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Autism and EMF? Plausibility of a pathophysiological link – Part I

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Abstract

Although autism spectrum conditions (ASCs) are defined behaviorally, they also involve multileveled disturbances of underlying biology that find striking parallels in the physiological impacts of electromagnetic frequency and radiofrequency exposures (EMF/RFR). Part I of this paper will review the critical contributions pathophysiology may make to the etiology, pathogenesis and ongoing generation of core features of ASCs. We will review pathophysiological damage to core cellular processes that are associated both with ASCs and with biological effects of EMF/RFR exposures that contribute to chronically disrupted homeostasis. Many studies of people with ASCs have identified oxidative stress and evidence of free radical damage, cellular stress proteins, and deficiencies of antioxidants such as glutathione. Elevated intracellular calcium in ASCs may be due to genetics or may be downstream of inflammation or environmental exposures. Cell membrane lipids may be peroxidized, mitochondria may be dysfunctional, and various kinds of immune system disturbances are common. Brain oxidative stress and inflammation as well as measures consistent with blood–brain barrier and brain perfusion compromise have been documented. Part II of this paper will review how behaviors in ASCs may emerge from alterations of electrophysiological oscillatory synchronization, how EMF/RFR could contribute to these by de-tuning the organism, and policy implications of these vulnerabilities. Changes in brain and autonomic nervous system electrophysiological function and sensory processing predominate, seizures are common, and sleep disruption is close to universal. All of these phenomena also occur with EMF/RFR exposure that can add to system overload ('allostatic load') in ASCs by increasing risk, and worsening challenging biological problems and symptoms; conversely, reducing exposure might ameliorate symptoms of ASCs by reducing obstruction of physiological repair. Various vital but vulnerable mechanisms such as calcium channels may be disrupted by environmental agents, various genes associated with autism or the interaction of both. With dramatic increases in reported ASCs that are coincident in time with the deployment of wireless technologies, we need aggressive investigation of potential ASC – EMF/RFR links. The evidence is sufficient to warrant new public exposure standards benchmarked to low-intensity (non-thermal) exposure levels now known to be biologically disruptive, and strong, interim precautionary practices are advocated.

Keywords: Autism; EMF/RFR; Cellular stress; Oxidative stress; Mitochondrial dysfunction; Oscillatory synchronization; Environment; Radiofrequency; Wireless; Children; Fetus

1. Introduction

The premise of this review is that although scant attention has been paid to possible links between electromagnetic fields and radiofrequency radiation exposures (EMF/RFR) and Autism Spectrum Conditions (ASCs), such links probably exist. The rationale for this premise is that the physiological impacts of EMF/RFR and a host of increasingly well-documented pathophysiological phenomena in ASCs have remarkable similarities, spanning from cellular and oxidative stress to malfunctioning membranes, channels and barriers to genotoxicity, mitochondrial dysfunction, immune abnormalities, inflammatory issues, neuropathological disruption and electrophysiological dysregulation – in short, multi-scale contributors to de-tuning the organism. Additional support may be found in the parallels between the rise in reported cases of ASCs and the remarkable increases in EMF/RFR exposures over the past few decades

Reviewing these similarities does not prove that these parallels imply causality. Moreover, the physiological processes affected by EMF/RFR are also impacted by other environmental factors, and are known to be present in myriad other chronic illnesses. A set of in-depth reviews on the

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science and public health policy implications of EMF/RFR has been published in a special issue of Pathophysiology 16 (2,3) 2009. This two-volume special issue of Pathophysiology offers a broad perspective on the nature of health impacts of man-made EMFs, documenting biological effects and health impacts of EMFs including genotoxicity, neurotoxicity, reproductive and developmental effects, physiological stress, blood–brain barrier effects, immune system effects, various cancers including breast cancer, glioma and acoustic neuroma, Alzheimer's disease; and the science as a guide to public health policy implications for EMF diseases [1]. Many of these reviews have been updated in the BioInitiative 2012 Report [2], with 1800 new papers added. Further reinforcement is published in seminal research reviews including the two-volume Non-Thermal effects and Mechanisms of Interaction between Electromagnetic Fields and Living Matter, Giuliani L and Soffritti, M (Eds.), ICEMS, Ramazzini Institute, Bologna, Italy (2010) [3]; the World Health Organization INTERPHONE Final Report (2010) [4]; and the WHO International Agency for Research on Cancer RFR Monograph [5] designating RFR as a Group 2B Possible Human Carcinogen. The National Academy of Sciences Committee on Identification of Research Needs Relating to Potential Biological or Adverse Health Effects of Wireless Communication Devices (2008) [6] called for health research on wireless effects on children and adolescents and pregnant women; wireless personal computers and base station antennas; multiple element base station antennas under highest radiated power conditions; hand-held cell phones; and better dosimetric absorbed power calculations using realistic anatomic models for both men, women and children of different height and ages. Yet EMF/RFR does not need to be a unique contributor to ASCs to add significantly to system overload ('allostatic load') and dysfunction [7]. Even so these pathophysiological overlaps do suggest that the potential for an EMF/RFR-ASC connection should be taken seriously, and that their biological fragility may make many with ASCs more likely to experience adverse EMF/RFR impacts. This is a sufficient basis to recommend that precautionary measures should be implemented, that further research should be prioritized, and that policy level interventions based on existing and emerging data should be designed and pursued. Moreover, pursuing this link could help us understand ASCs better and find more ways to improve the lives of people with ASCs and of so many others.

This paper is divided into two parts. Part I (http://dx.doi.org/10.1016/j.pathophys.2013.08.001) describes the pathophysiology and dynamism of common behavioral manifestations in autism, and pathophysiological damage to core cellular processes that is associated both with ASCs and with impacts of EMF/RFR. Part II (http://dx.doi.org/10.1016/j.pathophys.2013.08.002) reviews how behaviors in ASCs may emerge from alterations of electrophysiological oscillatory synchronization and how EMF/RFR could contribute to these by de-tuning the organism. Part II also discusses public health implications, and proposes recommendations for harm prevention and health promotion.

2. Physiological pathogenesis and mechanisms of autism spectrum conditions

2.1. How are biology and behavior related?

Appreciating the plausibility of a link between ASCs and EMF/RFR requires considering the relationship between ASC's behavioral and biological features. ASCs were first labeled as 'autism' in 1943 by Leo Kanner, a child psychiatrist who extracted several key behavioral features, related to communication and social interaction challenges and a tendency toward restricted interests and repetitive behaviors [8]. There has been some modification of the characterization of these behavioral features, but ASCs are still defined behaviorally, although sensory issues such as hypo- or hyper-reactivity have recently been included in the diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders or DSM-V) [9,10].

2.1.1. Transduction is fundamental but poorly understood

To evaluate how an environmental factor such as EMF/RFR could lead to autism and/or influence its severity or incidence, we examine how effects of EMF/RFR exposure may be transduced into changes in nervous system electrical activity, and how these in turn generate the set of behaviors we have categorized as 'autism.'[11] This means not taking behaviors as given, or as purely determined by genetics, but exploring the full range of biology that generates these features and challenges.

2.1.2. More than brain

Although 'autism' has long been considered to be a psychiatric or neurological brain-based disorder [12,13], people diagnosed with ASCs often have many biological features including systemic pathophysiological disturbances (such as oxidative stress, mitochondrial dysfunction and metabolic and immune abnormalities) [14–17] as well as symptomatic medical comorbidities (such as gastrointestinal distress, recurrent infections, epilepsy, autonomic dysregulation and sleep disruption) [18–26] in addition to the core defining behaviors [27]. Because of variability among individuals, the relevance of many of these biological features has been dismissed as secondary and not intrinsically related to the 'autism.'

2.1.3. Heterogeneity: more genetic and environmental than physiological

Presently large numbers of genes and environmental contributors to ASCs are under consideration. Over 800 genes have been associated with ASCs, and over 100 different rare genetic syndromes are frequently accompanied by ASCs, but

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no clear unifying mechanism has been identified [28–33]. Similarly, a large number of potential environmental contributors are under investigation ranging from toxicants and Vitamin D deficiency or failure to take prenatal vitamins to air pollution and stress or infection in pregnancy [34–41].

By contrast, a smaller set of disturbances are showing up physiologically as common across substantial numbers of people with ASCs – as well as in myriad other chronic conditions whose prevalence also appears to be increasing [42,43]. These include oxidative stress, inflammation, and mitochondrial dysfunction. EMF/RFR exposure is associated with many of the same biological effects and chronic health conditions [1]. This environmentally vulnerable physiology [44], which may serve as final common pathways triggered by diverse genetic and environmental contributors, will be discussed in Section 3 of Part I as well as in Part II; it may or may not need to rest on underlying genetic vulnerability.

2.1.4. EMF/RFR research may help us understand how ASCs 'work'

Some correlations between biological and behavioral features have been identified – e.g., a higher level of immune abnormalities correlates with more aberrant behaviors [26,45–50]. In order to move beyond correlations to identifying *mechanisms* by which the *transduction of pathophysiology into behavior* might actually occur, an important component is studying the relationship between systemic pathophysiology and nervous system electrophysiology.

The brain is simultaneously a tissue-based physical organ that can be compromised by cellular pathophysiology as well as altered developmental processes and an information processing system that operates through networks of synchronized electrical oscillations (brain waves) – and EMF/RFR impacts may occur directly at both of these levels. To date the emphasis in ASC research has largely been on 'structure-function' relationships that have been anatomy-centered. Thus, exploring how EMF/RFR impacts ASCs may answer questions of how pathophysiological and electrophysiological information-processing interacts.

2.2. Time courses of mechanisms

Researchers have mainly looked for causes of autism in mechanisms that occur early and create permanent change or damage. This approach is logical if one assumes that genetic influences are overwhelmingly predominant, and 'autism' is a fixed lifelong trait. However evidence is emerging that ASCs may be more state-like and variable than trait-like and fixed.

2.2.1. Plasticity

A remarkable shift is occurring in conceptual thinking about ASCs and brain plasticity [51]. There are growing numbers of reports of improvement and loss of diagnosis, reversal of neurological symptoms in a growing number of mouse models of genetic syndromes that in humans prominently feature autism [52–62], short-term pharmaceutically-induced improvement in brain connectivity [63], and transient reversal or abeyance of symptomatology under various circumstances (including fever, fluid-only diet, and certain antibiotic treatments [50,64]). Reversals undermine the idea that ASCs derive from an intrinsically 'broken brain', and short time frames of marked improvement cannot be accounted for by remodeling of the brain's anatomical substrate [65]. 'Brain waves' and their synchronization, on the other hand, could easily vary over short time periods.

Also, evidence of average to superior intelligence in most people with autism [66,67], as well as of domains of perceptual superiority [68–76], call into question the assumption that ASCs are intrinsically associated with cognitive deficits.

2.2.2. Mechanisms that operate actively throughout the life-course

EMF/RFR effects can occur within minutes (Blank, 2009) and may, in part, explain clinical reports of 'intermittent autism' – for example, some children with mitochondrial disease who have ups and downs of their bioenergetics status 'have autism' on their bad days but don't display autistic features on their good days [77]. These children with their vulnerable, barely compensated mitochondria could very well be teetering right at the brink of a minimally adequate interface of metabolic and electrophysiological dysfunction. Everyday exposures to allergens, infection, pesticide on the school playground, as well as EMF/RFR interference with electrophysiology might reasonably contribute to the bad days. Stabilizing more optimal nervous system performance [78] including through environmental control of excessive EMF/RFR exposure could perhaps achieve more 'good days'.

2.2.3. Pathophysiology and allostatic load

The model of 'allostatic load' – the sum total of stressors and burdens [79]– may be central to understanding how the many risk factors interact to create autism – and to create a spectrum of levels of severity across so many of ASD's associated features. This accumulation increases chronic stress, and a growing number of papers document indicators of chronic stress in individuals with ASCs (as will be discussed in Part II). The 'allostatic load' concept dovetails well with a model of progressive exacerbation of pathophysiological disturbances that occurs in the pathogenesis of many chronic diseases [43]. It is also critical to understand that many different environmental factors converge upon a much smaller number of environmentally vulnerable physiological mechanisms [44], so that large numbers of small exposures may have effects from small numbers of large exposures.

EMF/RFR exposures have demonstrated biological effects at just about every level at which biology and physiology have been shown to be disrupted in ASCs. Further EMF/RFR has been shown to potentiate the impact of various toxicants when both exposures occur together [80]; this may be additive or more than additive. This suggests that EMF/RFR may synergize with other contributors and make things worse. A cascade of exposures interacting with vulnerabilities in

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an individual can potentially lead to a tipping point for that person, such as the phenomenon of autistic regression experienced by a substantial subset of people with ASCs.

Just a few decades ago, EMF/RFR exposures were not present in the environment at today's levels. Levels have increased several thousand-fold or more in the past two decades from wireless technology alone; with unplanned side effects from pulsed RFR that is a newly classified Group 2B possible human carcinogen [5]. Nearly six billion people globally own wireless phones. Many millions are exposed to wireless exposures from use of wireless devices and wireless antenna facilities [81]. For this as well as for physiological reasons, 'allostatic loading' as a viable concept for the study of ASCs should reasonably address EMF/RFR as one of the exposures of relevance to the overall stress load, since it is now a chronic and unremitting exposure in daily life at environmentally relevant levels shown to cause bioeffects from preconception and pregnancy through infancy, childhood and the whole life-course.

3. Parallels in pathophysiology

This section will review parallels in pathophysiology between ASCs and impacts of EMF/RFR. It will begin with a review of mechanisms of direct impact and damage at the level of molecules, cells, tissues and genes. It will then move on to consider how these levels of damage lead to degradation of the integrity of functional systems including mitochondrial bioenergetics, melatonin metabolism, immune function and nervous system physiology. The review of parallels concludes with electromagnetic signaling and synchronized oscillation from membranes to nervous system. It will discuss how the ensemble of pathophysiological disturbances, which are themselves final common pathways that can be caused or worsened by many stressors, combine to converge upon electrophysiology. This leads to the implication that 'aberrant' neural systems and somatic function and behaviors might be better understood as consequences or 'outputs' of disturbed underlying physiology to which EMF/RFR is a plausible contributor.

3.1. Damage: means and domains

ASCs have been conceptualized as 'neurodevelopmental' which has focused attention on how genes and environment could alter brain development. This leads to the unstated presumption that virtually everything important about the brain in ASCs has to do with differences in the way it was formed, and that all "malfunction" derives from this "malformation." In genetics this has led to a hunt for neurodevelopmental genes. There is no question that environmental impacts can alter brain development, and impact brain function across the lifespan.

However the influence of the environment on neurodevelopmental conditions such as ASCs does not stop there. Evidence is accumulating showing that increased expression of genes associated with physiological dysregulation, as well as *single-nucleotide polymorphisms* (SNPs) associated with these issues, may be if anything more prominent than alterations of 'neurodevelopmental' genes [82]. In a study of gene expression in ASCs, Down syndrome and Rett syndrome, these authors state, "*(O)ur results surprisingly converge upon immune, and not neurodevelopmental genes, as the most consistently shared abnormality in genome-wide expression patterns. A dysregulated immune response, accompanied by enhanced oxidative stress and abnormal mitochondrial metabolism seemingly represents the common molecular underpinning of these neurodevelopmental disorders.*" Others have also found pathophysiology-related genes as figuring most prominently in alterations of gene expression in ASC [83–86]. SNPs associated with methylation abnormalities, impaired glutathione synthesis and mitochondrial dysfunction also have been identified as significant risk factors.

Genetics may create risk, but the actual nervous system and health consequences probably come from dysfunction at the physiological level. As mentioned, evidence for pathophysiological dysfunction in ASCs increasingly abounds. In particular, a growing body of evidence widely reported in both the EMF/RFR and ASC literature documents immune aberrations, low total and reduced glutathione levels, lower activity of the anti-oxidative stress system and mitochondrial dysfunction. These phenomena may be both genetically and environmentally modulated. As will be discussed further below, they are certainly pertinent to the neurodevelopment of the brain, which has been by far the dominant focus autism research, but it does not stop there as they can significantly modulate brain function in real time, as well as shape the function of the entire organism, including the autonomic system, the cardiovascular, endocrine, immune, gastrointestinal and reproductive systems and more. These systemic impacts may in turn feed back into the nervous system, modulating how it functions.

3.1.1. Cellular stress

3.1.1.1. Oxidative stress. Autism (ASC) research indicates that oxidative stress may be a common attribute amongst many individuals with autism. In the past decade the literature on this has moved from a trickle to a flood. Studies document reduced antioxidant capacity, increased indicators of oxidative stress and free radical damage, alterations in nutritional status consistent with oxidative stress, altered lipid profiles, and pertinent changes not only in blood but also in brain tissue. Associations of ASCs with environmental exposures such as air pollution and pesticides are indirectly supportive as well, since such exposures are linked in other literature to oxidative stress [43,87–101].

Reactive oxygen species are produced as a normal consequence of mitochondrial oxidative metabolism as well as other reactions, but when their number exceeds the cell's antioxidant capacity a situation of oxidative stress develops. It

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is certainly the case that oxidative stress can be a consequence of exposures to chemical toxicants, or of the interactive impacts of toxicants, nutritional insufficiencies and genetic vulnerabilities. This set of risk factors has received considerable attention for the potential roles each component and various possible combinations could play in causing or exacerbating autism.

Less often mentioned in the ASC pathophysiology literature is that it is also well established that EMF/RFR exposures can be associated with oxidative damage. Published scientific papers that demonstrate the depth of EMF and RFR evidence reporting oxidative damage in human and animal models are profiled by Lai and colleagues [102–104]. These cellular effects can occur at low-intensity, legal levels of exposure that are now 'common environmental levels' for pregnant women, the fetus, the infant, the very young child, and the growing child as well as for adults. Electromagnetic fields (EMF) can enhance free radical activity in cells [105,106] particularly via the Fenton reaction, and prolonging the exposure causes a larger increase, indicating a cumulative effect. The Fenton reaction is a catalytic process of iron to convert hydrogen peroxides, a product of oxidative respiration in the mitochondria, into hydroxyl free radical, which is a very potent and toxic free radical [103,104]. Free radicals damage and kill organelles and cells by damaging macromolecules, such as DNA, protein and membrane components.

Further indications of a link to oxidative stress are findings that EMF and RFR at very low intensities can modulate glutamate, glutathione and GABA, and affect mitochondrial metabolism. Alterations in all these substances and processes have been documented in ASCs [25,86,89,90,92,107–127]. On the EMF/RFR side, Campisi et al. (2010) report that increased glutamate levels from 900 MHz cell phone frequency radiation on primary rat neocortical astroglial cell cultures induced a significant increase in ROS levels and DNA fragmentation after only 20 min with pulsed RFR at non-thermal levels [128].

Fragopoulou et al. (2012) conducted proteomics analysis of proteins involved in brain regulation in mice as a consequence of prolonged exposure to EMF [129]. They identified altered expression of 143 proteins, ranging from as low as 0.003-fold downregulation up to 114-fold overexpression with affected proteins including neural function-related proteins including Glial Fibrillary Acidic Protein (GFAP), alpha-synuclein, Glia Maturation Factor beta (GMF), apolipoprotein E (apoE), heat shock proteins, and cytoskeletal proteins (i.e., neurofilaments and tropomodulin), as well as proteins of brain metabolism such as aspartate aminotransferase and glutamate dehydrogenase. The authors pointed out that oxidative stress was consistent with some of these changes.

Aberrations in glutathione metabolism and deficiencies in reserves of reduced glutathione are increasingly associated with ASCs, both systemically and in the brain. The parallel with EMF/RFR impacts here is strong, since glutathione reduction associated with EMF/RFR is reported in at least twenty three relevant research studies in both human and animal studies since 1998, including the following citations [130–144]. It is increasingly appreciated that glutathione is a final common pathway, a critical piece of environmentally vulnerable physiology, as glutathione reserves are compromised by an enormous number of environmental stressors, so that the cumulative impact upon glutathione may be far greater than could be predicted by the magnitude of any specific exposure [145], which supports an 'allostatic loading' model.

Also of note are studies showing that the effects of EMF/RFR can be reduced by supplementation with antioxidants and radical scavengers. As an example, Vitamins E and C reduced adverse impacts on rat endometrium from 900 MHz EMR exposure [137]. Gingko biloba has also prevented mobile phone-induced increases in malondialdehyde and nitric oxide levels in brain tissue as well as decreases in brain superoxide dismutase and glutathione peroxidase activities and increases in brain xanthine oxidase and adenosine deaminase activities, and treated rats were spared the histopathological cell injury found in the untreated rats [146]. Substantial further literature on antioxidants and radical scavengers is reviewed in Belyaev's contribution to the Bioinitiative 2012 Report [147].

3.1.1.2. Stress protein (heat shock protein) responses. Another well-documented effect of exposure to low-intensity extremely low frequency and RFR is the creation of stress proteins (heat shock proteins) indicating that a cell is being placed under physiological stress [148–154]. Heat shock proteins are in a family of inducible proteins that are initiated when any increased need for protection from stray electrons occurs [155,156]. The HSP response is generally associated with heat shock, exposure to toxic chemicals and heavy metals, and other environmental insults. HSP is a signal of cells in distress. Plants, animals and bacteria all produce stress proteins to survive environmental stressors like high temperatures, lack of oxygen, heavy metal poisoning, and oxidative stress. It should also be noted that the generation of HSP stress proteins can have constructive medical applications, such as protection from reperfusion of the heart following ischemic injury [157]. Another concomitant impact of cellular stress can be protein misfolding, which has been documented in association with exposure to EMF/RFR [158,159].

Although a number of papers have demonstrated increases in HSPs in people with ASCs [160–164], it has been investigated far less often than oxidative stress. Part of the research needed to study possible influences of EMF/RFR on ASCs would be more careful study of HSPs in ASCs.

3.1.2. Membranes and channels

3.1.2.1. Cell membranes and lipid peroxidation. Cell and organelle membranes play roles in partitioning cells from the extracellular milieu as well as in sustaining boundaries and regulating flow of materials between cellular compartments needing different metabolic parameters for their activities.

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They also play critical roles in maintaining electrical differences and the flow of electricity.

Adey (2002) summarized studies that report cell membranes as the site of initial field transductive coupling.

"*Collective evidence points to cell membrane receptors as the probable site of first tissue interactions with both ELF and microwave fields for many neurotransmitters* [165], *hormones* [166,167], *growth-regulating enzyme expression* [168–171], *and cancer-promoting chemicals* [172,173]. *In none of these studies does tissue heating appear involved causally in the responses.*" [174]

Membranes are well-known targets of oxidative stress. Membrane damage is a major route through which free radical damage proliferates through the cellular system. Lipid peroxidation of membranes most often affects polyunsaturated fatty acids such as EPA and DHA which are the most abundant and vulnerable lipids in the brain where the damage they sustain can have serious impacts – DHA is 40% of PUFAs (brain polyunsaturated fatty acids). Lipid peroxidation of membranes has been identified as an effect of EMF/RFR in multiple studies [175,176]. A variety of other mechanisms for membrane alteration related to EMF/RFR have been intimated in the literature. Physicochemical properties of membranes such as phase transition of phosphatidylcholine can be shifted by non-thermal effects of microwave radiation [177]. Membrane potential and currents may also be impacted by pulsed radiofrequency fields [178]. This has been observed graphically in altered cellular movement in Paramecium caudatum, with these cells becoming broader, with a broader-appearing cytopharynx, with their pulse vesicles having difficult in expelling their content outside the cell, and with less efficient movement of cilia [179] which the authors suggested might be due to targeting of the cellular membrane. The impacts on this unicellular organism may help us imagine what the impact of EMF/RFR might be on cells with some structural similarities, such as columnar epithelial cells and ciliated cells in mucosal surfaces in the respiratory system, digestive tract, uterus and fallopian tubes and central spinal cord.

Indications of lipid peroxidation of membranes has been documented in ASCs, including malonaldehyde and isoprostanes, as well as alteration of membrane phospholipids and prostaglandins [98,100,115,162,180–184]. In one study the isoprostane levels showed a biomodal distribution with the majority of ASC subjects showing moderate increase but a smaller group showing dramatic increases [183]. Thromboxane, reflecting platelet activation, was also elevated in one study [98]. Given that this phenomenon has been identified in many people with ASCs, it is plausible that such individuals will likely be more vulnerable to having such cellular injuries caused, worsened or both by EMF/RFR exposures.

3.1.2.2. Calcium channels. EMF/RFR exposures have been shown to alter or disturb calcium signaling [185] through a variety of mechanisms, including membrane leakage [186], alteration of calcium-binding proteins and GFAP reactivity [187,188], and altered ultrastructural distribution of calcium and calcium-activated ATPases after exposure [189]. Adey (2002) provided an overview of key studies on calcium efflux and the importance of calcium in cell signaling. "*Early studies described calcium efflux from brain tissue in response to ELF exposures* [190,191], *and to ELF-modulated RF fields* [190–193]. *Calcium efflux from isolated brain subcellular particles (synaptosomes) with dimensions under 1.0 μm also exhibit an ELF modulation frequency-dependence in calcium efflux, responding to 16 Hz sinusoidal modulation, but not to 50 Hz modulation, nor to an unmodulated RF carrier* [194]. *In the same and different cell culture lines, the growth regulating and stress responsive enzyme ornithine decarboxylase (ODC) responds to ELF fields* [170,195] *and to ELF-modulated RF fields.*" [168,170,171,196].

Dutta et al. (1992) reported:

"*Radio-frequency electromagnetic radiation (RFR) at 915 and 147 MHz, when sinusoidally amplitude modulated (AM) at 16 Hz, has been shown to enhance release of calcium ions from neuroblastoma cells in culture. The dose-response relation is unusual, consisting of two power-density "windows" in which enhanced efflux occurs, separated by power-density regions in which no effect is observed. Thus RFR affects both calcium-ion release and AChE activity in nervous system-derived cells in culture in a common dose-dependent manner.*" [197]

Alterations in calcium signaling impacts are of central importance in ASC pathophysiology, and have been documented to occur with some EMF/RFR exposures. Calcium channels play an important role in regulating neuronal excitability. Disturbance during development may be contributory to the development of ASCs, and is often associated with vulnerability to seizures. Gene alterations associated with a number of voltage-gated calcium channels have been identified in ASCs [198–202]. However, based on an examination of patient laboratory and phenotype data it has been argued that aberrant calcium signaling could be downstream: Palmieri and Persico (2010) suggest that "*an abnormal neuroimmune response as a relevant player in elevating intracellular Ca^{2+} levels, deranging neurodevelopment, driving oxidative stress, and ultimately affecting synaptic function and neural connectivity especially in long-range neuronal pathways physiologically responsible for integrated information processing*" [203]. Peng and Jou (2010) have in turn shown how increased intracellular calcium can cause oxidative stress, and a vicious circle: "*. . . mitochondrial ROS [reactive oxygen species]rise can modulate Ca^{2+} dynamics and augment Ca^{2+} surge. The reciprocal interactions between Ca^{2+} induced ROS increase and ROS modulated Ca^{2+} upsurge may cause a feedforward, self-amplified loop creating cellular damage far beyond direct Ca^{2+} induced damage*" [204].

Environmental as well as genetic routes to calcium signaling dysfunction have been identified [205] including chemicals such as the polyaromatic hydrocarbons.

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PCB-95 in particular modulates the calcium-dependent signaling pathway responsible for activity-dependent dendritic growth [206,207]. In fact, once a genetic mutation has been associated with altering a critical signaling pathway and conferring risk for autism, chemicals or other environmental agents can be identified that target the same pathways and also confer ASC risk. Stamou et al. (2012) have reviewed this strategy of identifying multiple mechanisms converging on common signaling pathways regarding Ca(2+)-dependent mechanisms as well as extracellular signal-regulated kinases (ERK)/phosphatidylinositol-3-kinases (PI3K) and neuroligin-neurexin-SHANK [208]. From this point of view, there may be no particular reason to privilege genetic mutations in their contribution to a disturbance of calcium signaling, since whether this function becomes derailed due to a genetic mutation, from a chemical toxin or from EMF/RFR perturbation of calcium signaling, the functional effect is comparable.

3.1.3. Junctions and barriers

The damage discussed so far has been at the molecular and subcellular level. However impacts from this level reverberate up to larger scales in the system. Where membranes create boundaries between cells and subcellular compartments, barriers do this at a larger scale. Cells become capable of forming barriers between each other through tight junctions which block substances and cells from 'slipping through the cracks,' so to speak, between the cells. Conversely, gap junctions are subcellular structures providing openings that allow physical passage of materials between cells otherwise separated by membranes.

Such connections between cells can also be altered by electromagnetic fields and radiofrequency exposures, at least under certain circumstances. High frequency magnetic fields have been observed to be associated with a sharp decrease in intercellular gap junction-like structures, in spite of increased gene expression for pertinent proteins [209]. Changes in tight junctions have been observed upon exposure to microwave and x-ray irradiation [210].

A number of papers in the ASC research field document problems pertinent to junctions. Connexin abnormalities have been documented in neuropathological studies [211] and MacFabe and colleagues identified lipid alterations associated with oxidative stress, membrane fluidity and the modulation of gap junction coupling [212]. Decrease in platelet endothelial cell adhesion molecule-1 were reduced and this reduction correlated with repetitive behavior and abnormal brain growth; adhesion molecules modulate permeability and signaling at the blood–brain barrier as well as leukocyte infiltration into the central nervous system [213].

EMF and RFR might also compromise biologically important barrier structures that separate blood flow from organs like the brain [214]. This raises important questions regarding whether other 'barriers' that keep blood flow separate from the gut (gut-blood barrier), or the placenta (blood–placenta barrier) or the eye (ocular-blood barrier) may also be rendered pathologically leaky, and allow albumin, toxins, pro-inflammatory cytokines and infectious agents to cross these barriers, which may invoke immune responses in the intestines, and may impact the developing fetus [215]. While there are a fair number of negative studies, there are also many studies showing and association between EMF/RFR and pathological leakage of the blood–brain barrier (BBB), as well as evidence in animal studies of damage to brain cells and damage to or death of neurons. Such leakage has been shown to be potentiated by physiological factors such as diabetes and insulin (Gulturk et al., 2010) and has also potentiated viral lethality in a dose-dependent fashion (Lange et al., 1991). Many of the positive findings were associated with non-thermal exposures comparable to normal cell phone radiation exposure [216–222]. There are scattered reports of increased permeability across other membranes and barriers, such as the blood–testicle barrier in mice (Wang, 2008; Wang et al., 2010 and the rat liver canalicular membrane [223]). A 1992 study by Kues et al. reported that "*studies in our laboratory have established that pulsed microwaves at 2.45 GHz and 10 mW/cm^2 are associated with production of corneal endothelial lesions and with disruption of the blood–aqueous barrier in the non-human primate eye*" [224]. A recent study showing impact of high-frequency electromagnetic fields on trophoblastic connexins [209] may indicate the vulnerability of the placenta and placental barrier function to electromagnetic fields. A thorough review and methodological discussion of literature regarding EMF/RFR impacts on the BBB is provided by Salford in Section 10 of the BioIniative 2012 Report [214].

BBB integrity can be compromised by oxidative stress which can lead to increased permeability [225], and the resultant extravasation of albumin into brain parenchyma can be excitotoxic and neurotoxic [226,227]. The interaction of these factors may contribute to a feed-forward vicious cycle that can result in progressive synaptic and neuronal dysfunction as seen in various neurodegenerative diseases [228].

The evidence suggesting possible existence of barrier function compromise in people with ASCs is largely indirect. The existence of brain neuroinflammation in ASCs has been documented in a growing number of studies [160,229,230], and this is known to be associated with BBB permeability [231–233]. In a review of clinical MRI findings in ASCs 19/59 showed white matter signal abnormalities [234], which in other settings have been associated with cerebral hypoperfusion, though not necessarily in the same locations as the hyperintensities [235,236]. Blood flow abnormalities, predominantly hypoperfusion, documented in a few dozen PET and SPECT studies, could also be caused by and/or associated with physiological phenomena associated with vascular permeability as will be revisited below. Increased intestinal permeability has been documented (although its absence has also been documented) [237–243] and discussed in the context of food exposures, particularly gluten [244–250]. The reactivity to large numbers of different foods, clinically observed in many children with autism, has been framed by

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some as a manifestation of indiscriminate exposure of the immune system and the brain to food proteins on account of intestinal permeability as well as BBB permeability [251]. This reactivity could in turn feed in to aberrant immune responsivity which in turn could further amplify barrier vulnerability [248].

A number of studies have made an association between an increased risk of having a child with autism and maternal infection during pregnancy. This phenomenon looks like it is a result of the maternal immune system response rather than being due to an impact deriving from a specific infectious agent; but the potential for an accompanying compromise of the placental barrier is also conceivable in this setting. Under these circumstances the fetal risk of exposure to maternal blood toxins, cytokines and stress proteins in utero could potentially be increased if placenta barrier (BPB) function were impaired. The integrity, or compromise thereto, of the maternal-fetal interface via the placenta is an important modulator of brain development [252].

3.1.4. Genetic alterations and reproductive impacts

The overwhelming emphasis in recent decades in autism research has been on genetics, and on finding linkages between genes, brain and behavior, in part because of the high heritability of autism that was calculated from the concordance rates of monozygotic (identical) vs. dizygotic (fraternal) twins found in by a series of small twin studies performed some decades ago. In recent years the genetic premises of this seemingly obvious framing of autism as overwhelmingly genetic have been undermined at several levels [253]. First, the number of reported cases is increasing, making it more difficult to maintain that ASCs are purely genetic because these increases can only be partly explained away by greater awareness or other data artifacts [254,255]. Second, the complexity of the ways we understand how genes might relate to autism has grown, from an expectation a decade ago that a small number of genes (even less than a dozen) would explain everything to an identification of close to a thousand genes associated with autism with common threads linking only a small subset [256,257], as well as 'de novo' mutations present in ASC children but not their parents and even 'boutique' mutations not shared beyond an individual family. Moreover, a recent twin study that was much larger than any of the prior such studies identified a modest genetic role but a substantial environmental role [258]. Indeed even concordance between identical twins appears to be influenced by whether the twins shared a placenta [259]. All of this calls into question the idea that genetics can be presumed to be the 'cause' of autism simply based upon heritability calculations, and upgrades the importance of looking not only at the environment and environmentally vulnerable physiology, but also at acquired mutations.

3.1.4.1. Genotoxicity. Genotoxicity has been proposed as a mechanism for the generation of 'de novo' mutations (found in children but not their parents) being found in ASCs [260]. Reviews and published scientific papers on genotoxicity and EMF report that both ELF-EMF and RFR exposures are genotoxic – i.e., damaging to DNA – under certain conditions of exposure, including under conditions of intermittent and/or chronic ELF and RFR exposure that are of low-intensity and below current world safety standards [104,105,261–266]. Types of genetic damage reported have included DNA fragmentation and single- and double-strand DNA breaks, micronucleation and chromosome aberrations, all of which indicate genetic instability [102,103].

Researchers have recently identified large numbers of de novo mutations, more likely to be transmitted by fathers than by mothers to their children [267–269]. This is consistent with the EMF/RFR literature that repeatedly documents DNA damage to sperm from cell phone radiation (see Section 3.1.4.1.2). The Eichler team at the University of Washington found that 39% of the 126 most severe or disruptive mutations map to a network associated with chromatin remodeling that has already been ranked as significant amongst autism candidate genes [268]. Although the relationship between the prominence of chromatin-related gene mutations and the impacts of EMF/RFR on chromatin condensation has not been clarified, the parallels support further investigation.

3.1.4.1.1. Contributors to genotoxicity.

- Oxidative stress and free radical damage to DNA

  Oxidative stress and excessive free radical production are very well known to be potentially genotoxic. They can be a consequence of myriad environmental factors, including but by no means limited to EMF/RFR. The DNA damage that can result could very well be one cause of 'de novo' mutations which to date have been found in only a small percentage of individuals with ASCs. Although there is not a consensus at this time about the rates or causes of de novo mutations in ASCs, environmentally triggered oxidative stress and free radical damage that we know are present in large numbers of people with ASCs can be genotoxic, and this warrants a serious investigation of the potential contribution of EMF and RFR to de novo mutations in ASC. Further, the huge increases in exposure to EMF/RFR in daily life due to electrification and the global saturation of RFR from wireless technologies [81] reinforce this need.
- Challenge to DNA repair mechanisms

  When the rate of damage to DNA exceeds the rate at which DNA can be repaired, there is the possibility of retaining mutations and initiating pathology. Failure to trigger DNA damage repair mechanisms, or incomplete or failed repair, may be a consequence of a variety of commonplace stressors, including EMF/RFR exposure. A decrease in DNA repair efficiency has been reported to result from exposure to low-intensity RFR in human stem cells, and other cells. Mobile phone frequency GSM exposure at the frequency of 915 MHz consistently inhibited DNA repair foci in lymphocytes [270–272]. Belyaev, Markova and colleagues (2005), and Markova et al. (2009)

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reported that very low-intensity microwave radiation from mobile phones inhibits DNA repair processes in human stem cells. A significant reduction in 53BP1 (tumor suppressor p53 binding protein 1) foci was found in cells exposed to microwave radiofrequency radiation within one hour of exposure. Fibroblast cells were impacted in this fashion but adapted over time, whereas stem cells were similarly affected (inhibited 53BP1 foci) but did not adapt to microwave radiation during chronic exposure [270,271]. Additional challenges to DNA repair mechanisms include not only toxicants and other damaging inputs but also nutritional insufficiencies of substances important to the proper functioning of DNA repair mechanisms, including Vitamin D, essential fatty acids, and minerals such as selenium and molybdenum [273]. The high possibility that various such contributors may combine supports an 'allostatic load' model of environmental injury and genotoxicity.

- Chromatin condensation

  The work of Markova, Belyaev and others has repeatedly shown that RFR exposure can cause chromatin condensation, which is a hallmark of DNA damage. Belyaev (1997) reported that super-low intensity RFR resulted in changes in genes, and chromatin condensation of DNA at intensities comparable to exposures from cell towers (typically at RFR levels of 0.1 to one microwatt per centimeter squared ($\mu W/cm^2$)) [274]. Significant microwave (MW)-induced changes in chromatin conformation were observed when rat thymocytes were analyzed between 30–60 min after exposure to MW [275].

  In recent studies, human lymphocytes from peripheral blood of healthy and hypersensitive to EMF persons were exposed to non-thermal microwave radiation (NT MW) from the GSM mobile phones [270,271]. NT MW induced changes in chromatin conformation similar to those induced by heat shock, which remained up to 24 h after exposure. The same group has reported that contrary to human fibroblast cells, which were able to adapt during chronic exposure to GSM/UMTS low intensity RFR exposure, human stem cells did not adapt [272].

3.1.4.1.2. Gonadal and germline impacts. De novo mutations have been shown to be more of a problem related to paternal age [268,276–279], and this may be related to the impact of environmental factors such as EMF/RFR on the stem cell genome, particularly in sperm which have no DNA repair capacity. Vulnerability of testes and ova, and of sperm and egg cells, relates to the tissue milieu in which damage to the germline can take place, as well as on the greater vulnerability of stem cells. Several international laboratories have replicated studies showing adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket [106,280–284]. Other studies conclude that usage of cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure [175,284,285]. Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line [134,286–290]. Of note, altered fatty acids consistent with oxidative stress have been found in sperm cells in male infertility [291,292].

There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al. (2012) report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in *Drosophila melanogaster* [293]. Gul et al. (2009) report rats exposed to stand-by level RFR (phones on but not transmitting calls) caused decrease in the number of ovarian follicles in pups born to these exposed dams [294]. Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than 1.0 $\mu W/cm^2$ [295].

3.1.4.1.3. Implications of genotoxicity. The issue of genotoxicity puts the contribution of genetic variation into a different light – as something that needs to be accounted for, not necessarily assumed as the starting point. In this regard it has been speculated that the apparent higher rates of autism in Silicon Valley, discussed in the past as related to 'geek genes'[296], might be conditioned by higher levels of exposure to EMF/RFR. The relationship between the greater vulnerability of male sperm than of female eggs to adverse effects of EMF/RFR exposure and the marked (4:1) predominance of paternal origin of de novo point mutations (4:1 bias), also deserves further careful attention [268].

3.1.5. Implications of damage

We have reviewed parallels between ASC and EMF/RFR in molecular, cellular and tissue damage, including cellular stress (oxidative stress, the heat shock response and protein misfolding), injury of membranes, aberrant calcium signaling, and compromise of cell junctions and barriers. The genotoxicity of EMF/RFR was reviewed in relation to issues of environmental contributions to autism and of the phenomenon of de novo mutations. The compromise of the tissue substrate appears to have many commonalities in ASCs and in EMF/RFR exposures. Also notable was the possibility of attenuating some of the damage through increasing antioxidant status.

Regarding Rett syndrome, a genetic syndrome often associated with autistic behaviors, these commonalities come to mind in considering the implications of a recent study documenting arrest of symptomatology in a mouse model of Rett syndrome through a bone marrow transplant of wild-type microglia [297,298]. The introduction of these competent microglia cells did not directly target the neuronal defect associated with the MECP2 gene mutation; instead the benefits of the transplant were due to overcoming the inhibition of phagocytosis caused by the MECP2 mutation that was absent in the wild-type microglia. Phagocytosis involves removing debris. This suggests that while research has focused on how

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specific molecular defects, particularly in the synapse, may contribute to Rett pathophysiology, there may also be an important contribution from cellular debris, misfolded proteins and other disordered cellular structure and function. Such disorder could be accumulating in cells under the conditions of pathophysiological disarray reviewed above. Based on this study as well as on the levels of damage just reviewed, cellular problems that are pertinent to ASCs most likely go beyond any specific defect introduced by a mutation. Additionally it is conceivable that many of the mutations may be not part of normal background variation but instead collateral damage from the same environmental factors that are also driving the damage to the physiology.

3.1.6. Summary of Part I and preview of Part II

The data reviewed above in Part I of this two part paper documents a series of parallels between the pathophysiological and genotoxic impacts of EMF/RFR and the pathophysiological underpinnings of ASCs. DNA damage, immune and blood–brain barrier disruption, cellular and oxidative stress, calcium channel, disturbed circadian rhythms, hormone dysregulation, and degraded cognition, sleep, autonomic regulation and brainwave activity all have commonalities between ASCs and EMF/RFR, and the disruption of disruption fertility and reproduction associated with EMF/RFR may also be related to the increasing incidence of ASCs. All of this argues for reduction of exposures now, and better coordinated research in these areas.

These pathophysiological parallels are laid out after identifying the dynamic features of ASCs that could plausibly arise out of such pathophysiological dysregulation. The importance of transduction between levels was also discussed in Part I, and will be elucidated in much more detail in Part II where more detail will be given about the possible interfaces between the cellular and molecular pathophysiology reviewed above and the higher-level disruption of physiological systems, brain tissue and nervous system electrophysiology.

The emergence of ever larger amounts of data is transforming our understanding of ASCs from static encephalopathies based on genetically caused brain damage to dynamic encephalopathies where challenging behaviors emanate from physiologically disrupted systems. In parallel, the emergence of ever larger bodies of evidence supporting a large array of non-thermal but profound pathophysiological impacts of EMF/RFR is transforming our understanding of the nature of EMF/RFR impacts on the organism.

At present our policies toward ASCs are based on outdated assumptions about autism being a genetic, behavioral condition, whereas our medical, educational and public health policies related to treatment and prevention could be much more effective if we took whole-body, gene-environment considerations into account, because there are many lifestyle and environmental modifications that could reduce morbidity and probably incidence of ASCs as well.

At present our EMF/RFR standards are based on outdated purely thermal considerations, whereas the evidence is now overwhelming that limiting regulations in this way does not address the much broader array of risks and harm now known to be created by EMF/RFR.

In particular, the now well-documented genotoxic impacts of EMF/RFR, placed in parallel with the huge rise in reported cases of ASCs as well as with the de novo mutations associated with some cases of ASCs (as well as other conditions), make it urgent for us to place the issue of acquired as well as inherited genetic damage on the front burner for scientific investigation and policy remediation.

With the rising numbers people with ASCs and other childhood health and developmental disorders, and with the challenges to our prior assumptions posed ever more strongly by emerging evidence, we need to look for and act upon risk factors that are largely avoidable or preventable. We would argue that the evidence is sufficient to warrant new public exposure standards benchmarked to low-intensity (non-thermal) exposure levels causing biological disruption and strong, interim precautionary practices are advocated. Further evidence to support the pathophysiological support for parallels between ASCs and EMF/RFR impacts and for taking action will be offered in Part II.

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