 18 were newly recruited from Central Switzerland, and 2 were newly recruited from the Basel canton. Follow-up investigations were conducted approximately 1 y after each baseline until April 2016. Participating adolescents were recruited through an initial telephone contact by the head of the school and a subsequent informational visit in their respective classes by the study managers. Participation was voluntary and the informed consent of both adolescents and a parent was compulsory.

The data were collected during school lessons and consisted of completing a paper questionnaire to assess the adolescents' mobile phone and media usage as well as their psychological and somatic health and socioeconomic factors. Computerized cognitive testing was performed immediately afterward. Additionally, a subsample of 148 volunteers from both study waves was recruited to conduct personal RF-EMF measurements as described in detail for the first study wave ($n = 90$) by Roser et al. (2017). These participants were intentionally sampled depending on their place of residence and school in order to be representative of the entire far-field exposure range of the complete study sample. Participants were required to carry a portable measurement device (exposimeter) with an integrated Global Positioning System (GPS) for 3 consecutive days. Simultaneously, a time–activity app on a smartphone in flight mode had to be filled in to later link the RF-EMF records to a particular activity or place.

Ethical approval for conducting the study was received from the ethical committee of the canton of Lucerne, Switzerland, on 9 May 2012 (EKLU 12025 and EKBB 80/12).

Outcome Assessment: Memory Performance

Cognitive performance was measured using a standardized computerized testing system consisting of the figural and verbal memory subtest of the Intelligenz-Struktur-Test (IST) (Liepmann et al. 2007). For the verbal memory task, participants were given 1 min to memorize five sets of two to five words grouped by their common higher semantic category (e.g., city: Amsterdam, Rome, Hamburg, Madrid, York). The target words were presented by starting with a different letter each time. Immediately after the presenting phase, participants were given a letter and they had to recall the word starting with that letter and report the higher semantic category to which it belonged. This was repeated for 11 words, producing a maximum score of 11 points for the verbal memory task. For the figural memory task, participants were given 1 min to memorize 13 pairs of abstract figures, and immediately afterward one item per pair was shown and participants were asked to choose the correct counterpart out of five possible options. The matching task was repeated for 13 symbols, resulting in a maximum score of 13 points. For each of the two tests, 2 min were given to complete the matching task. Each student started with the verbal memory task.

For the statistical analyses, the difference between the continuous test score values at follow-up minus the baseline values were used as outcome. The coefficient of the outcome–exposure association corresponds directly to the change in score: A positive coefficient thus indicates an improvement in memory between baseline and follow-up in relation to the exposure of interest, whereas a negative association indicates a decrease in memory. In the age group of our study, without considering any exposure, one would generally expect an increase in verbal memory and an increase or little change in figural memory between baseline and follow-up. However, memory development during adolescence may vary largely interindividually (Luciana et al. 2005; Schneider and Pressley 2013).

Exposure: Mobile Phone and General Media Use

The detailed usage of mobile phones and other wireless communication devices was assessed via questionnaire. Questions focused on the average amount and type of mobile phone and media usage per day. Exposures of primary interest were those expected to produce relatively high RF-EMF exposure: specifically, the daily duration and number of calls on mobile and cordless phones. In addition, we asked whether students preferentially held mobile phones on the right or left side of their heads when making calls or whether they had no preference. Further, participants were asked about headset use while calling, which is an important factor for RF exposure because exposure to the body decreases rapidly with increasing distance from the device (Lauer et al. 2013). We also asked about activities that might be correlated with phone use but that would be expected to result in relatively low RF-EMF exposures, including the number of text messages sent per day, daily duration of data traffic on the student's mobile phone, daily duration of gaming on electronic devices, the frequency of social network use, and whether the student's mobile phone was left on or turned off at night. In addition, we used the brief MPPUS-10 scale to assess problematic mobile phone use in the students (Foerster et al. 2015).

For the self-reported usage measures included in the linear regression analysis (daily frequency of text messages, daily duration of mobile phone data traffic, daily duration of gaming, and daily duration of cordless phone use), we calculated the cumulative usage by taking the mean difference between baseline and follow-up, and interpreting this value as usage per day.

Detailed data records of daily quantitative mobile phone use from the 6 months preceding the baseline examination date until the follow-up investigations were obtained from the Swiss mobile phone network operators [Swisscom, Sunrise, and Salt (formerly known as Orange)] if adolescents and one of their parents had given additional written informed consent. These participants are subsequently referred to herein as the operator sample. The operator records included the number and duration of calls, number of text messages sent per day, and the daily volume of data traffic. In addition, the identity of the network (UMTS or GSM) used to start each phone call was obtained from the operators Swisscom and Salt, whereas the third operator, Sunrise, did not provide this information. The daily cumulative mobile phone call duration was calculated by summing up all recorded call durations between baseline and follow-up and dividing this sum by the recorded days between baseline and follow-up to obtain daily usage.

A comparison of self-reported mobile phone use with operator-recorded use indicated severe overestimation of self-reported mobile phone use. To avoid bias, we calibrated self-reported mobile phone call duration for participants without operator records. The calibration equation was derived from the operator sample using a multilevel linear regression model that was clustered by schools with average operator-recorded mobile phone call duration per day as dependent variable and the following predictors to be found relevant (likelihood ratio test for the nonclustered model including or excluding the predictor): age, gender, daily frequency of mobile phone calls at follow-up, daily frequency of text messages at follow-up, daily duration of mobile phone data traffic at follow-up, and daily duration of cordless phone calls at follow-up as well as the difference in daily duration of mobile phone calls between follow-up and baseline (see Table S1). Subsequently, the predicted values from the calibration model were used as estimated daily call duration for the participants without operator data. A similar model was constructed to predict the proportion of calls made on the UMTS network, with the following predictors to be found relevant: the place of residence (urban vs. rural—the UMTS proportion was usually lower in rural areas), UMTS exposure (as a proportion of total downlink) at place of residence obtained by geospatial propagation model (see below), and the number of smartphones at the home as well as the duration of mobile data traffic—all of which were indicators of a higher UMTS proportion. The proportion of GSM network was assumed to be 1 – proportion(UMTS). The distinction between both networks used was important in determining RF-EMF exposure because, compared with calls executed on the UMTS network, calls on the GSM network have been associated with irradiation levels heightened by a factor of 100–500 (Gati et al. 2009; Persson et al. 2012). For the participants for whom operator-recorded data was available, the objectively recorded data (cumulative call duration and, if applicable, network proportion) was used for all further analysis, including the RF-dose estimation.

Individual Cumulative RF-EMF Brain Dose

Individual RF-EMF brain dose was calculated using an updated dosimetric model described in detail by Roser et al. (2015) that considers RF-EMF exposure-relevant behaviors and circumstances from near- and far-field sources. Near field refers to the use of RF-EMF–emitting devices close to the body (e.g., mobile phones, wireless Internet), whereas far field refers to the surrounding environmental RF-EMF exposure (e.g., from fixed-site transmitters, W-LAN access points, people using mobile phones nearby).

The first step in dose modeling consists of simulating SARs of the brain gray matter for each exposure-relevant behavior and circumstance [for details see "1. Numeric simulations of brain gray matter specific absorption rates (SAR)" in the Supplemental Material]. SAR is a quantity that indicates the rate at which RF-EMF is absorbed in a certain mass or volume of tissue. SAR values are determined using numeric simulations based on two adolescent human body models from the phantom "virtual population," an 11-y-old girl (Billie) and a 14-y-old boy (Louis) (Gosselin et al. 2014). For near-field sources, SARs were simulated for three scenarios (positions of the emitting device with relation to the body): (*a*) device held close to the ear, (*b*) device kept in the pocket of trousers, and (*c*) device held at a distance of 20 cm to the ear (headset scenario).

SAR values were transformed to dose values by multiplying the SAR with relevant exposure durations (see Table S1). The following near-field exposures were considered in the model: daily duration of mobile phone use (separated by 2G/3G and headset use); daily duration of mobile phone data traffic (separated by transfer via WiFi and mobile phone network); daily duration of cordless phone calls (considering the phone's eco mode if applicable); daily duration of WiFi use on laptop, PC, and tablet; and daily duration of carrying the participant's own mobile phone close to body (e.g., in a pocket). The average output power of these devices was derived from the literature [for details see "1. Numeric simulations of brain gray matter specific absorption rates (SAR)" in the Supplemental Material].

The far-field dose modeling included exposure from mobile phone base stations (downlink) broadcasting (radio and TV), WiFi, DECT (Digital Enhanced Cordless Telecommunications base stations at the home), and far-field exposure from the mobile phones of other nearby people (uplink). Downlink and broadcasting exposure at home and at school was modeled for each participant by means of the geospatial NISMap software (Bürgi et al. 2010).The model is based on accurate operation parameters of all stationary mobile phone and broadcast transmitters and the three-dimensional building and topography model of the study area. Semi-empirical propagation algorithms such as COST-Walfisch-Ikegami (Cichon and Kürner 1999) were used to predict RF-EMF exposure at the receptor points, taking into account, for example, the shielding effects of buildings and topography. Duration of exposure at school was assumed to be 35 h per week in order to eventually obtain the average downlink and broadcasting exposure.

WiFi, uplink, and DECT cannot be modeled by NISMap. Thus, for WiFi and uplink factors, predicting exposure to these sources were identified by linear regression from personal measurement data available from 148 study participants (see Table S1). Relevant predictors for 24-h personal WiFi exposure were the mobile phone operator, presence of WiFi at school, the daily duration of mobile data traffic, and the study wave (2012–2014 vs. 2014–2016). Predictors of uplink were the mobile phone operator, mobile phone status at night (on vs. off), the number of smartphones at the home, the time spent in public transport (train and bus), and the study wave. Because no valuable predictors for DECT could be identified, it was assumed to be the mean DECT exposure as derived from personal measurements in 148 participants. These 24-h far-field exposure values were then transformed to SAR values of the brain gray matter using plane-wave-simulations in the Finite-Different Time-Domain-based simulation software SEMCAD-X, version 16 from SPEAG, Zürich, Switzerland (see Table S2). In a final step, the individual RF-EMF brain gray matter dose for each participant was calculated by summing up the contributions of all different near- and far-field exposure scenarios.

Statistical Analysis

All analyses were conducted for the complete sample as well as separately for the two subsamples investigated during 2012–2014 and 2014–2016, respectively. Following the protocol used in our previous analysis, three different types of exposure variable were considered: (*a*) cumulative RF-EMF brain dose, (*b*) cumulative wireless device use related to RF-EMF exposure (cordless phone calls and mobile phone calls), and (*c*) cumulative wireless device use not or only marginally related to RF-EMF exposure (duration of data traffic, duration of gaming, number of text messages sent). Outcome variables were changes in figural and verbal memory score (follow-up minus baseline) over 1 y.

Separate linear exposure–response models were used to estimate associations between each outcome (the change in verbal or figural memory scores from baseline to follow-up, respectively) and each primary exposure variable (modeled as a continuous variable). All models were adjusted for age, gender, nationality (Swiss, Swiss and other, other), school level [in ascending order according to the school system in Switzerland based on academic expectations: secondary school level C, secondary school level B, secondary school level A, college preparatory high school], frequency of physical activity at follow-up (defined as working out for at least 40 min: ≤1 to 3 times per month, 1 time per week, 2–3 times per week, 4–6 times per week, daily), days of alcohol consumption per month at follow-up (none, ≤1 time per month, 2–4 times per month, 2–3 times per week), change in height between baseline and follow-up (as a proxy for developmental speed between both time points), duration between baseline and follow-up in months, and education of parents (training school, college preparatory high school, college or higher education, university).

In the second step, a laterality analysis of RF-EMF brain dose (head laterality was not considered in the RF-EMF dose model) was conducted given that the figural memory involves mainly the right hemisphere, whereas verbal memory processing is more left sided (Golby et al. 2001; Nagel et al. 2013). Because most of the study participants indicated they held their phone on the right side of their head, we dichotomized the participants into right-side users vs. left-side users and users with no preference (combined). Laterality analyses were performed using data for the entire sample and were repeated after restriction to the operator sample. To facilitate comparisons among the different exposure variables, all effect estimates are expressed as the difference in test scores associated with an interquartile range (IQR) increase in exposure.

Missing values in the confounder variables were either imputed via linear regression (17 missing values at follow-up for alcohol consumption were predicted by age, gender, school class, and school level; 14 missing values at baseline and 12 missing values at follow-up for information on height were predicted by weight, age, and gender) or by imputation, replacing the missing values with the most common category (i.e., 2 missing values at follow-up for frequency of physical activity were replaced by the most common category "2–3 times per week", and 167 missing values for educational level of the parents were replaced by the most common category "Training school"). Statistical analyses were carried out using STATA (version 14; StataCorp).

To evaluate residual confounding from unmeasured factors related to communication device use, we performed stratified analyses across five subgroups representing five different media usage profiles derived by means of latent class analysis of 11 media use variables from the baseline questionnaire data (Foerster and Röösli 2017). The following five classes were identified: Low Use, Medium Use, Call Preference, Gaming, and High Social Use (see Figure S1).

We performed separate linear regression models restricted to students in each of the five media usage groups and estimated differences in each outcome with an IQR increase (defined for the population as a whole) in cumulative RF-EMF brain dose. Next, we performed random effects meta-analyses to derive a summary estimate for each outcome in each subgroup and assessed heterogeneity using the I^2 statistic (Higgins et al. 2003). We assumed that physical effects of RF-EMF would have a similar impact across media use subgroups, independent of any psychological or cognitive effects of media use; therefore, evidence of heterogeneity among the five group-specific estimates would be consistent with uncontrolled psychobehavioral confounding.

Results

In total, 895 adolescents between 12 and 17 y of age were enrolled in the baseline investigation of the HERMES study. The first sampling wave included 439 [mean age ± standard deviation (SD): 14.0 ± 0.85)] students recruited from 57 classes in 24 schools. During the second wave, 456 students (14.1 ± 0.86 y of age) from 44 classes and 22 schools were recruited. A total of 843 participants (96.8% of wave-1 students, $n = 425$; and 91.7% of wave-2 students, $n = 418$) took part in the follow-up investigation 1 y later (Table 1). The average time between baseline and follow-up was 12.5 months. Of these students, 827 (98.1%) owned a mobile phone. The sample included more girls ($n = 457$, 56.4%) than boys ($n = 368$, 43.6%). Objectively recorded operator data for at least 6 months between baseline and follow-up were available for 322 participants (38.8%).

Outcome and Exposure Distributions

Due to technical problems with the computerized testing system, completed tests for both time points were available for only 676 (80.2%) of the participants for verbal memory and 670 (79.5%) for figural memory, respectively (Table 2). While the verbal memory score increased from baseline to follow-up (mean unit increase ± SD = 1.1 ± 3.0), figural memory score did not increase in general (mean increase of 0.2 ± 3.2). The intraclass correlation coefficient (ICC) within individuals was 0.76 for the verbal score, and 0.81 for the figural memory score.

The mean duration of self-reported mobile phone call time was 17.2 ± 27.6 min/d, in contrast with a mean operator-recorded time of 3.2 ± 13.3 min/d. After calibration based on multilevel regression of the subgroup with operator data, the estimated mean mobile phone call time for the sample as a whole was 10.6 ± 13.7 min/d. Mean self-reported cordless phone call duration was 6.2 ± 6.6 min/d (operator data were not available for calibration of cordless phone use). For media exposures associated with low RF-EMF, average daily durations were 56.7 ± 34.3 min/d for mobile phone data traffic and 43.0 ± 56.9 min/d for gaming, and the mean number of text messages sent per day was 35 ± 21.

The estimated mean cumulative RF-EMF brain dose for the population as a whole was 858 ± 1,027 mJ/kg per day when estimated using calibrated mobile phone call durations (mean 10.6 min/d) (Table 2). In the operator data sample ($n = 322$), the estimated mean cumulative RF-EMF brain dose based on recorded call durations (mean 3.2 min/d) was 469 ± 814 mJ/kg per day.

On average, the daily cumulative call duration accounted for 80.3% of the estimated cumulative RF-EMF brain dose in the population as a whole (see Table S3). The proportion for calls executed on the GSM network was much higher (79.8%) compared with the UMTS network (0. 5%). In comparison, when using only data from the operator data sample ($n = 322$), duration of mobile phone use accounted for 66% of estimated cumulative RF-EMF dose (data not shown).

Estimated cumulative RF-EMF brain doses varied among the five media use groups, primarily due to differences in mobile phone call duration (Table 2; see also Figure S1). For example, the Call Preference group ($n = 119$), which had calibrated daily mobile phone and cordless call duration estimates of 15.9 ± 11.9 and 10.8 ± 9.6 min/d, respectively, had a mean estimated daily RF-EMF brain dose of 1,214 ± 1,259 mJ/kg per day, compared with 551 ± 1,029 mJ/kg per day for the Low Use group ($n = 198$), mean calibrated mobile and cordless phone call duration estimates of 5.9 ± 7.7 and 6.0 ± 5.6 min/d, respectively.

Associations between Changes in Memory Performance and RF-EMF Dose and Media Usage

In the population as a whole, none of the exposure variables were significantly associated ($p < 0.05$) with changes in verbal memory scores (Table 3, Figure 1). However, there was a nonsignificant association with the cumulative duration of data traffic and the increase in verbal memory score [score change per IQR: 0.34; 95% confidence interval (CI): −0.05, 0.72; IQR: 55.4 min/d], which was consistent over both study waves (Figure 2).

Table 1. Distributions among different sociodemographic and lifestyle variables for all participants taking part in the follow-up investigations and the five media use groups separately.

Characteristic	Total [n (%)][a]	Gamer [n (%)][a]	Media use[b] [n (%)][a]	Low use [n (%)][a]	Call preference [n (%)][a]	High social use [n (%)][a]
n (total)	843 (100)	97 (12)	223 (26)	207 (25)	119 (14)	197 (23)
Age [y (min–max)]	14.0 (10.3–17.0)	14.1 (12.2–16.4)	13.9 (10.4–17.0)	13.8 (11.8–15.8)	14.3 (12.3–16.6)	14.1 (12.5–16.1)
Sex						
Female	475 (56.4)	96 (99.0)	102 (45.7)	90 (43.5)	32 (26.9)	48 (24.4)
Male	368 (43.6)	1 (1.0)	121 (54.3)	117 (56.5)	87 (73.1)	149 (75.6)
Sample						
Sample 1 (2012–2013)	425 (50.4)	40 (41.2)	51 (22.9)	191 (92.3)	118 (99.2)	25 (12.7)
Sample 2 (2014–2015)	418 (49.6)	57 (58.8)	172 (77.1)	16 (7.7)	1 (0.8)	172 (87.3)
Nationality						
Swiss	646 (76.6)	75 (77.3)	175 (78.5)	174 (84.1)	89 (74.8)	133 (67.5)
Swiss and foreign	120 (14.2)	11 (11.3)	31 (13.9)	25 (12.1)	19 (16)	34 (17.3)
Foreign	77 (9.2)	11 (11.3)	17 (7.6)	8 (3.9)	11 (9.2)	30 (15.2)
School level[c]						
Secondary school level C	151 (17.9)	23 (23.7)	30 (13.5)	22 (10.6)	34 (28.6)	42 (21.3)
Secondary school level B	242 (28.7)	36 (37.1)	69 (30.9)	43 (20.8)	30 (25.2)	64 (32.5)
Secondary school level A	272 (32.3)	20 (20.6)	68 (30.5)	80 (38.7)	41 (34.5)	63 (32)
High school level	178 (21.1)	18 (18.6 %)	56 (25.1)	62 (30)	14 (11.8)	28 (14.2)
Highest education of the parents[d]						
Training school	496 (58.8)	58 (59.8)	129 (57.9)	88 (42.5)	73 (61.3)	148 (75.1)
College preparatory high school	50 (5.9)	6 (6.2)	15 (6.7)	14 (6.8)	4 (3.4)	11 (5.6)
College of higher education	235 (27.9)	22 (22.7)	63 (28.3)	81 (39.1)	37 (31.1)	32 (16.2)
University	62 (7.4)	11 (11.3)	16 (7.2)	24 (11.6)	5 (4.2)	6 (3.1)
Physically active (FUP)[e]						
≤1 to 3 times per month	128 (15.2)	11 (11.3)	30 (13.5)	28 (13.5)	19 (16)	40 (20.4)
1 time per week	170 (20.2)	16 (16.5)	39 (17.5)	43 (20.8)	31 (26.1)	41 (20.9)
2–3 times per week	316 (37.4)	40 (41.2)	81 (36.3)	83 (40.1)	43 (36.1)	68 (34.7)
4–6 times per week	159 (18.9)	21 (21.7)	48 (21.5)	36 (17.4)	18 (15.1)	36 (18.4)
Daily	70 (8.3)	9 (9.3)	25 (11.2)	17 (8.2)	8 (6.7)	11 (5.6)
Number of days with alcohol consumption (FUP)[f]						
None	469 (55.6)	47 (48.5)	138 (61.9)	142 (68.6)	48 (40.3)	94 (47.7)
≤1 time per month	200 (23.7)	28 (28.9)	51 (22.9)	41 (19.8)	35 (29.4)	45 (22.8)
2–4 times per month	139 (16.5)	13 (13.4)	32 (14.4)	19 (9.2)	29 (24.4)	46 (23.4)
2–3 times per week	35 (4.2)	9 (9.3)	2 (0.9)	5 (2.4)	7 (5.9)	12 (6.1)
Change in height (cm ± SD) (follow-up–baseline)[g]	3.7 ± 6.7	5.8 ± 4.1	4.4 ± 4.4	4.4 ± 4.8	1.2 ± 13.7	2.5 ± 3.9

Note: FUP, follow-up; max, maximum value; min, minimum value; SD, standard deviation.
[a]Numbers are n (%) unless notes otherwise.
[b]Media use groups determined by latent class analysis on 11 qualitatively different media use variables as described in Foerster and Röösli (2017).
[c]According to the school system in Switzerland, school levels imply differing academic expectations (in ascending order: secondary school level C, secondary school level B, secondary school level A, college preparatory high school); 167 missing values for educational level of the parents replaced by the most common category "Training school."
[d]Highest level of education achieved by at least one of the parents.
[e]Physical activity defined as working out at least 40 min with perspiration; two values missing at follow-up for frequency of physical activity were replaced by the most common category "2–3 times per week."
[f]Seventeen values missing at follow-up for alcohol consumption were imputed via linear regression imputation predicted by age, gender, school class, and school level.
[g]Fourteen values missing at baseline and 12 values missing at follow-up for information on height were predicted by weight, age, and gender.

Changes in figural memory score were negatively correlated with cordless phone calls and, in tendency, with the duration of mobile phone calls and the cumulative RF-EMF brain dose (Figure 2). The association with RF-EMF brain dose was nonsignificant in the full sample (−0.22 (95% CI: −0.47, 0.03; IQR: 953 mJ/kg per day) and significant in the operator data sample (−0.26 (95% CI: −0.42, −0.10; IQR: 341 mJ/kg per day). When analyzing the two subsamples separately, for both study waves, nonsignificant negative effect estimates for the RF-EMF dose were seen, although the magnitude of this effect was greater for the second ($n = 288$) compared with the first wave ($n = 375$) but with a wider confidence interval for the second wave (first wave: −0.14 (95% CI: −0.42, 0.14); second wave: (−0.58 (95% CI: −1.17, 0.01); IQR: 953 mJ/kg per day). No association was observed with variables that were only marginally related to RF-EMF exposure (cumulative duration of data traffic, cumulative gaming duration, and cumulative number of text messages).

The association between figural memory score and cumulative brain dose became significant when analysis was restricted to users with right-side preference (full sample: $n = 532$; operator sample: $n = 217$) in the laterality analysis (full sample: −0.38; 95% CI: −0.67, −0.09; IQR: 953 mJ/kg per day; operator sample: −0.29 (95% CI: −0.46, −0.11; IQR: 341 mJ/kg per day) (Figure 3). When restricted to left-side/no-preference users, the effect estimates were, in general, imprecise due to the small sample size (full sample: $n = 137$; operator sample: $n = 57$). However, a significant negative association was found for verbal memory in the operator sample (−0.51; 95% CI: −0.89, −0.13; IQR: 341 mJ/kg per day).

Meta-Analysis over Media Use Groups

The pooled random effects estimate for the association between cumulative brain dose and figural memory score over the five media use groups (−0.39; 95% CI: −0.69, −0.09; IQR: 953 mJ/kg per day) was consistent with the main analysis, and did not support heterogeneity among the groups ($I^2 = 0.0\%$). The pooled effect for verbal memory score was 0.02 (−0.24, 0.31; IQR: 953 mJ/kg per day; $I^2 = 0.0\%$) (see Figure S2).

Discussion

In the present study, an IQR increase in estimated cumulative RF-EMF brain dose was associated with a nonsignificant decrease in figural memory score, but was not associated with verbal memory

Table 2. Descriptive statistics for all different exposure variables used in linear regression models for the whole sample and the five media use groups separately.

Variable	Total			Low use			Media use[a]			Gaming			Call preference			High social use		
	n	mean ± SD	IQR[b]	*n*	mean ± SD	IQR	*n*	mean ± SD	IQR	*n*	mean ± SD	IQR	*n*	mean ± SD	IQR	*n*	mean ± SD	IQR
Whole sample																		
Verbal memory score[c]																		
Baseline	751	4.9 ± 2.8	4.0	196	5.3 ± 2.7	3.5	191	4.8 ± 2.7	4.0	88	4.8 ± 2.8	3.5	110	4.8 ± 2.8	4.0	166	4.6 ± 3.0	5.0
Follow-up	738	5.9 ± 2.7	4.0	187	6.5 ± 2.6	5.0	193	5.9 ± 2.8	4.0	84	5.5 ± 2.7	4.0	110	5.8 ± 2.8	4.0	164	5.6 ± 2.8	4.0
Difference (follow-up–baseline)	676	1.1 ± 3.0	4.0	180	1.3 ± 2.9	4.0	168	1.0 ± 3.0	4.0	78	0.8 ± 2.7	3.0	106	1.2 ± 2.9	4.0	144	1.2 ± 3.3	4.5
Figural memory score[c]																		
Baseline	740	7.8 ± 2.8	4.0	195	8.5 ± 2.5	3.0	189	7.3 ± 2.8	4.0	86	6.9 ± 2.7	4.0	110	8.1 ± 2.7	4.0	160	7.6 ± 3.1	4.0
Follow-up	742	7.9 ± 3.3	6.0	189	8.5 ± 3.2	5.0	194	8.0 ± 3.2	5.0	85	6.8 ± 3.5	6.0	110	7.5 ± 3.3	5.0	164	7.7 ± 3.5	6.0
Difference (follow-up–baseline)	670	0.2 ± 3.2	4.0	180	0.1 ± 2.8	4.0	168	0.7 ± 3.0	4.0	77	−0.3 ± 3.6	6.0	106	−0.5 ± 3.2	5.0	139	0.5 ± 3.6	5.0
Usage related to EMF exposure to the head																		
Cordless phone calls [min/d]	843	6.2 ± 6.6	5.1	207	6.0 ± 5.6	5.1	223	4.7 ± 4.1	4.0	97	4.0 ± 3.6	2.3	119	10.8 ± 9.6	11.3	197	6.5 ± 7.6	5.1
Mobile phone calls [min/d][d]	843	10.6 ± 13.7	12.6	207	5.9 ± 7.7	7.4	223	9.0 ± 12.8	10.2	97	9.9 ± 12.3	15.7	119	15.9 ± 11.9	13.2	197	14.4 ± 18.4	15.3
Mobile phone calls, self-reported [min/d]	843	17.2 ± 27.6	16.3	207	7.3 ± 10.9	7.0	223	11.4 ± 19.1	9.9	97	13.8 ± 34.5	9.4	119	31.1 ± 35.8	27.5	197	26.7 ± 32.1	27.4
Usage marginally related to EMF exposure to the head																		
Data traffic [min/d]	843	56.7 ± 34.3	55.4	207	27.6 ± 25.2	35.5	223	51.3 ± 28.3	43.4	97	59.2 ± 30.5	44.7	119	66.7 ± 26.5	41.4	197	86.1 ± 27.3	44.8
Gaming [min/d]	843	43.0 ± 56.9	55.7	207	38.6 ± 48.6	51.3	223	20.9 ± 33.9	29.3	97	116.1 ± 63.2	63.6	119	49.6 ± 62.0	56.8	197	32.7 ± 50.2	40.0
Texts sent [number/d]	843	35 ± 21	40	207	15 ± 12	17	223	32 ± 18	30	97	36 ± 20	35	119	43 ± 17	24	197	54 ± 12	13
Cumulative brain dose [mJ/kg per day][e]	830	858 ± 1,027	953	198	551 ± 1,029	471	221	753 ± 824	800	97	806 ± 956	997	118	1,214 ± 1,259	1,391	196	1,098 ± 1,003	1,110
Sample with operator data																		
Duration mobile phone calls [min/d]	322	3.2 ± 13.3	1.8	116	1.1 ± 2.9	0.8	63	4.2 ± 4.1	1.7	30	1.7 ± 3.1	1.2	65	2.8 ± 3.8	2.7	48	8.8 ± 29.2	8.0
Cumulative brain dose [mJ/kg per day][e]	318	469 ± 814	341	115	357 ± 918	187	61	465 ± 638	324	30	344 ± 694	152	65	620 ± 793	517	47	607 ± 842	443

Note: EMF, electromagnetic field; IQR, interquartile range; SD, standard deviation.

[a]Media use groups were determined by latent class analysis on 11 qualitatively different media use variables as described in Foerster and Röösli (2017).

[b]User-group–specific IQRs are displayed for descriptive purposes. For reporting user-group–specific IQRs (see Figure S2), the whole population IQR was used.

[c]Due to technical problems with the computerized testing system, completed tests for both time points were only available for a reduced number of participants.

[d]Adjusted via multilevel linear regression estimates calibrated on the objectively recorded duration of calls obtained by mobile phone operators. Models were clustered over schools and the following predictors were selected from the self-reported questionnaire data: age, gender, daily frequency of mobile phone calls at follow-up, daily frequency of text messages at follow-up, daily duration of mobile phone data traffic at follow-up, daily duration of cordless phone calls at follow-up, difference in daily duration of mobile phone calls between follow-up and baseline.

[e]Cumulative brain dose derived based on the following cumulative exposure variables. Near-field bands (if not indicated otherwise, taken from the questionnaire): daily duration of mobile phone calls (for the whole sample: calibrated via operator data; for the operator sample: operator recorded), network proportions of UMTS and GSM (for the whole sample: calibrated via operator data and far-field UMTS proportion; for the operator sample: operator recorded), proportion of headset use, daily duration of cordless phone calls, daily duration of mobile phone data traffic on WiFi and 3G, daily duration of WiFi use via laptop, PC, and tablet, daily duration of mobile phone held close to body; far-field bands: Uplink from surrounding mobile phones and Wifi (modeled via linear regression estimation based on questionnaire and personal measurements), downlink GSM900, downlink GSM1800, downlink UMTS, radio/broadcast, TV [(determined by geospatial propagation modeling using the NISMap software (Bürgi et al. 2010)], DECT (mean of the measurements).

Table 3. Results of adjusted linear exposure models for the whole sample and the two subsamples (2012–2014 and 2014–2016).

Exposure	*n*	IQR	Whole sample [adjusted[a] (95% CI)]	*n*	Sample 2012–2014 [adjusted[a] (95% CI)]	*n*	Sample 2014–2016 [adjusted[a] (95% CI)]
Whole sample							
Usage related to EMF exposure to the head							
Verbal memory							
Cordless phone calls [min/d]	676	5.1	−0.02 (−0.20, 0.15)	375	−0.05 (−0.26, 0.15)	301	−0.10 (−0.46, 0.25)
Mobile phone calls [min/d][b]	676	12.6	−0.01 (−0.29, 0.27)	375	0.08 (−0.31, 0.46)	301	−0.15 (−0.57, 0.26)
Figural memory							
Cordless phone calls [min/d]	670	5.1	−0.23 (−0.42, −0.04)	381	−0.23 (−0.45, −0.02)	289	−0.21 (−0.64, 0.22)
Mobile phone calls [min/d][b]	670	12.6	−0.21 (−0.51, 0.09)	381	0.01 (−0.40, 0.41)	289	−0.44 (−0.90, 0.02)
Cumulative brain dose [mJ/kg per day][c]							
Verbal memory	675	953	0.02 (−0.22, 0.26)	372	0.01 (−0.26, 0.27)	293	0.03 (−0.52, 0.58)
Figural memory	669	953	−0.22 (−0.47, 0.03)	381	−0.14 (−0.42, 0.14)	288	−0.58 (−1.17, 0.01)
Usage marginally related to EMF exposure to the head							
Verbal memory							
Data traffic [min/d]	676	55.4	0.34 (−0.05, 0.72)	375	0.48 (−0.04, 1.00)	301	0.33 (−0.28, 0.94)
Gaming [min/d]	676	55.7	−0.03 (−0.30, 0.25)	375	0.04 (−0.33, 0.40)	301	−0.16 (−0.59, 0.27)
Texts sent (units/d)	676	40	0.16 (−0.31, 0.63)	375	0.40 (−0.21, 1.02)	301	0.00 (−0.75, 0.75)
Figural memory							
Data traffic [min/d]	670	55.4	−0.05 (−0.46, 0.37)	381	0.18 (−0.37, 0.73)	289	−0.47 (−1.14, 0.21)
Gaming [min/d]	670	55.7	−0.12 (−0.41, 0.17)	381	0.02 (−0.36, 0.41)	289	−0.36 (−0.83, 0.12)
Texts sent (units/d]	670	40	0.04 (−0.45, 0.54)	381	0.20 (−0.45, 0.84)	289	−0.22 (−1.05, 0.62)
Sample with operator data							
Verbal memory							
Mobile phone calls [min/d]	277	1.8	−0.01 (−0.10, 0.08)	210	0.15 (−0.06, 0.37)	67	−0.01 (−0.13, 0.11)
Cumulative brain dose [mJ/kg per day][c]	273	341	0.02 (−0.14, 0.18)	209	0.05 (−0.12, 0.21)	64	−0.30 (−1.04, 0.44)
Figural memory							
Mobile phone calls [min/d]	278	1.8	−0.03 (−0.12, 0.06)	212	−0.18 (−0.39, 0.04)	66	0.03 (−0.11, 0.16)
Cumulative brain dose [mJ/kg per day][c]	274	341	−0.26 (−0.42, −0.10)	211	−0.25 (−0.41, −0.09)	63	−0.35 (−1.20, 0.50)

Note: Coefficients relate to change score per IQR of exposure shown in the column "IQR." CI, confidence interval; EMF, electromagnetic field.
[a]All models adjusted for age, gender, school level, education of the parents, alcohol consumption at follow-up, physical activity at follow-up, change in height (follow-up–baseline) and time between baseline and follow-up.
[b]Self-reported use calibrated with the objectively recorded duration of calls as described in Table S1.
[c]Cumulative brain dose derived based on the following cumulative exposure variables. Near-field bands (if not indicated otherwise, taken from the questionnaire): daily duration of mobile phone calls (for the whole sample: calibrated via operator data; for the operator sample: operator recorded), network proportions of UMTS and GSM (for the whole sample: calibrated via operator data and far-field UMTS proportion; for the operator sample: operator recorded), proportion of headset use, daily duration of cordless phone calls, daily duration of mobile phone data traffic on WiFi and 3G, daily duration of WiFi use via laptop, PC, and tablet, daily duration of mobile phone held close to body; far-field bands [if not indicated otherwise, exposure was determined by geospatial propagation modeling using the NISMap software (Bürgi et al. 2010)]: Uplink from surrounding mobile phones (modeled via linear regression estimation based on questionnaire and personal measurements), downlink GSM900, downlink GSM1800, downlink UMTS, WiFi (modeled via linear regression estimation based on questionnaire and personal measurements), radio/broadcast, TV, DECT.

score. This inverse association of cumulative RF-EMF brain dose was consistently seen in the full sample analysis and the subgroup analysis of the two study waves (2012–2014 vs. 2014–2016), media usage groups, and the operator sample although the strength of the association differed somewhat. The association was stronger in the second than in the first wave (however, with a wider confidence interval) and statistically significant in the operator sample, but not in the whole sample with self-reported exposure (after calibration using operator data). A significant decrease in figural memory score with cumulative brain dose was further seen in laterality analysis for right-side users of both the full sample and the operator sample only. In left-side users, in contrast, we found a significant decrease in verbal memory score for the operator sample. However, there was no such association for the full sample and estimates for the left-side users were in general imprecise due to the small sample size and also less consistent. The more consistent association of right-side users with a decrease for figural memory and the decrease for verbal memory score seen in left-side users of the operator sample might be related to the lateralization of memory processes (Golby et al. 2001) and requires further study.

Regarding wireless media usage not related to high RF-EMF exposure, a nonsignificant positive association for cumulative duration of mobile phone data traffic and verbal memory score change was observed, whereas the coefficients for text messages and gaming were generally small. It is conceivable that a positive significant association of verbal memory and data traffic could cover a potential negative RF-EMF effect on verbal memory if data traffic and RF-EMF dose are highly correlated. To control for this, we post hoc calculated the Spearman's correlation and fitted a regression model on verbal memory including both variables and adjusted for the same confounding variables as before. Spearman's correlation was weak ($\rho = 0.25$), and the linear regression estimates for neither RF-EMF dose nor duration of data traffic changed majorly in the mutually adjusted model (data not shown).

Strengths and Limitations

The present study is unique in its approach to overcoming the main challenges in epidemiological research on RF-EMF. We estimated individual RF-EMF brain doses for the population as a whole using objectively recorded operator data from a subset of participants to calibrate self-reported call duration and thus reduce misclassification. The operator-recorded data allowed us to estimate the very exposure-relevant proportion of calls on the GSM and UMTS networks (Erdreich et al. 2007; Gati et al. 2009). In our sample, the respective brain dose contributions were 79.8% (GSM) and 0.5% (UMTS) (see Table S2).

The modeling allowed addressing the associations with mobile phone use and RF-EMF brain dose separately to evaluate potential residual confounding of lifestyle and media use related to wireless device use itself. These factors might act on human health, cognition, and behavior independently from a potential biological radiation effect (Kuss et al. 2014; Kuss and Griffiths 2011, 2012; Roser et al. 2016). To control for such confounding, we adjusted our analysis for age, gender, school level, parents' education, alcohol consumption, and physical activity at follow-up, and the time and change in height between baseline and

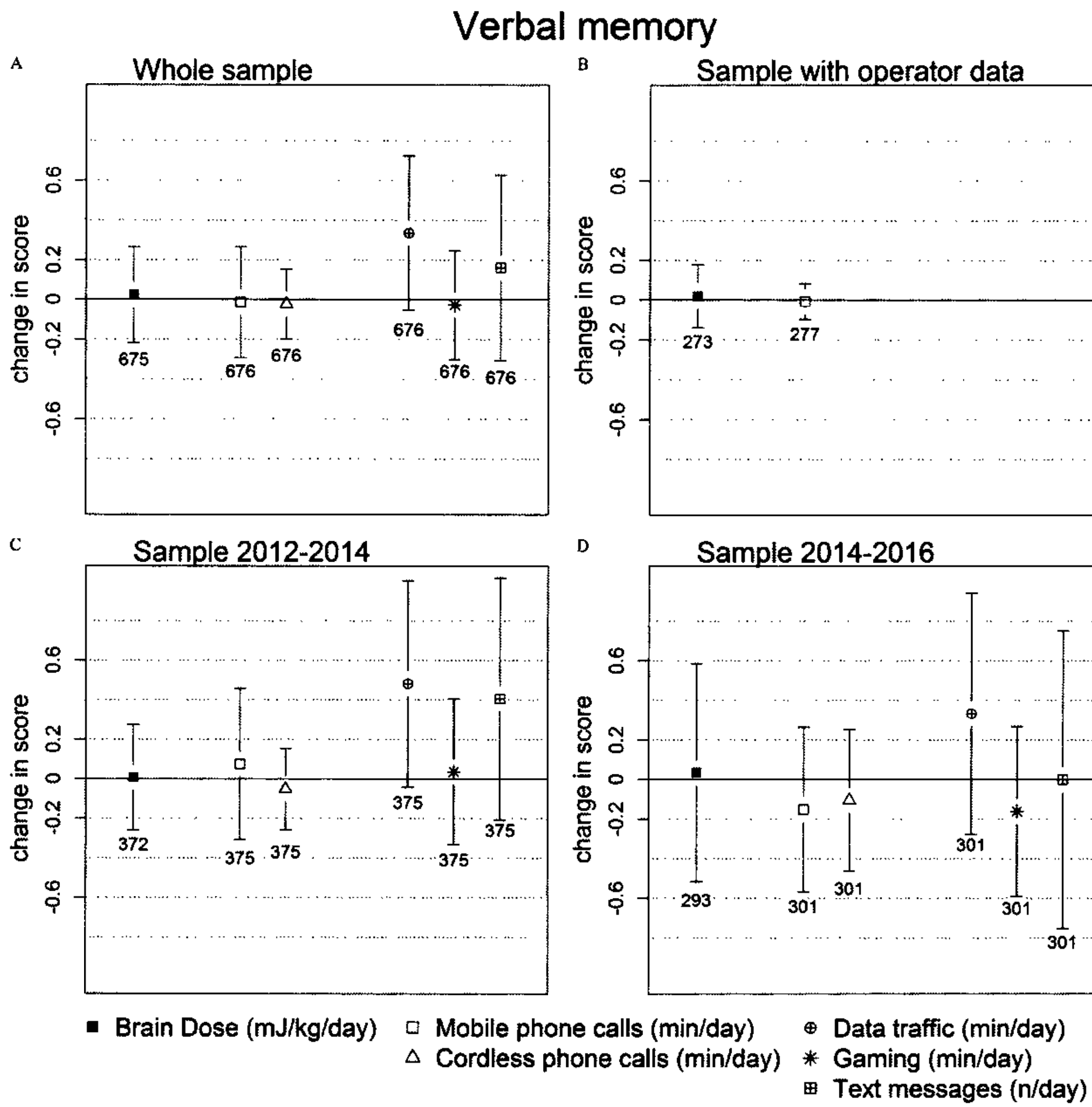

Figure 1. Results of linear exposure–response models for change in verbal memory scores (follow-up–baseline): estimates relate to change in memory score for (*A*) the whole sample per interquartile range (IQR) of exposure of the whole sample; (*B*) the operator sample per IQR of operator sample; (*C*) the sample 2012–2013 per IQR of exposure of the whole sample; and (*D*) the sample 2014–2015 per IQR of exposure of the whole sample. IQRs of the whole sample: brain dose, 953 mJ/kg per day; mobile phone calls, 12.6 min/d; cordless phone calls, 5.1 min/d; data traffic, 55.4 min/d; gaming, 55.7 min/d; and text messages, 40 per day. IQRs of the operator data, brain dose: 341 mJ/kg per day; and mobile phone calls, 1.8 min/d. All models were adjusted for age, gender, baseline score, nationality, school level, physical activity, alcohol, and education of parents and change in height and time between baseline and follow-up investigation. Number of observations for each calculation is indicated below each estimate.

follow-up. In addition, we estimated associations with media exposures associated with low RF-EMF exposures (minutes of gaming, minutes of mobile phone data traffic, and numbers of texts sent each day) to assess the potential impact of media use unrelated to RF-EMF.

In addition, we applied a new approach to control for residual confounding by stratifying the analysis for the RF-EMF brain dose over independent patterns of media use. Separate estimates for students classified according to the five media use patterns were similar among the groups for both verbal and figural memory, with I^2 statistics indicating little or no heterogeneity, and pooled estimates were consistent with estimates based on the main analysis. This pattern does not support major bias from uncontrolled confounding and is compatible with associations due to biophysical effects of RF-EMF, rather than effects of media use unrelated to RF-EMF. However, sample sizes within the five media use groups were small, and residual confounding cannot be ruled out based on this analysis.

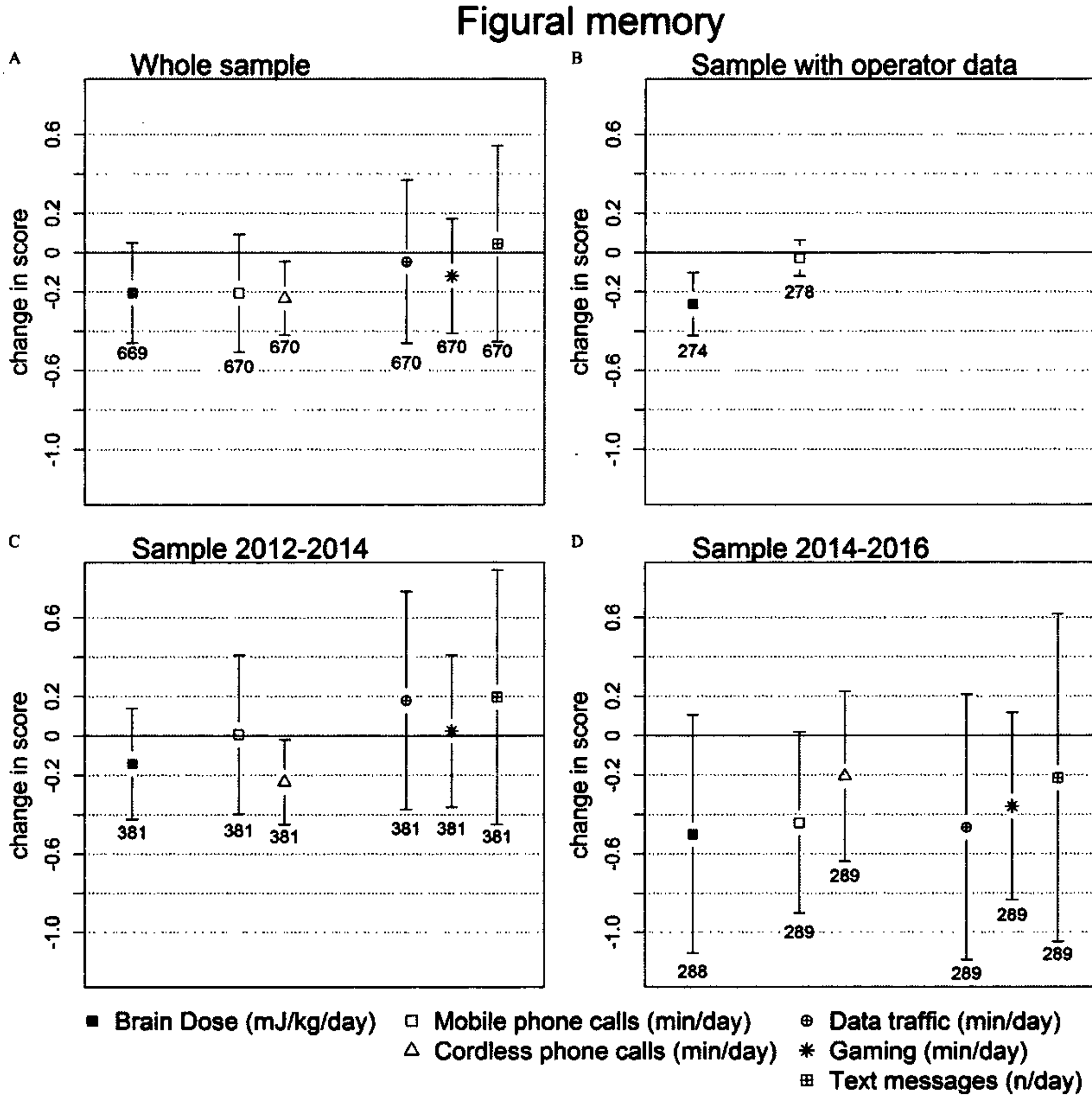

Figure 2. Results of linear exposure–response models for change in figural memory scores; (follow-up–baseline estimates relate to change in memory score for (*A*) the whole sample per interquartile range (IQR) of exposure of the whole sample; (*B*) the operator sample per IQR of operator sample; (*C*) the sample 2012–2013 per IQR of exposure of the whole sample; and (*D*) the sample 2014–2015 per IQR of exposure of the whole sample. IQRs of the whole sample: brain dose, 953 mJ/kg per day; mobile phone calls, 12.6 min/d; cordless phone calls, 5.1 min/d; data traffic, 55.4 min/d; gaming, 55.7 min/d; and text messages, 40 per day. IQRs of the operator data: brain dose, 341 mJ/kg per day; and mobile phone calls, 1.8 min/d. All models were adjusted for age, gender, baseline score, nationality, school level, physical activity, alcohol, and education of parents and change in height and time between baseline and follow-up investigation. Number of observations for each calculation is indicated below each estimate.

This study put a lot of emphasis on the exposure assessment and dose calculation. Information for the far-field exposure was retrieved from propagation models (Bürgi et al. 2010) and from personal measurements in 148 children (Roser et al. 2017). Operator-recorded mobile phone data is an asset, and, to our knowledge, it has not been available for other epidemiological studies of children and adolescents. Although operator data are objectively recorded, they have a disadvantage in that calls on other people's phones are not recorded. Furthermore, information on short message services does not represent texting behavior of adolescents using mostly Internet-based applications such as WhatsApp, and besides, the duration of data traffic and cordless phone use was not available from the operator. Thus, for these variables, the corresponding self-reported data had to be used for dose estimation as in the operator sample.

Uncertainty in the exposure assessment and in the RF-EMF dose calculations cannot be avoided. Estimation of SAR assumes a typical distance between emitting devices and body and average

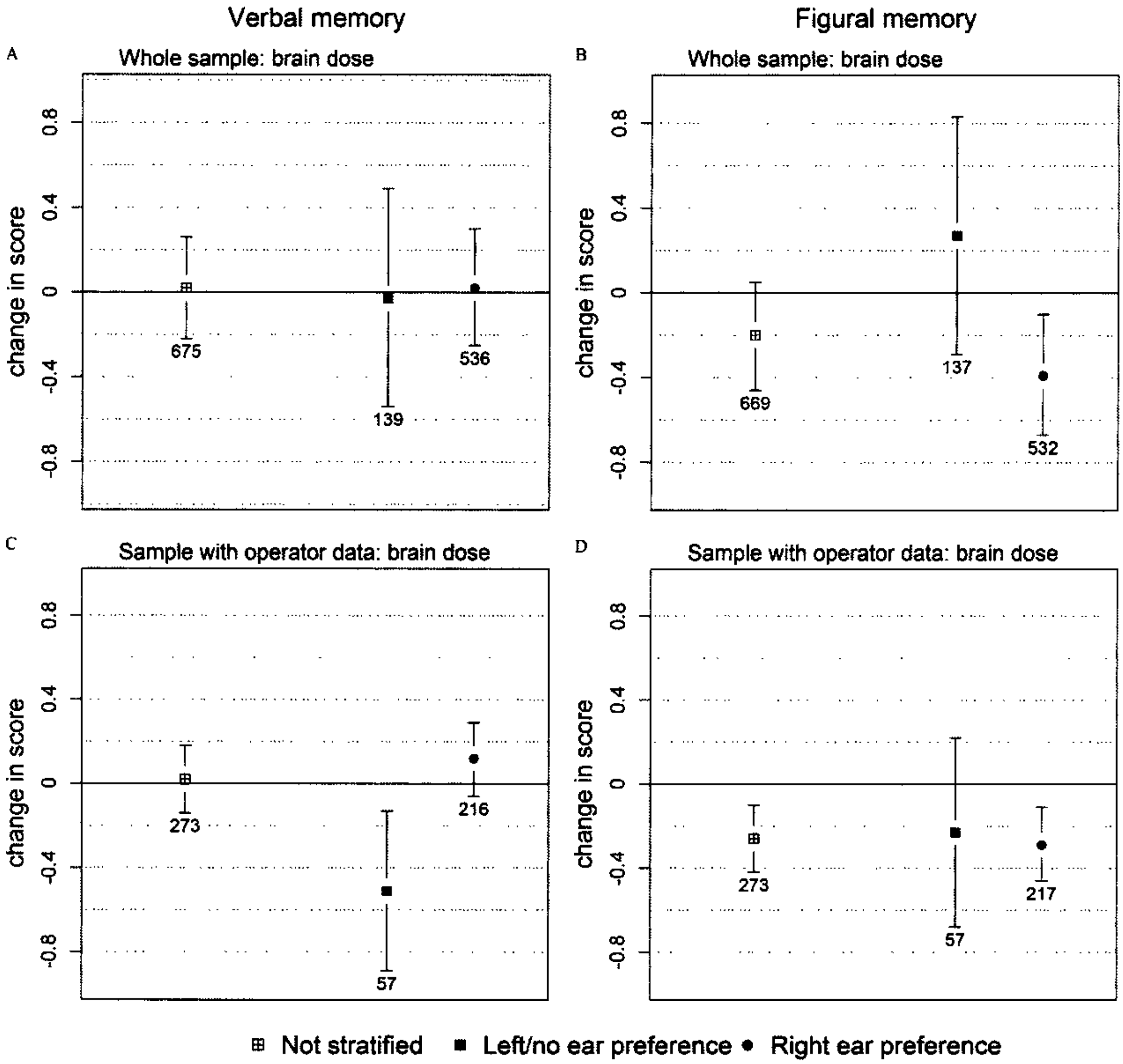

Figure 3. Results of the laterality analysis for the adjusted linear exposure response for the brain dose on changes in verbal and figural memory scores of the Intelligenz-Struktur-Test (IST). Estimates relate to (*A*) change in verbal memory score per interquartile range (IQR) of exposure for the whole sample; (*B*) change in figural memory score per IQR of exposure for the whole sample; (*C*) change in verbal memory score for the operator sample per IQR of the operator sample; and (*D*) change in figural memory score for the operator sample per IQR of the operator sample. Brain dose was derived via individual exposure modeling of relevant near- and far-field exposure sources. The most relevant predictors—duration of mobile phone calls and network proportion—were derived directly by network operators for the operator data sample. For the whole sample, these parameters were calibrated via multilevel linear regression models, predicting these parameters by self-reported questionnaire data, fitted for the operator sample. Change in memory score per IQR range of exposure. IQR for the whole sample, 953 mJ/kg per day; and IQR for the operator sample, 341 mJ/kg per day.

absorption characteristics of the body. But all of these aspects are variable in reality. A validation study could not be confirmed given than dose is not directly measurable and can only be computed.

Our study participants were recruited from the four common public school levels in urban and rural areas of Switzerland. Neither private nor religious schools were included because they play a minor role in Switzerland. All schools were located in Swiss German-speaking cantons, although Switzerland also has large French-, Italian-, and Rhaeto- Romanic-speaking areas. Generalizability might thus be restricted to public schools in German-speaking Switzerland. However, because RF-EMF brain dose is a biological measure, the exposure route should not differ among adolescents in general. Loss to follow-up was low (5.8%), but selection bias cannot be ruled out given that participation rates at baseline were only 37% for the first-wave (2012–2014) but 56% for the second-wave (2014–2016) study samples.

Comparison with Previous Analysis

The association between memory and RF-EMF exposure in the 2012–2014 sample has been analyzed previously (Schoeni et al. 2015). In the present work, we applied an improved RF-EMF dose estimation to the whole HERMES sample. The Spearman's correlation between the resulting new RF-EMF brain dose and the former dose estimate in the 2012–2014 sample was $\rho = 0.58$, demonstrating inherent uncertainties in dose estimation. The main difference compared with the previous dose modeling (Roser et al. 2015) was the use of operator calibrated self-reported call duration and different SAR values. Our new estimate of the first sample wave was of similar magnitude but less significant [−0.14 (−0.42, 0.14) per IQR of 953 mJ/kg per day] than in the previous analysis reported by Schoeni et al. (2015) [−0.26 (95% CI: −0.42, −0.10) per IQR of 1,579 mJ/kg per day].

Compared with the previous analyses, we have improved the dose calculations by various aspects. First, in the previous study, self-reported mobile phone use data was used for the dose calculation. It is well known that adolescents tend to overestimate duration of use and that the extent of overestimation is related to various sociodemographic factors (Aydin et al. 2011). This time, we used operator-recorded mobile phone data to adjust self-reported mobile phone use in order to reduce the overestimation of self-reported use. Consecutively, this led to a lower average RF-EMF dose estimation that might be closer to reality. The calibration was based on the assumption, that the factor and pattern by which participants overestimate their use could be extrapolated from the operator data sample. However, it must be noted that a large majority (approximately 75%) of the operator sample were participants from the first study wave. This might affect the generalizability of the operator sample–based estimates to the sample as a whole, in particular if relationships among self-reported variables considered for calibration and the operator-recorded data would be different for the first and second study wave due to increasing dissemination of smartphones in the study sample and the expansion of the UMTS network in the study region. However, differences in media usage behavior between the study waves might be more related to smartphone-specific applications rather than mobile phone calls (Foerster and Röösli 2017). Second, in the framework of the EU project GERoNiMO (Generalized EMF Research using Novel MethOds), new SAR estimates have been computed for various near- and far-field exposure conditions. Most relevant, these SAR estimates are based on the adolescent models Billie and Louis from the virtual population [for details see "1. Numeric simulations of brain gray matter specific absorption rates (SAR)" in the Supplemental Material], whereas in the past only SAR calculations from adult phantoms were available.

Brain Exposure and Differential Memory-Related Neuronal Circuits

Our findings require confirmation in other populations but suggest that RF-EMF brain exposure may have an adverse effect on figural memory functions in adolescents. The decrease in figural memory score with an IQR increase in exposure was 0.22 (95% CI: −0.47, 0.03; IQR: 953 mJ/kg per day) in the full sample ($n = 669$) and 0.26 (95% CI: −0.42, −0.10; 341 mJ/kg per day) in the operator sample ($n = 274$). To put this difference into context, in our main model adjusting for various factors, we observed a mean difference in figural memory score of 0.41 (95% CI: 0.13, 0.69) between adolescents from a lower school level (e.g., secondary school level C) to the next higher one (i.e., secondary school level B). Memory functions continue to develop in adolescents, and the ability to maintain and manipulate multiple spatial units (which is tested by the figural memory task) continues to develops until 15 y of age (Luciana et al. 2005).

Different brain areas and activation patterns are involved in neural memory processing, which is measured by different cognitive tests. Due to the differing specificity of cognitive tests, results often cannot be compared directly. Although we found decreases in figural memory, some experimental and epidemiological studies on RF-EMF found improvements in working memory performance. Working memory is usually assessed via reaction time tasks such as the *n*-back paradigm, where participants need to react in an accurate manner on a stimulus after a short time interval as fast as possible. This type of memory is also known as working attention and is related to very early stages of memory where stimuli are held actively in mind before being stored (Baddeley and Hitch 1974). For working memory, main brain activity is seen in executive structures involved in decision-making, predominantly the anterior cingulate and dorsolateral and inferior prefrontal cortices (Jansma et al. 2000). In addition to voluntary encoding, the memory processes evaluated in our study require consolidation (storage) of a stimulus and its subsequent recognition (retrieval) after a short period of time. In these later stages of memory, the activation shifts toward the temporal (verbal and object information processing) or parietal (spatial information processing) areas and later to the hippocampal and parahippocampal areas (memory storage and retrieval) (Brewer et al. 1998; Schacter and Wagner 1999; Schon et al. 2004). The memory tasks used in the present study might be more reliable for detecting alterations in adolescents' memory functions given that its execution involves more areas prone to high RF-EMF exposure from a mobile phone at the ear. This may partly contribute to the ambiguous results between our study and studies testing the working memory. However differences among populations with regard to specific exposures (or exposure patterns), differences in susceptibility, and other noncausal factors related to uncontrolled confounding or other sources of bias cannot be completely excluded.

Visual memory tasks similar to those applied in our study were also used in the Australian MoRPhEUS and ExPOSURE cohort studies in adolescents and primary school children. In line with our results, these studies found less accurate answers in the most frequent mobile phone and cordless phone callers (Abramson et al. 2009; Redmayne et al. 2013).

Although preliminary, findings from the laterality analysis might reflect separate lateralized neural pathways for verbal and figural memory. Figural and spatial memory processing are associated more with the right hemisphere of the brain, and verbal and auditory processing with the left hemisphere (Golby et al. 2001; Nagel et al. 2013). A more detailed description of the neural paths involved in the generation of new memory gives the influential model of working memory of Baddeley and Hitch (1974). The model differentiates between the visuospatial sketchpad for visual and the phonological loop for verbal information, running through the right and left temporal lobe, respectively. Evidence of a possible laterality effect in our study population might be consistent with impairment of this component step in object information memory processing.

How RF-EMF interacts with the brain is still unclear and no biophysical model exists for SAR values that do not noticeably increase the body temperature (International Commission on Non-Ionizing Radiation Protection 2010; Redmayne 2016). It may be speculated that our results are related to relatively consistently observed alterations in the electroencephalogram (EEG) during sleep in randomized crossover studies of participants exposed to mobile phone radiation prior to sleep (Loughran et al. 2012; Lustenberger et al. 2013; Regel et al. 2007; Schmid et al. 2012). Disturbed sleep negatively affects memory consolidation, in particular, in relation to abstract and complex tasks involving higher brain functions (Kopasz et al. 2010). Lustenberger et al. (2013) observed reduced overnight performance improvement in a motor sequence task after a night with RF-EMF exposure compared with the sham condition. Thus, future studies should clarify whether RF-EMF has an impact on sleep-facilitated learning processes via altered sleep brain activity.

Conclusion

We found preliminary evidence suggesting that RF-EMF may affect brain functions such as figural memory in regions that are most exposed during mobile phone use. Our findings do not provide conclusive evidence of causal effects and should be interpreted with caution until confirmed in other populations. Associations with media use parameters with low RF-EMF exposures did not provide clear or consistent support of effects of media use unrelated to RF-EMF (with the possible exception of consistent positive associations between verbal memory and data traffic duration). It is not yet clear which brain processes could be potentially affected and what biophysical mechanism may play a role. Potential long-term risk can be minimized by avoiding high brain-exposure situations as occurs when using a mobile phone with maximum power close to the ear because of, for example, bad network quality.

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Wi-Fi is an important threat to human health☆

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ABSTRACT

Repeated Wi-Fi studies show that Wi-Fi causes oxidative stress, sperm/testicular damage, neuropsychiatric effects including EEG changes, apoptosis, cellular DNA damage, endocrine changes, and calcium overload. Each of these effects are also caused by exposures to other microwave frequency EMFs, with each such effect being documented in from 10 to 16 reviews. Therefore, each of these seven EMF effects are established effects of Wi-Fi and of other microwave frequency EMFs. Each of these seven is also produced by downstream effects of the main action of such EMFs, voltage-gated calcium channel (VGCC) activation. While VGCC activation via EMF interaction with the VGCC voltage sensor seems to be the predominant mechanism of action of EMFs, other mechanisms appear to have minor roles. Minor roles include activation of other voltage-gated ion channels, calcium cyclotron resonance and the geomagnetic magnetoreception mechanism. Five properties of non-thermal EMF effects are discussed. These are that pulsed EMFs are, in most cases, more active than are non-pulsed EMFs; artificial EMFs are polarized and such polarized EMFs are much more active than non-polarized EMFs; dose-response curves are non-linear and non-monotone; EMF effects are often cumulative; and EMFs may impact young people more than adults. These general findings and data presented earlier on Wi-Fi effects were used to assess the Foster and Moulder (F&M) review of Wi-Fi. The F&M study claimed that there were seven important studies of Wi-Fi that each showed no effect. However, none of these were Wi-Fi studies, with each differing from genuine Wi-Fi in three distinct ways. F&M could, at most conclude that there was no statistically significant evidence of an effect. The tiny numbers studied in each of these seven F&M-linked studies show that each of them lack power to make any substantive conclusions. In conclusion, there are seven repeatedly found Wi-Fi effects which have also been shown to be caused by other similar EMF exposures. Each of the seven should be considered, therefore, as established effects of Wi-Fi.

1. Introduction

Wi-Fi (also known as WiFi or WLAN) is a wireless network involving at least one Wi-Fi antenna connected to the internet and a series of computers, laptops and/or other wireless devices communicating wirelessly with the Wi-Fi antenna. In this way, each such wireless communication device can communicate wirelessly with the internet. All the studies reviewed here were of Wi-Fi using the 2.4 GHz band, although there is also a 5 GHz band reserved for possible Wi-Fi use.

Telecommunications industry-linked individuals and groups have claimed that there are no and cannot possibly be any health impacts of Wi-Fi (Foster and Moulder, 2013; Berezow and Bloom, 2017). However with Wi-Fi exposures becoming more and more common and with many of our exposures being without our consent, there is much concern about possible Wi-Fi health effects. This paper is not focused on anecdotal reports but rather on 23 controlled, scientific studies of such health-related effects in animals, cells including human cells in culture and in human beings (Table 1).

Each of the effects reported above in from 2 to 11 studies, have an extensive literature for their occurrence in response to various other non-thermal microwave frequency EMFs, discussed in detail below. These include (see Table 1) findings that Wi-Fi exposures produce impacts on the testis leading to lowered male fertility; oxidative stress; apoptosis (a process that has an important causal role in neurodegenerative disease); cellular DNA damage (a process causing cancer and germ line mutations); neuropsychiatric changes including EEG changes; hormonal changes.

The discussion here focuses on those Wi-Fi effects which have been found by multiple Wi-Fi studies and have been previously confirmed by non-thermal exposures to other microwave frequency EMFs. The 1971/72 U.S. Office of Naval Medical Research study (Glaser, 1971) reported the following changes related to testis or sperm: 1. Decreased testosterone leading to lowered testis size. 2. Histological changes in testicular epithelial structure. 3. Gross testicular histological changes. 4.

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Table 1
Summary of health impacts of Wi-Fi EMF exposures.

Citation(s)	Health Effects
Atasoy et al. (2013); Ozorak et al. (2013); Aynali et al. (2013); Çiftçi et al. (2015); Tök et al. (2014); Çiğ and Nazıroğlu (2015); Ghazizadeh and Nazıroğlu (2014); Yüksel et al. (2016); Othman et al. (2017a, 2017b); Topsakal et al. (2017)	Oxidative stress, in some studies effects lowered by antioxidants
Atasoy et al. (2013); Shokri et al. (2015); Dasdag et al. (2015); Avendaño et al. (2012); Yildiring et al. (2015); Özorak et al. (2013); Oni et al. (2011); Akdag et al. (2016)	Sperm/testicular damage, male infertility
Papageorgiou et al. (2011); Maganioti et al. (2010); Othman et al. (2017a, 2017b); Hassanshahi et al. (2017)	Neuropsychiatric changes including EEG; prenatal Wi-Fi leads to post-natal neural development, increased cholinesterase; decreased special learning; Wi-Fi led to greatly lowered ability to distinguish familiar from novel objects, changes in GABA and cholinergic transmission
Shokri et al. (2015); Dasdag et al. (2015); Çiğ and Nazıroğlu (2015); Topsakal et al. (2017)	Apoptosis (programmed cell death), elevated apoptotic markers
Avendaño et al. (2012); Atasoy et al. (2013); Akdag et al. (2016)	Cellular DNA damage
Saili et al. (2015); Yuksel et al. (2016); Topsakal et al. (2017)	Endocrine changes incl.: Catecholamines, pancreatic endocrine dysfunction, prolactin, progesterone and estrogen
Çiğ and Nazıroğlu (2015); Ghazizadeh and Nazıroğlu (2014)	Calcium overload
Aynali et al. (2013)	Melatonin lowering; sleep disruption
Othman et al. (2017a)	MicroRNA expression (brain)
Othman et al. (2017a)	Abnormal postnatal development
Çiftçi et al. (2015)	Disrupts development of teeth
Saili et al. (2015)	Cardiac changes, blood pressure disruption; erythrocyte damage
Lee et al. (2014)	Growth stimulation of adipose stem cells (role in obesity?)

Decreased spermatogenesis. Glaser (1971) also reported a total of 35 neurological/neuropsychiatric effects of non-thermal EMF exposures, including 9 central nervous system effects, 4 autonomic system effects, 17 psychological disorders, 4 behavioral changes and EEG changes. It also reported 7 types of chromosomal aberrations several of which are known to be caused by chromosomal double stranded DNA breaks, 8 types of endocrine changes, and cell death (what we now call apoptosis). Glaser (1971) also provided over 1000 different citations each reporting various types of non-thermal microwave frequency EMF effects. Consequently, the existence of 5 types of Wi-Fi effects, each supported by multiple Wi-Fi studies were already well-supported *as general non-thermal EMF effects* back in 1971, 47 years ago: effects on the testis and sperm production, neurological/neuropsychiatric effects, endocrine effects, attacks on cellular DNA and increased apoptosis/cell death.

The 146 page review published by Tolgskaya and Gordon (1973) found that in studies of histological changes in rodents, the three most sensitive organs in the body to non-thermal microwave EMFs were the nervous system (including the brain), followed closely by the heart and the testis. They also reported changes in neuroendocrine tissues and increased cell death in multiple tissues. Thus those pre-1973 rodent studies already showed that other EMFs caused 4 of the repeated, recently documented Wi-Fi effects: changes in testis structure/function, neurological effects, increased cell death (possibly via apoptosis) and endocrine effects. Findings from our longer list of EMF reviews of non-thermal effects are summarized in Table 2.

Each of the 7 Wi-Fi effects found in 2–11 studies (Table 1), have also been found to be caused by other microwave frequency EMFs, in a much larger literature (Table 2). From 10 to 16 reviews extensively document each of these seven effects as general microwave frequency effects (Table 2). These are, therefore, general effects produced by such EMFs. Each of these 7 repeatedly found Wi-Fi effects should, therefore, be considered established Wi-Fi effects. The author is not aware of any genuine Wi-Fi studies on these 7 effects that reported no statistically significant evidence of effect.

Each of these 7 is very serious: Oxidative stress has causal roles in most chronic human diseases; cellular DNA damage can cause cancer, thus producing a partial explanation for EMF cancer causation; because such DNA damage occurs in sperm cells (Atasoy et al., 2013; Avendaño et al., 2012; Akdag et al., 2016; Adams et al., 2014; Liu et al., 2014; Asghari et al., 2016), such damage is highly likely to produce mutations that impact future generations; calcium overload is highly likely to be the cause of each of these various other effects, as discussed below; apoptosis has central roles in neurodegenerative diseases; the neuropsychiatric effects are almost certainly caused by the impact of EMFs on brain structure which is extensively documented and, in my opinion, produces many impacts (Pall, 2016b). A recent meta-analysis shows major lowering of sperm counts and sperm quality in many countries around the world, with declines of over 50% in all advanced technology countries (Levine et al., 2017). The senior author of this study suggested that this effect alone may lead to human extinction (No authors listed, 2017). Given the major impact of EMF exposures on sperm count and quality in human and in animal studies, the pattern of evidence on male fertility is very worrying.

One thing needs to be clarified, here, however. In the two studies on calcium overload following Wi-Fi exposure, such overload was measured a substantial time period following exposure. Overload was shown to be caused, to a substantial effect, by increased TRPV1 receptor activity (Çiğ and Nazıroğlu, 2015; Ghazizadeh and Nazıroğlu, 2014). The TRPV1 receptor is known to be activated by oxidative stress. It is my view, discussed in detail below, that there is a central mechanism that acts to produce excessive intracellular calcium immediately following EMF exposure and that the oxidative stress/TRPV1 activation is secondary.

We have then, major impacts of non-thermal EMF exposures on both of the most important intercellular regulatory systems in the body, the nervous system and the endocrine systems. We have major impacts on what may be the most important intracellular regulatory system, the calcium regulatory system. And we also have non-thermal EMFs attacking the DNA of our cells, putting our biological inheritance at great risk. As living organisms, EMFs attack each of the most important functions that go to the heart of our human complexities.

Despite all of these clear and important, non-thermal effects, and the fact that there was substantial evidence for many of them already known before 1973, our current U.S. and international safety guidelines are still based on considering only thermal effects.

2. Wi-Fi and other wireless communication EMFs are pulsed, leading to larger biological impacts; These EMFs are also polarized, also producing larger effects; Dose response curves are often both non-linear and non-monotone

There are three patterns of EMF action, each of which is very important and each of which is almost universally ignored by the

Table 2
Reviews of Non-thermal Effects of Microwave Frequency EMFs Similar to Those Found in Multiple Wi-Fi Studies.

Non-thermal effects	Citations
Cellular DNA damage	Glaser (1971); Yakymenko et al. (1999); Aitken and De Iuliis (2007); Hardell and Sage (2008); Hazout et al. (2008); Phillips et al. (2009); Ruediger (2009); Makker et al. (2009); Yakymenko and Sidorik (2010); Batista Napotnik et al. (2010); Yakymenko et al. (2011); Pall (2013, 2015b); Asghari et al. (2016); Pall (2018)
Changes in testis structure, lowered sperm count/ quality	Glaser (1971); Tolgskaya and Gordon (1973); Aitken and De Iuliis (2007); Hazout et al. (2008); Desai et al. (2009); Gye and Park (2012); Nazıroğlu et al. (2013); Carpenter (2013); Adams et al. (2014); Liu et al. (2014); Houston et al. (2016); La Vignera et al. (2012); Makker et al. (2009)
Neurological/neuropsychiatric effects	Glaser (1971); Tolgskaya and Gordon (1973); Raines (1981); Lai (1994); Grigor'ev (1996); Hardell and Sage (2008); Makker et al. (2009); Khurana et al. (2010); Levitt and Lai (2010); Consales et al. (2012); Carpenter (2013); Pall (2016b); Belyaev et al. (2016); Sangün et al. (2016); Kaplan et al. (2016)
Apoptosis/cell death	Glaser (1971); Tolgskaya and Gordon (1973); Raines (1981); Yakymenko et al. (1999); Batista Napotnik et al. (2010); Yakymenko and Sidorik (2010); Pall (2013, 2016b); Asghari et al. (2016); Sangün et al. (2016)
Calcium overload	Adey (1981, 1988); Walleczek (1992); Yakymenko et al. (1999); Gye and Park (2012); Pall (2013, 2015a, 2015b, 2016a, 2016b)); Asghari et al. (2016)
Endocrine effects	Glaser (1971); Tolgskaya and Gordon (1973); Raines (1981); Hardell and Sage (2008); Gye and Park (2012); Hardell and Sage (2008); Makker et al. (2009); Pall (2015b); Sangün et al. (2016); Asghari et al. (2016)
Oxidative stress, free radical damage	Raines (1981); Houston et al. (2016); Hardell and Sage (2008); Hazout et al. (2008); Desai et al. (2009); Yakymenko and Sidorik (2010); Yakymenko et al. (2011); Consales et al. (2012); La Vignera et al. (2012); Nazıroğlu et al. (2013); Yakymenko et al. (2015); Pall (2013, 2018); Dasdag and Akdag (2016); Wang and Zhang (2017)

telecommunications industry and industry-linked organizations. The most extensively reviewed of these is that pulsed EMFs are usually much more biologically active than are non-pulsed (also known as continuous wave) EMFs of identical frequency and similar average intensity (Osipov, 1965; Pollack and Healer, 1967; Creighton et al., 1987; Grigor'ev, 1996; Belyaev, 2005, 2015; Markov, 2007; Van Boxem et al., 2014; Pall, 2015b; Panagopoulos et al., 2015b). This pattern of action is particularly important because all wireless communication devices, including Wi-Fi (Panagopoulos et al., 2015b; Maret, 2015) communicate via pulsations and are likely to be particularly dangerous as consequence of this. Panagopoulos et al., 2015b have argued that the more pulsed they are, the more damaging EMFs will be and while this may still be questioned, it may well be a roughly applicable generalization.

It is also true that artificial EMFs are polarized and this makes artificial EMFs particularly dangerous (Belyaev, 2005, 2015; Panagopoulos et al., 2015a). Polarized EMFs put much larger forces of electrically charged chemical groups than do non-polarized EMFs (Panagopoulos et al., 2015a), an observation that is relevant to the main mechanism of EMF action in living cells discussed below.

It has often been found that there are windows of exposure where specific intensity ranges produce maximum biological effects, which drop off going to both lower or higher intensities (Belyaev, 2005, 2015; Pall, 2015b). It can be seen from this that dose-response curves are often both non-linear and non-monotone whereas industry linked groups often assume a linear and therefore monotone dose-response curve.

3. EMF effects are often cumulative and irreversible

One question that has been raised about the effects of these low-intensity EMFs producing biological effects is are they cumulative? I am aware of three different types of evidence for cumulative effects. Three of the human occupational exposure studies from the 1970's reviewed in Raines (1981), showed that effects increased substantially with increasing time of exposure to a particular type and intensity of EMF.

The impacts of such EMFs on animal brains were reviewed in Tolgskaya and Gordon (1973) and discussed in Pall (2016b). Initially exposures over period of 1–2 months produced relatively modest changes in structure of the brain and the neurons and when exposures ceased, most of the structural changes disappeared – that is the changes were largely reversible. However more months of exposure produced much more severe impacts on brain and neuronal structure and these were irreversible (Tolgskaya and Gordon, 1973; Pall, 2016b).

Magras and Xenos (1997) put pairs of young mice into cages on the ground at two locations each with somewhat different exposures within an antenna park. The exposure levels at both sites were well within safety guidelines, so if the safety guidelines have any biological relevance, there should have been no apparent effects. It takes about 30 days for mice to go through gestation. At the higher level exposure, the pairs produced one litter of lower than normal size, and a second litter with lowered numbers of progeny; after that they were completely sterile or had extremely low fertility (Magras and Xenos, 1997). At the other site, the mating pairs produced four litters, with decreasing numbers of progeny over time followed by complete sterility. In both groups, the mating and possible subsequent gestatation for the fifth possible litter were performed under conditions of no EMF exposure, but the fertility effects were not reversed; therefore fertility effects may become irreversible, suggesting a similar pattern to the brain related effects of EMFs. It should be noted that Özorak el al (2013) showed that Wi-Fi exposure impacted animal reproduction and that (Atasoy et al., 2013; Shokri et al., 2015; Dasdag et al., 2015; Avendaño et al., 2012; Yildiring et al., 2015; Oni et al., 2011; Akdag et al., 2016) suggest this as well from the Wi-Fi impacts on testis structure and sperm production.

Mutation accumulation produced by cellular DNA damage is likely to be both cumulative and irreversible, as well, because later mutations are highly unlikely to reverse previously occurring mutations.

We have therefore reason to think that such effects as brain damage to animal brains, neuropsychiatric effects in humans, reproductive dysfunction in mice and mutational effects, are each cumulative. Those same effects may be completely or largely irreversible. One thing that this should tell us is that the short-term Wi-Fi studies shown in Table 1 may *greatly underestimate* the damage Wi-Fi may do over much longer time periods. Given the fact that Wi-Fi has been placed in most schools, hotels, restaurants, coffee shops, commercial aircraft and airports as well as in many homes and that Wi-Fi hot spots are becoming increasingly common in cities around the world, we should expect massive cumulative Wi-Fi effects in many people. A second tentative inference is that false assurances of safety on the part of industry are likely to lead to much more severe effects on people exposed to Wi-Fi or other EMFs; rather than leading them to protect themselves or their children by avoiding exposures or demanding that others stop non-voluntary exposures, they are likely to avoid protective changes or be prevented from doing such protective changes. A third inference is that these effects may be among the more difficult ones for us to attribute to EMF exposure. We are much more aware of effects that occur rapidly than those that take months or years before they become readily apparent.

4. Wi-Fi and other EMFs may be particularly damaging to young people

Most arguments that have been made that microwave frequency EMFs may be much more damaging to young children have centered on the much smaller skulls and skull thickness in young children, increasing the exposure of their brains to EMFs (Gandhi and Kang, 2001; Gandhi et al., 2012). However there are other arguments to be made. EMFs have been shown to be particularly active in producing effects on embryonic stem cells (Lee et al., 2014; Belyaev et al., 2009; Markovà et al., 2010; Czyz et al., 2004; Xu et al., 2016; Bhargav et al., 2015; Odaci et al., 2008; Uchugonova et al., 2008; Wang et al., 2015; Teven et al., 2012). Because such stem cells occur at much higher cell densities in children, with stem cell densities the highest in the fetus and decreasing with increasing age (Belyaev et al., 2009; Markovà et al., 2010), impacts on young children are likely to be much higher than in adults. The decreased DNA repair and increased DNA damage following EMF exposure strongly suggest that young children may be increasingly susceptible to cancer following such exposures (Belyaev et al., 2009; Markovà et al., 2010; Czyz et al., 2004). EMF action on stem cells may also cause young children to be particularly susceptible to disruption of brain development (Xu et al., 2016; Bhargav et al., 2015), something that may be relevant to autism causation. These are all very problematic issues and we cannot rule out the possibility that there are other problematic issues as well. Redmayne and Johansson (2015) reviewed the literature showing that there are age-related effects, such that young people are more sensitive to EMF effects. It follows from these various findings that the placement of Wi-Fi into schools around the country may well be a high level threat to the health of our children as well being a threat to teachers and any very sensitive fetuses teachers may be carrying, as well.

5. How do EMF exposures lead to non-thermal health impacts?

The author found the answer to this question in the already published scientific literature (Pall, 2013). That study showed that in 24 different studies [there are now a total of 26 Pall (2015b)], effects of low-intensity EMFs, including microwave frequency and also extremely low frequency EMFs, static electrical fields and static magnetic fields could be blocked by calcium channel blockers, drugs that are specific for blocking voltage-gated calcium channels (VGCCs). There were 5 different types of calcium channel blockers used in these studies, each thought to be highly specific, each structurally distinct and each binding to a different site on the VGCCs. In studies where multiple effects were studied, all studied effects were blocked or greatly lowered by calcium channel blockers. These studies show that EMFs produce diverse non-thermal effects via VGCC activation Pall (2013, 2014, 2015a, 2015b, 2016a, 2016b)) in many human and animal cells. In plant cells, EMFs activate somewhat similar calcium channels and produce somewhat similar effects on oxidative stress, cellular DNA damage and calcium signaling (Pall, 2016a). Furthermore, many different effects shown to be produced in repeated studies by EMF exposures, including the effects discussed above, can be produced by downstream effects of VGCC activation, via increased $[Ca2+]i$, as discussed in detail below.

Before leaving this issue, it is important to discuss why the VGCCs are so sensitive to activation by these low-intensity EMFs. The VGCCs each have a voltage sensor which is made up of 4 alpha helixes in the plasma membrane, with each such helix having 5 positive charges on it, for a total of 20 positive charges (Pall, 2015b). These voltage sensor helixes are each called S4 helixes because each is the fourth helix in a distinct multi-helix domain. Each of these voltage sensor charges is within the lipid bilayer part of the plasma membrane. The electrical forces on the voltage sensor are very high for three distinct reasons (Pall, 2015b, 2015a, 2016a). 1. The 20 charges on the voltage sensor make the forces on voltage sensor 20 times higher than the forces on a single charge. 2. Because these charges are within the lipid bilayer section of the membrane where the dielectric constant is about 1/120th of the dielectric constant of the aqueous parts of the cell, the law of physics called Coulomb's law, predicts that the forces on those charges will be approximately 120 times higher than the forces on charges in the aqueous parts of the cell. 3. Because the plasma membrane has a high electrical resistance whereas the aqueous parts of the cell are highly conductive, the electrical gradient across the plasma membrane is estimated to be concentrated about 3000-fold. The combination of these effects means that comparing the forces on the voltage sensor with the forces on singly charged groups in the aqueous parts of the cell, the forces on the voltage sensor are approximately $20 \times 120 \times 3000 = 7.2$ million times higher (Pall, 2015b). The physics predicts, therefore, extraordinarily strong forces activating the VGCCs via the voltage sensor. It follows that the biology tells us that the VGCCs are the main target of the EMFs and the physics tells us why they are the main target. Thus the physics and biology are pointing in the same direction.

There are also additional findings pointing to the voltage sensor as the direct target of the EMFs. In addition to the VGCCs, there are also voltage-gated sodium, potassium and chloride channels, with each of these having a voltage sensor similar to those found in the VGCCs. Lu et al. (2015) reported that voltage gated sodium channels, in addition to the VGCCs were activated by EMFs. Tabor et al. (2014) found that Mauthner cells, specialized neurons with special roles in triggering rapid escape mechanisms in fish, were almost instantaneously activated by electrical pulses, which acted via voltage-gated sodium channel activation to subsequently produce large $[Ca2+]i$ increases. Zhang et al. (2016) reported that in addition to the VGCCs, potassium and chloride channels were each activated by EMFs, although these other voltage-gated ion channels had relatively modest roles compared with the VGCCs in producing biological effects. Each of these three studies, the Lu et al. (2015) study, the Tabor et al. (2014) study and the Zhang et al. (2016) study used specific blockers for these other voltage-gated ion channels to determine their roles. The Tabor et al. (2014) study also used genetic probing to determine the role of the voltage-gated sodium channels. Lu et al. (2015) also used whole cell patch clamp measurements to measure the rapid influx of both sodium and calcium into the cell via the voltage-gated channels following EMF exposure. Sodium influx, particularly in electrically active cells, act in the normal physiology to depolarize the plasma membrane, leading to VGCC activation such that the voltage-gated sodium channels may act primarily via indirect activation of the VGCCs. In summary then, we have evidence that in animal including human cells, seven distinct classes of voltage-gated ion channels are each activated by EMF exposures: From the Pall (2013) review, four classes of voltage-gated ion channels were shown from calcium channel blocker studies, to be activated by EMFs, L-type, T-type, N-type and P/Q –type VGCCs. In this paragraph we have evidence that three other channels are also activated, voltage-gated sodium channels, voltage-gated potassium channels and voltage-gated chloride channels. Furthermore the plant studies strongly suggest that the so called TPC channels, which contain a similar voltage sensor, are activated in plants allowing calcium influx into plants to produce similar EMF-induced responses (Pall, 2016a). One can put those observations together with the powerful findings from the physics, that the electrical forces on the voltage-sensor are stunningly strong, something like 7.2 million times stronger than the forces on the singly charged groups in the aqueous phases of the cell. Now you have a stunningly powerful argument that the voltage sensor is the predominant direct target of the EMFs.

There is one additional finding that should be discussed here. In a study published by Pilla (2012), it was found that pulsed EMFs produced an "instantaneous" increase in calcium/calmodulin-dependent nitric oxide synthesis in cells in culture. What Pilla (2012) showed was that following EMF exposure, the cells in culture, must have produced a large increase in $[Ca2+]i$, this in turn produced a large increase in nitric oxide synthesis, the nitric oxide diffused out of the cells and out of the aqueous medium above the cells into the gas phase, where the nitric oxide was detected by a nitric oxide electrode. This entire sequence occurred in less than 5 s. This eliminates almost any conceivable indirect effect, except possibly via plasma membrane depolarization. Therefore that the pulsed EMFs are acting directly on the voltage sensors of the VGCCs and possibly the voltage-gated sodium channels, to produce the [Ca2 +]i increase.

Why is it that the VGCCs, acting via calcium influx, seem to be much more important in producing EMF effects than are the other voltage-gated ion channels? Probably for three reasons: 1. Ca^{2+} ions under resting conditions in cells have about a 10,000-fold concentration gradient driving them into the cell, and over a million-fold electrochemical gradient also driving them into the cell. Because of this, one can have huge calcium influxes upon channel activation. 2. [Ca2 +]i produces many important regulatory effects, such that over activation of those effects can have very large pathophysiological consequences. 3. Sustained elevation of [Ca2+]i produces major cell damage.

6. How can the Wi-Fi effects be produced by EMF triggered VGCC activation?

Can the various effects produced by Wi-Fi and by other microwave frequency EMFs be produced by the downstream effects of VGCC activation? In order to determine that, one needs to consider the various downstream effects of VGCC activation, summarized in Fig. 1 and how these are likely to produce each of the effects of Wi-Fi and other microwave frequency EMFs. Let's consider Fig. 1.

As shown in the top left section of Fig. 1, microwave and lower frequency EMFs act via VGCC activation to produce increases in intracellular calcium [Ca2+]i. All of the downsteam effects of VGCC activation considered in Fig. 1 are produced by elevated (often excessive) [Ca2+]i.

Just to the right of [Ca2+]i in Fig. 1, you will see that elevated [Ca2+]i produced increases in nitric oxide (NO) synthesis. This is because two of the three types of enzymes producing NO are calcium-dependent. There is an NO signaling pathway that goes through increased cGMP and increased protein kinase G activity. Protein kinase G can act by raising the activity of the transcriptional regulatory factor, Nrf2, to produce the therapeutic effects produced by EMF exposures (Pilla, 2013; Pall, 2014; Pall and Levine, 2015).

High levels of NO can bind to heme groups on cytochromes (uppermost section, Fig. 1) inhibiting cytochrome oxidase, the terminal oxidase in the mitochondria, inhibiting ATP synthesis. NO can also inhibit cytochrome P450s involved in steroid hormone synthesis, lowering levels of estrogen, progesterone and testosterone (sex hormones).

The main pathophysiological effects of EMF exposures are produced via excessive calcium signaling (lower left) and the peroxynitrite pathway (lower right). Peroxynitrite levels are elevated because both NO and superoxide are elevated by increased [Ca2+]i with NO and superoxide reacting with each other to form peroxynitrite. Peroxynitrite and its CO_2 adduct, can break down to produce reactive free radicals, hydroxyl radical, carbonate radical and NO_2 radical which produce oxidative stress. These various oxidants act to produce greatly elevated NF-kappaB activity, leading to inflammation. All of this biochemistry and physiology is well-accepted and widely known with a single exception: The role of protein kinase G in raising Nrf2 has only recently been reviewed (Pall and Levine, 2015).

The ways in which these mechanisms can produce each of the seven effects produced by Wi-Fi, as well as other microwave frequency EMFs, are described in Table 3.

It can be seen from Table 3, that there are plausible mechanisms by which each of those seven effects can be produced by VGCC activation via known pathways. Given the complexities of biology, the mechanisms described in Table 3 may, in some cases, be over simplified.

There is one other finding, not related to the Wi-Fi findings, that is included in Table 3. A question that was raised in review of the paper was whether the heat shock stress elevation found following EMF exposure in many studies, could be produced by VGCC activation. As you can see from Table 3, it can be.

7. Other proposed biophysical mechanisms

One question that can be asked is how the VGCC activation mechanism compares with other biophysical models of non-thermal EMF effects. Belyaev (2015) has discussed a number of what he describes as biophysical models which are, therefore considered here. These models are basically theoretical models of how the weak electrical forces of the EMFs can interact with biologically plausible structures to produce non-thermal effects.

The first of these Belyaev considers is Fröhlich's theory. This is where there are "coherent longitudinal vibrations of electrically polar structures." The mechanism of Fröhlich's theory will not be considered here (the reader is referred to Belyaev, 2015). The author considers this to be a plausible mechanism for possible production of some non-thermal EMF effects. However, there are no specific testable predictions made by the theory that suggest how it could be tested, given the fact that there may be multiple possible targets of the EMFs according to

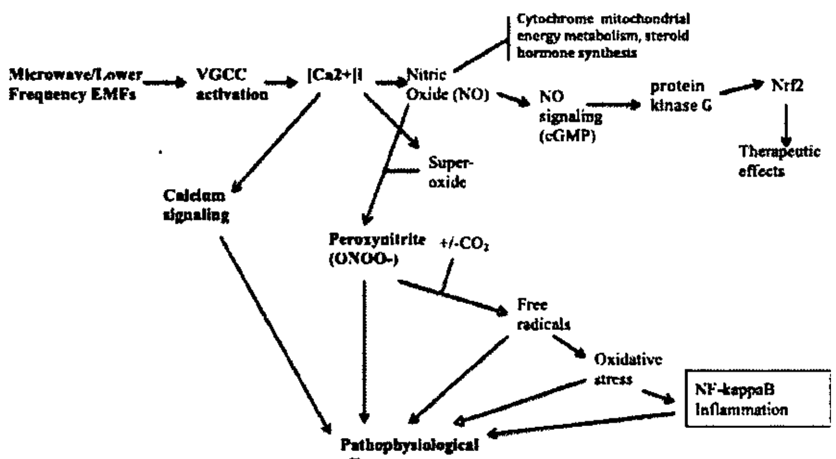

Fig. 1. Various pathways of action by which EMF VGCC activation can produce effects produced by EMF exposure (modified, with permission from Pall, 2015b).

Table 3
How Eight Established Effects of Wi-Fi and Other EMFs Can Be Produced by VGCC Activation.

EMF effect	Probable mechanism(s)
Oxidative stress	Produced by elevated levels of peroxynitrite and the free radical breakdown products of peroxynitrite and its CO_2 adduct. Four studies of EMF exposure, cited in Pall (2013) showed that oxidative stress following exposure was associated with major elevation of 3-nitrotyrosine, a marker of peroxynitrite, thus confirming this interpretation. Two other studies each found 3-nitrotyrosine elevation, both following 35 GHz exposures (Sypniewska et al. (2010); Kalns et al., 2000).
Lowered male/female fertility, elevated spontaneous abortion, lowered libido	Both the lowered male fertility and lowered female fertility are associated with and presumably caused by the oxidative stress in the male and female reproductive organs. Spontaneous abortion is often caused by chromosomal mutations, so the germ line mutations may have a causal role. Lowered libido may be caused by lowered estrogen, progesterone and testosterone levels. It seems likely that these explanations may be greatly oversimplified. One mechanism that may be important in lowered fertility is that VGCC activation and consequent high [Ca2+]i levels is known to have a key role in avoiding polyspermy. Consquently, if this if triggered before any fertilization of an egg has occurred, it may prevent any sperm from fertilizing and egg.
Neurological/ neuropsychiatric effects	Of all cells in the body, the neurons have the highest densities of VGCCs, due in part to the VGCC role and [Ca2+]i role in the release of every neurotransmitter in the nervous system. Calcium signaling regulates synaptic structure and function in 5 different ways, each likely to be involved here. Oxidative stress and apoptosis are both thought to have important roles. Lowered sleep and increased fatigue are likely to involve lowered nocturnal melatonin and increased nocturnal norepinephrine.
Apoptosis	Apoptosis can be produced by excessive Ca2+ levels in the mitochondria and by double strand breaks in cellular DNA; it seems likely that both are involved following EMF exposure. A third mechanism for triggering apopotosis, endoplasmic reticulum stress (see bottom row in this Table), may also be involved.
Cellular DNA damage	Cellular DNA damage is produced by the free radical breakdown products of peroxynitrite directly attacking the DNA [see Pall (2018) for discussion].
Changes in non-steroid hormone levels	The release of non-steroid hormones is produced by VGCC activation and [Ca2+]i elevation. The immediate effects of EMF exposures is to increase hormone release and to raise, therefore, hormone levels. However many hormone systems become "exhausted" as a consequence of chronic EMF exposures. The mechanism of exhaustion is still uncertain, but it may involve oxidative stress and inflammation.
Lowered steroid hormone	Steroid hormones are synthesized through the action of cytochrome P450 enzymes; activity of these hormones is inhibited by binding of high levels of nitric oxide (NO) leading to lowered hormone synthesis.
Calcium overload	Produced by excessive activity of the VGCCs; secondary calcium overload is produced by oxidative stress activation of TRPV1, TRPM2 and possibly some other TRP receptors, opening the calcium channel of these receptors.
Heat shock protein induction	There is a large literature showing that excessive [Ca2+]i induces very large increases in heat shock proteins. This is thought to be produced by complex calcium signaling changes involving the endoplasmic reticulum, mitochondria and the cytosol and also involving excessive [Ca2+]i producing increasing protein misfolding (Garbuz, 2017; Park et al., 2014; Krebs et al., 2011). It should be noted that some calcium is essential for proper protein folding in the endoplasmic reticulum such that only excessive calcium leads to misfolding and consequent endoplasmic reticulum stress.

Fröhlich's theory.

A second possible mechanism involves the spin state of radical pairs. When radical pairs are generated from the breakdown of a non-radical molecule, these radical pairs often react back with each other to form another non-radical molecule, not necessarily identical to the original non-radical. What is postulated by this theory is that EMFs can interact with one or both radicals, changing their spin state and greatly lowering their ability to react back with each other, thus generating increased free radicals and therefore increased oxidative stress. The potential strong point of this theory is that it provides an explanation for the oxidative stress found following EMF exposure. However, as noted under oxidative stress in Table 3, there are 6 studies where oxidative stress following EMF exposure was associated with very high levels of 3-nitrotyrosine, a specific marker of peroxynitrite elevation. These studies argue, therefore, that oxidative stress following EMF exposure is produced by peroxynitrite elevation and is not primarily produced by this radical pair mechanism. It follows from this that the proposed radical pair mechanism cannot even explain the properties of oxidative stress production, let alone the various consequences of non-thermal EMF exposure that do not involve oxidative stress. Does that mean that the radical pair mechanism has no possible role in producing non-thermal EMF effects? No, but it does argue there is no evidence for any such role.

A third mechanism discussed in Belyaev (2015) is the electrosoliton theory proposed by Brizhik and colleagues, involving a "self reinforcing solitary wave packet." Brizhik and her colleagues discussed this in the context of reaching a threshold minimum energy state where both charged molecules and the EMF is in a coherent state, such that charge movement can ratchet from one state to another. This concept shows substantial similarity to what is thought to occur in the activation of the voltage sensor, that is discussed above. There we have four alpha helixes, each designated an S4 helix and with each S4 helix having 5 positive charges, with the 4 S4 helixes together making up the voltage sensor. Most of those positive charges are 3 amino acid residues apart from each other, such that the closest charged residues stick out from the helix pretty much on the same side of the helix. Three of those positive charges are electrostatically attracted to negative residues on other helixes thought to be in fixed positions. What is thought to happen in activation is that there a ratcheting of the S4 helixes toward the extracellular space, ratcheting such that the negative charges are now bound to a positive charge 3 residues away from the one that was previously bound. The ratcheting also produces some turning of the S4 helix. This needs to occur several times on each of the four S4 helixes to open the channel and allow calcium ions to flow. While I don't completely understand the Brizhik electrosoliton model, it may well be relevant to our understanding the VGCC activation, because the mechanism of the voltage sensor is similar to what Brizhik and her colleagues propose to occur in the electrosoliton model. Both the electrosoliton model and the voltage sensor activation mechanism involve both charge movements and ratcheting. In order to test these biophysical models one needs to have a specific mechanism where it may apply and where such tests can be done. In the case of the voltage sensor of the VGCCs, these tests have already been done.

These models are basically theoretical models of how the weak electrical forces of the EMFs can interact with biologically plausible structures to produce non-thermal effects. Their theoretical support is their strong point. They are weak, however, in providing any compelling evidence that they have causal roles in producing non-thermal changes in cells in culture or in whole animal (or human) studies. They are also weak because they do not provide stated explanations for the range of EMF effects that have been documented.

Belyaev (2015) discusses microwave hearing in this context. He discusses the findings showing that people can hear microwave fields that are pulsed, including pulsed low intensity EMFs. While there is no doubt that these are very interesting observations on what are clearly non-thermal effects, they do not provide a biophysical model explaining how microwave hearing may occur. It is important, therefore to ask whether such microwave hearing could be caused by VGCC activation. It has been shown that hearing involves the activation of the VGCCs (Joiner and Lee, 2015). Furthermore, various otolaryngological conditions, including tinnitus, involve excessive VGCC activity, such that the calcium channel blocker, nimodipine is useful in their treatment (Monzani et al., 2015). These findings tells us that microwave hearing may be produced by VGCC activation. Consequently, microwave hearing may be interpreted as providing further support for the VGCC mechanism.

Following microwave hearing, Dr. Belyaev (2015) discusses plasma membrane and ion models. Here the VGCC mechanisms fit into the scheme, as do the other voltage-gated ion channels and the plant TPC channels, all discussed above as being activated by their voltage sensor following EMF exposures.

Finally, Dr. Belyaev (2015) discusses possible direct effects of EMFs on DNA, possibly leading to changes in chromatin structure and/or nuclear structure. There is a literature showing that aqueous solutions of DNA absorb microwave EMFs much more efficiently than do identical solutions not containing DNA. This clearly shows that DNA has a high absorbance of the EMFs, Furthermore, there are studies showing such dissolved DNA, when it absorbs such EMFs, undergoes structural changes as measured by biophysical techniques. All of this suggests that DNA is a plausible potential target for the EMFs. The problem is what are the predicted effects of such changes in DNA structure in living cells and organisms? Dr. Belyaev spends almost a page and a half in his paper discussing various possible models of interactions of DNA or of chromatin with EMFs. But again, how do we test any of these in living cells to demonstrate a role of such DNA or chromatin changes in producing any specific or general biological effects? Given the extraordinary complexity of living cells and organisms, there are only two powerful ways of demonstrating causal roles in such living cells and organisms. These are to use genetics or to use specific pharmacological agents. The extraordinary power of each of these approaches comes from the fact that these approaches allow researchers to vary one variable at a time out of the thousands of interacting variables in a living cell, allowing us to ask does that specific variable have a causal role in determining a specific response. But these two approaches can be used when specific proteins have specific roles, not when you are looking at the role of DNA structural changes, Fröhlich's theory, radical pair mechanisms or electrosoliton models. Fortunately the VGCC mechanism does allow this approach by studying various classes of calcium channel blockers, so here we do have hard data on widespread causal roles of VGCC activation in producing EMF effects.

8. Two other models for producing non-thermal effects

With the possible exception of the electrosoliton model, the author does not find any of the models discussed by Dr. Belyaev (2015) to have substantial evidence for roles in producing EMF effects. There are two other models which may be more compelling, each of which either produces increased [Ca2+]i.

Six studies have supported the view that calcium cyclotron resonance, has a role in producing biological effects produced by *certain specific frequencies* which can interact with Ca^{2+} ions to produce a cyclotron-like resonance (Foletti et al., 2010; Gaetani et al., 2009; De Carlo et al., 2012; Lisi et al., 2008; Pazur and Rassadina, 2009; Pazur et al., 2006). In each case, the effects involved a very specific frequency which produces the calcium cyclotron resonance and in three studies, these frequencies were shown to produce increases in [Ca2+]i levels. In the De Carlo et al. (2012) study, the calcium channel blocker nifedipine was shown to greatly lower the apparent calcium cyclotron resonance effect. This finding strongly suggests that the calcium cyclotron resonance can feed Ca^{2+} ions into the VGCCs, thus increasing the flow of Ca^{2+} ions through the VGCCs into the cell following EMF exposure. The frequencies studied here for cyclotron resonance, one was close to 7 Hz and the other was close to 50 Hz, are both in the extremely low frequency range and consequently are not relevant to microwave frequency effects. The finding that only very specific calcium cyclotron resonance frequencies produce these effects is the main evidence for this mechanism.

It is now well established that there is a magnetoreception mechanism found in many animals that can detect and respond to the very low intensity geomagnetic field. This has been most studied in bees and in birds, both of whom use it for navigation. This has been suggested to involve tiny particles of magnetite which occur in bacterial, animal and plant cells, including human cells. Kirschvink (1992) first proposed a model of how such a mechanism might act. He proposed that magnetite particles may be tethered through a microtubule and/or microfilament or perhaps other fibers to a mechanosensitive channel, such that tiny magnetic forces could open the mechanosensitive channels, allowing cation flow into the cells. It is still uncertain what mechanosensitive channel or channels might be involved, but most of the candidates are channels that allow both sodium and calcium to flow into cells. Hsu et al. (2007) suggested that such magnetite particles were linked in honeybees to an undefined calcium channel, such that magnetic field exposure produces increases in [Ca2+]i. The worm Caenorhabditis elegans had been shown to have a geomagnetic orientation system. Vidal-Gadea et al. (2015) found that certain specific neurons in C. elegans which may be geomagnetic sensory neurons, very low intensity geomagnetic fields could produce increases in [Ca2+]i in those specific neurons, even when they had no synaptic inputs, suggesting that these neurons themselves acted as geomagnetic sensors.

Cadiou and McNaughton (2010) reviewed the literature on a magnetite-based magnetoreception system in birds and its role in avian migration. They also reviewed findings on neurons found in the trigeminal nerve of birds, where magnetic fields as low as 200 nT can activate specific neurons. Trains of action potentials are produced by magnetic fields, plateauing in the region of 20–100 mT. Latency in a study presented by Cadiou and McNaughton (2010) was about 4 s, but other studies have reported latencies of about 2.5 s. Therefore these are rapid effects. Cadiou and McNaughton (2010) also discuss possible roles mechanosensitive channels, including a model similar to that proposed by Kirschvink (1992) and also three other models, each involving different ways of coupling forces on magnetite to opening of a channel. Magnetoreception has also been reported to occur in a mammal, the mole-rat (Wegner et al., 2006). There are also studies of magnetic compass orientation in salmonids, newts, sea turtles and other rodents. There is evidence in Drosophila, that a magnetic structure attached to cryptochrome is involved in magnetoreception, as opposed to magnetite.

The two mechanisms described in this section have minor roles, only acting, as far as we can tell, in very specific situations. The calcium cyclotron resonance mechanism only acts with a few specific frequencies in the extremely low frequency range. The magnetoreception mechanism only acts, as far as one can tell, on detecting the weak geomagnetic fields and only acts, as far as one can tell, in certain specific neurons. It is possible that this view may change with regard to the magnetoreception mechanism but what is clear is that the VGCC mechanism is vastly more important than either of these mechanisms, acting in diverse cell types and acting to provide responses to a very wide frequency range and even to static electrical fields and static magnetic fields. Because static magnetic fields only place forces on moving electric charges, this produced a puzzle on how they can activate the VGCCs. Pall (2013) suggested that the solution to that puzzle is that the plasma membrane of animal cells is often moving, such that the charges in the voltage sensor are also moving and can, therefore, have forces placed on them by the static magnetic fields. These static magnetic fields, activating the VGCCs can be relative low intensity but probably must be much higher intensity than the extraordinarily weak geomagnetic fields. The reader is referred to Lu et al. (2015) for empirical information from an important static magnetic field study, where those static magnetic fields activate both VGCCs and voltage-gated sodium channels.

9. Foster and Moulder on Wi-Fi

The Foster and Moulder (2013) paper argues that there are no and cannot be any health effects of Wi- Fi. The first 7½ pages of the paper are, however, largely irrelevant to that issue. These pages discuss such issues as predicted peak power output, incident power density and the FCC and international safety guidelines. They also discuss specific absorption rate (SAR) values, a measure of heating. Because it is now established, as discussed above that thermal effects are not the relevant mechanism of non-thermal effects and that VGCC activation is the main mechanism of such effects, this whole section is irrelevant. Foster and Moulder (2013) discuss the issue of biological effects, praising 7 studies listed in table 4 of their paper as having "well-characterized exposure systems" of well defined SARS values, reporting that there were no effects in the rats or mice in those 7 studies. Those 7 studies are Laudisi et al. (2012), Sambucci et al. (2010), Aït-Aïssa et al. (2010, 2012, 2013) and Poulletier de Gannes et al. (2012, 2013). The first two studies come from one research group and the other five from another, albeit with some shared personnel.

Six or those seven studies (Sambucci et al., 2010; Aït-Aïssa et al., 2010, 2012, 2013; Poulletier de Gannes et al., 2012, 2013) used an exposure system described by Wu et al. (2009) that is important here and that was claimed to produce a near uniform exposure. Laudisi et al. (2012) used a somewhat similar exposure system of Ardoino et al. (2005), albeit another one that is also claimed to produce near uniform exposures. The important features here of the Wu et al. (2009) exposure system need to be examined in the light of the fact that, as discussed above, artificial EMFs are polarized with the polarization producing much larger biological effects than natural non-polarized EMFs (Belyaev, 2005, 2015; Panagopoulos et al., 2015a). The probable important feature of these polarized EMFs is that they put much larger forces on electrically charged groups (Panagopoulos et al., 2015a); since such forces are central to VGCC activation via the voltage sensor, as discussed above, they are likely to be central to the production of most biological effects. Let's examine Wu et al. (2009) with that issue in mind. It uses a large chamber surrounded by 1 mm aluminum mesh wire mesh to provide reflections of the EMFs. The chamber in which animals are exposed on a platform at its center, is also surrounded by antennae in all 6 directions (up, down, all four horizontal directions) such that each antenna is broadcasting with one polarization is opposed (at 180°) by another broadcasting with the 180° opposite polarization, as well as by four other antennae, broadcasting with 90° different polarization in each of the four possible directions. This produces a field that is more like a non-polarized EMF rather than the usual polarized artificial EMF. This move toward non-polarization is further exacerbated by the aluminum wire reverberation system whose reflections will generate vast numbers of reflections of different polarity, like a non-polarized EMF. The consequences of this is that the structure of this exposure system is clearly very different from that seen in Wi-Fi or any other artificially produced EMF that we may be exposed to, with biological effects produced via electrical forces being vastly less. Consequently this exposure system is not only inherently different from genuine Wi-Fi, it is predicted to be inherently less active than genuine Wi-Fi, regardless of what EMFs are being fed into the 6 antennae.

There is a second type of consequence of using such reverberation exposure systems. Because of the many reverberations occurring, the path lengths of different photons reaching a specific point in the exposed tissue, will often be quite different from each other, such that the phase of the EMFs produced will also be quite different from each other. This leads to the possibility of destructive interference and thus a second mechanism which is predicted to lead to substantial decreases in the intensity of the exposures. Because exposures are usually predicted by groups using such exposure chambers without considering such destructive interference, rather than being measured, the actual exposures may be substantially lower than are the predicted exposures. Both the polarization effect and the possible difference between predicted exposure and actual exposure were considered in an earlier study.

Vian et al. (2006), using a different reverberation exposure chamber, discussed in Fig. 1 of that paper, how the various reverberations lead to the initial polarized EMF being converted to a non-polarized or at least, less polarized EMF. They also on p. 69 if that paper compared the predicted with the measured amplitude and found that the measured amplitude was only 78% of the predicted amplitude. These findings suggest that both of the lowered polarization and destructive interference discussed in the previous two paragraphs can have substantial roles in lowering biological responses produced when using such reverberation exposure chambers.

Laudisi et al. (2012) used a different exposure system, that of Ardoino et al. (2005) where the vast majority of the exposure is produced from reflections off a long cylindrical surface in a TEM cell, where the curvature of the cylinder will also produce a largely non-polarized EMF and different reverberation paths and consequent destructive interference, may both be expected to occur. Consequently the predicted low biological activity of EMFs produced by the Wu et al. (2009) system may be expected to also occur from this TEM exposure system Ardoino et al. (2005). It is not possible to study biological effects of EMFs from Wi-Fi, cell phones or any other important exposures using such exposure systems because of the polarization changes they produce from the original polarized EMFs and because of destructive interference.

Let's now shift to the issue of the important role of pulsations in producing biological effects and ask whether the EMFs fed into the antennae have pulsation patterns similar or different from genuine Wi-Fi. Poulletier de Gannes et al. (2012) used a non-pulsed (continuous wave) as did Wu et al. (2009), an EMF which will have, therefore, much lower biological effects that genuine Wi-Fi with its myriad of pulsations (Maret, 2015). The other 6 studies (Laudisi et al., 2012; Sambucci et al., 2010; Aït-Aïssa et al., 2010, 2012, 2013; Poulletier de Gannes et al., 2013) used computers with Wi-Fi cards. Such Wi-Fi cards are designed to communicate with genuine Wi-Fi antennae, but are used here to communicate with each other, using two such computers to generate "Wi-Fi". How the EMFs so generated compare with the pulsations of genuine Wi-Fi is a complete mystery and none of these papers provide any information to allow the reader to make such a comparison. It follows that these studies (Laudisi et al., 2012; Sambucci et al., 2010; Aït-Aïssa et al., 2010, 2012, 2013; Poulletier de Gannes et al., 2013) are not studying genuine Wi-Fi, even before the effects of the reverberation chamber and the reader is left with no evidence to compare these original EMFs with genuine Wi-Fi. In summary, then none of the EMFs used in these studies are genuine Wi-Fi, with them differing from genuine Wi-Fi in three different ways: the antenna locations produce a substantial difference from genuine Wi-Fi regarding EMF polarization and this is further exacerbated by the effects of the aluminum mesh reverberation producing further lowering of any polarization; differences in path lengths of different photons produce substantial destructive interference; the initial EMF fed into the antennae differs substantially from genuine Wi-Fi, with the main concern here being due to the issue of pulsation patterns and biological effects.

Let's shift now to the claim made by Foster and Moulder (2013) that there were no effects found in any of these 7 studies. Rothman et al., Modern Epidemiology, 3rd Edition is a highly respected source of information, cited over 18,500 times according to the Google Scholar database. It states (p. 151, bottom) that: "A common misinterpretation of significance tests is that there no difference between two observed groups because the null test is not statistically significant, in that P is greater that the cutoff for declaring statistical significance (again, usually .05). This interpretation confuses a descriptive issue (whether two observed groups differ) with an inference about the superpopulation. The significance test refers only to the superpopulation, not the observed groups. To say that the difference is not statistically significant means only that one cannot reject the null hypothesis that the superpopulation groups are the same; it does not imply that the two groups are the same." It follows that the claim of "no effect" that Foster and Moulder (2013) make about each of these 7 studies in Table 4 of their paper is false because one can never legitimately make such a claim; one can at most claim that there were no statistically significant differences.

However there are other reasons to reject those claims that need to be considered for each of these 7 studies. Each of these 7 studies fails to provide raw numerical data, the lack of which is problematic, given the other flaws that follow. **1)**. Laudisi et al. (2012) finds in Table 2, that two T cell populations are statistically significantly different in prenatally exposed mice vs sham controls: DP and CD4SP cells are significantly affected by exposure in mice at 26 weeks after birth; CD4SP cells are affected in female mice at 5 weeks after birth ($P < .02$ in each case). Furthermore in each of the measurements in Laudisi et al. (2012), only 11 or 12 mice were studied, tiny numbers. It follows that claims in Foster and Moulder (2013) that there were no effects are false or misleading for 3 distinct reasons: You can never make such claims even in large studies; there were 3 comparisons each of which showed statistically significant effects; this study was done with tiny numbers of animals being compared and thus had extremely low statistical power. **2)**. Sambucci et al. (2010) also had a tiny numbers, with 11 or 12 per group studied in Table 2, from 6 to 35 studied in Table 3 and 6 to 12 studied in Table 4. The claims of no statistically significant effects in Figs. 2, 3, 4 and 5 are based on the tiny numbers in Table 3, are therefore, based on studies with very low statistical power. **3)**. The first part of the Aït-Aïssa et al. (2010) paper focused on GFAP values, a measure of gliosis, which is a risk factor for glioma formation. The groups studied in Fig. 4 of Aït-Aïssa et al. (2010) range from 3 to 10, so again we have tiny numbers and the authors report that none of the exposures, SAR = .08, = .4. or = 4 W/Kg produced statistically significant changes according to their statistical calculations. As in the other studies, no raw data are provided but Fig. 4 provides bar graph information which includes median values for each of the 10 different regions of the brain in these rats, control rats and also rats exposed either pre-natally or both pre-natally and post-natally. For 5 of those brain regions, M4, CA1, CA2, CA3 and DG, the median values are high enough that one can see which are higher and which are lower from the graph. It appears to this author that the median values go up from the sham exposures to the lowest intensity (= .08), that they drop going to the next intensity (= .4) and that they go up going to the highest intensity studies (= 4). You may recall (see above) that there are certain windows of exposure that give the highest biological response but with both lower and higher intensities giving lower responses. It follows that the complex apparent dose-response curve of Aït-Aïssa et al. (2010), can be explained by these window effects. The question is whether any such apparent changes are statistically significant? I did, therefore a Chi-square analysis of these data, to determine statistical significance, using both the only prenatal and both prenatal and postnatal exposures (see Fig. 4 in Aït-Aïssa et al., 2010). Those data show that in 10 out of 10 cases, the median value increased going from sham to .08 ($P < .002$.). Similarly, in 10 out of 10 cases, the median value drops going from .08 to .4 ($P < .002$). However in 8 out of 10 cases, the median value increases going from .4 to 4 ($P < .07$), falling just short of statistical significance. The median values increased with exposure, comparing the sham values with the values at 4 ($P < .02$). It follows from this, that three of the comparisons show statistically significant changes, and the fourth falls just short of statistical significance. Does this mean that that we should conclude that Wi-Fi can cause gliosis and thus possibly gliomas? No, but only because they did not study Wi-Fi. It should be noted, however that the long-term effects on the brain from pre-natal exposures may be relevant to autism causation.

4). Poulletier de Gannes et al. (2012) also suffered from tiny numbers in their study, with 12 to 15 rats studied in each group in Fig. 1, only 5 females in each group in Table 1, 12 to 15 rats in each group in both Table 2 and Table 3. **5)**. Aït-Aïssa et al. (2012) also suffers from tiny numbers of rats in the various studies. It used from 9 to 12 pregnant female rats in each group to attempt to assess EMFs impact of reproduction; it used 9 to 12 juvenile rats to determine if EMFs act to change antibody production; it used 9 to 12 young rats to determine whether EMFs impact growth over time. These tiny numbers mean that failure to find statistical significant changes has very low power to support any inferences. **6)**. Aït-Aïssa et al. (2013) had similar problems with tiny numbers, 6 to 12 in Fig. 5, 5 to 11 in Fig. 8 and 6 to 12 in Fig. 9. **7)**. Poulletier de Gannes et al. (2013) also suffers from tiny numbers. Fig. 1 groups each had 12 males or females and there were also groups of 12 studied in Table 1, Fig. 2 and Table 2. Regarding, the authors give no information regarding statistical significance or lack thereof; rather they only state that the values of these groups were "similar", without providing a definition of "similar". However in comparing the values of testis weight and epididymis weight at 4 W/Kg exposure vs sham control, they provided values for the mean and standard error of the mean (SEM). It is usually the case that when the mean values differ by more than 2.4 times the SEM, the difference is statistically significant. Here the testis weight, comparing sham with 4 W/Kg, values differed by 3.18 times the SEM and the epididymis weight differed by 3.40 times the SEM, each arguing strongly for statistical significance. This raises the question of why the authors failed to provide their P values?

An additional flaw of these 7 supposed Wi-Fi studies is that they each studied exposures of 2 h per day, 5 days per week except for one that only studied one hour per week, 5 days per day. Given that many people are exposed to Wi-Fi fields for 5, 6, 8 or more hours per day, this is another factor which argues that these studies may have been set up to minimize any effects seen.

To sum up the other flaws:

1. The 6 antennae of the reverberation chamber used in 6 out of 7 studies, minimized probable effects produced through the arrangement of the antennae in such a way as to greatly lower the polarization of the EMFs.
2. The use of 1 mm aluminum wires to produce the reverberation reflections, further decreases such polarization, again lowering probable effects. These structures are clearly very different from those found in genuine Wi-Fi, emphasizing the point that these are not genuine Wi-Fi studies, because of 1 and 2 here.
3. Differences in path lengths for different photons, produced by reverberation produce substantial destructive interference.
4. Furthermore the EMFs fed into the antennae are not genuine Wi-Fi either. It follows from this that claims that these are studies of genuine Wi-Fi made by both the authors of these individual studies and by Foster and Moulder (2013) are false.
5. The claims made by Foster and Moulder (2013) that there are no effects produced are also false; the most that may be legitimately concluded is that there is no statistically significant evidence of effects.
6. Each of the 7 studies used only tiny numbers of animals in each group studied, such that lack of statistical significance, because of the low power of these studies, drastically limits the drawing of inferences.
7. Finally, 3 out of 7 had evidence of statistically significant effects,

with each of these being ignored by Foster and Moulder.

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TO:

Rosemary Chiavetta, Sec.
PA Public Utility Commission
Keystone Bldg. 2nd floor-W
400 N. St.
Harrisburg, PA 17120

Label 228, March 2016

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