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Pathophysiology 20 (2013) 211–234

ISP PATHOPHYSIOLOGY

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Autism and EMF? Plausibility of a pathophysiological link part II

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Abstract

Autism spectrum conditions (ASCs) are defined behaviorally, but they also involve multileveled disturbances of underlying biology that find striking parallels in the physiological impacts of electromagnetic frequency and radiofrequency radiation exposures (EMF/RFR). Part I (Vol 776) of this paper reviewed the critical contributions pathophysiology may make to the etiology, pathogenesis and ongoing generation of behaviors currently defined as being core features of ASCs. We reviewed 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 documents 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. It details evidence for mitochondrial dysfunction, immune system dysregulation, neuroinflammation and brain blood flow alterations, altered electrophysiology, disruption of electromagnetic signaling, synchrony, and sensory processing, de-tuning of the brain and organism, with autistic behaviors as emergent properties emanating from this pathophysiology. 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 can worsen 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; Microwave

1. Recap of part I and summary of part II

Part I of this two-part article previously documented a series of parallels between the pathophysiological and genotoxic impacts of EMF/RFR and the pathophysiological, genetic and environmental underpinnings of ASCs. DNA damage, immune and blood–brain barrier disruption, cellular and oxidative stress, calcium channel dysfunction, disturbed circadian rhythms, hormone dysregulation, and degraded cognition, sleep, autonomic regulation and brainwave activity—all are associated with both ASCs and EMF/RFR; and the disruption of 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

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http://dx.doi.org/10.1016/j.pathophys.2013.08.002

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.

Part II elucidates in much more detail 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. It addresses mitochondrial dysfunction, immune system disregulation, neuroinflammation and brain blood flow alterations, altered electrophysiology, disruption of electromagnetic signaling, synchrony, and sensory processing, de-tuning of the brain and organism, and behavior as an emergent property. 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. 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 exposures 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) 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 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. The combined evidence in Parts I and II of this article provide substantial pathophysiological support for parallels between ASCs and EMF/RFR health impacts.

2. Parallels in pathophysiology

2.1. Degradation of the integrity of functional systems

EMF/RFR exposures can yield both psychological and physiological stress leading to chronically interrupted homeostasis. In the setting of molecular, cellular and tissue damage, one would predict that the organization and efficiency of a variety of organelles, organs and functional systems would also be degraded. In this section we will review disturbances from EMF/RFR in systems (including include oxidative and bioenergetics metabolism, immune function and electrophysiological oscillations) that include molecular and cellular components subject to the kinds of damage discussed in the previous section. We will review disturbances that have been associated with EMF/RFR, and consider the parallel disturbances that have been documented in ASCs.

2.1.1. Mitochondrial dysfunction

Mitochondria are broadly vulnerable, in part because the integrity of their membranes is vital to their optimal functioning—including channels and electrical gradients, and their membranes can be damaged by free radicals which can be generated in myriad ways. Moreover, just about every step in their metabolic pathways can be targeted by environmental agents, including toxicants and drugs, as well as mutations [1]. This supports a cumulative 'allostatic load' model for conditions in which mitochondrial dysfunction is an issue, which includes ASCs as well as myriad other chronic conditions.

Mitochondria are commonly discussed in terms of the biochemical pathways and cascades of events by which they metabolize glucose and generate energy. But in parallel with this level of function there also appears to be a dimension of electromagnetic radiation that is part of the activity of these organelles. For example, electromagnetic radiation can be propagated through the mitochondrial reticulum, which along with the mitochondria has a higher refractive index than the surrounding cell and can serve to propagate electromagnetic radiation within the network [2]. It is also the case that "*The physiological domain is characterized by small-amplitude oscillations in mitochondrial membrane potential (delta psi(m)) showing correlated behavior over a wide range of frequencies. . .. Under metabolic stress, when the balance between ROS [reactive oxygen species, or free radicals] generation and ROS scavenging [as by antioxidants] is perturbed, the mitochondrial network throughout the cell locks to one main low-frequency, high-amplitude oscillatory mode. This behavior has major pathological implications because the energy dissipation and cellular redox changes that occur during delta psi(m) depolarization result in suppression of electrical excitability and Ca2 + handling. . .*" [3].

These electromagnetic aspects of mitochondrial physiology and pathophysiology could very well be impacted by EMF/RFR.

Other types of mitochondrial damage have been documented in at least some of the studies that have examined the impacts of EMF/RFR upon mitochondria. These include reduced or absent mitochondrial cristae [4–6], mitochondrial DNA damage [7], swelling and crystallization [5], alterations and decreases in various lipids suggesting an increase in their use in cellular energetics [8], damage to mitochondrial DNA [7], and altered mobility and lipid peroxidation after exposures [9]. Also noted has been enhancement of brain mitochondrial function in Alzheimer's transgenic mice and normal mice [10]. The existent of positive as well as negative effects gives an indication of the high context dependence of exposure impacts, including physical factors such as frequency, duration, and tissue characteristics [11].

By now there is a large amount of evidence for biochemical and other abnormalities in a large portion of children with autism that are consistent with mitochondrial dysfunction [12–14]. Recently published postmortem brain tissue studies that have added a new dimension of evidence for mitochondrial abnormalities in ASCs will be reviewed in the section on alteration of brain cells below.

Secondary mitochondrial dysfunction (i.e. environmentally triggered rather than rooted directly in genetic mutations) [15–18] could result among other things from the already discussed potential for EMF/RFR to damage channels, membranes and mitochondria themselves as well as from toxicant exposures and immune challenges. In a meta-analysis of studies of children with ASC and mitochondrial disorder, the spectrum of severity varied, and 79% of the cases were identified by laboratory findings without associated genetic abnormalities [16].

2.1.2. Melatonin dysregulation

2.1.2.1. Melatonin, mitochondria, glutathione, oxidative stress. Melatonin is well-known for its role in regulation of circadian rhythms, but it also plays important metabolic and regulatory roles in relation to cellular protection, mitochondrial malfunction and glutathione synthesis [19–21]. It also helps prevent the breakdown of the mitochondrial membrane potential, decrease electron leakage, and thereby reduce the formation of superoxide anions [22]. Pharmacological doses of melatonin not only scavenge reactive oxygen and nitrogen species, but enhance levels of glutathione and the expression and activities of some glutathione-related enzymes [21,23].

2.1.2.2. Melatonin can attenuate or prevent some EMF/RFR effects. Melatonin may have a protective effect in the setting of some EMF/RFR exposures, apparently in relation to these functions just described. EMF/RFR can impact melatonin; one example is exposure to 900 MHz microwave radiation promoted oxidation, which reduced levels of melatonin and increased creatine kinase and caspase-3 in exposed as compared to sham exposed rats [24].

Melatonin can attenuate or prevent oxidative damage from EMF/RFR exposure. In an experiment exposing rats to microwave radiation (MW) from a GSM-900 mobile phone with and without melatonin treatment to study renal impacts [25], the untreated exposed rats showed increases of lipid peroxidation markers as reduction of the activities of superoxide dismutase, catalase and glutathione peroxidase indicating decrement in antioxidant status. However these negative effects were inhibited in the exposed rats treated with melatonin. Melatonin also inhibited the emergence of preneoplastic liver lesions in rats exposed to EMFs [26]. The development of DNA strand breaks was observed in RFR exposed rats; this DNA damage was blocked by melatonin [27]. Exposure of cultured cortical neurons to EMF led to an increase in 8-hydroxyguanine in neuronal mitochondria, a common biomarker of DNA oxidative damage, along with a reduction in the copy number of mitochondrial DNA and the levels of mitochondrial RNA transcripts; but these effects could all be prevented by pretreatment with melatonin [7]. In a study of skin lesion induced by exposure to cell phone radiation, the skin changes in the irradiated group (which included thicker stratum corneum, epidermal atrophy, papillamatosis, basil cell proliferation, increased epidermal granular cell layer and capillary proliferation, impaired collagen tissue distribution and separation of collagen bundles in dermis) were prevented (except for hypergranulosis) by melatonin treatment [28]. Melatonin as well as caffeic acid phenyethyl ester (an antioxidant) both protected against retinal oxidative stress in rates exposed long-term to mobile phone irradiation [29]. Nitric oxide (NO) was increased in nasal and sinus mucosa in rats after EMF exposure, with this NO possibly acting as a defense mechanism suggesting tissue damage; but this was prevented by pretreatment with melatonin [30]. Melatonin treatment significantly prevented the increase in the MDA (malondyaldehyde, a marker of lipid peroxidation) content and XO (xanthine oxidase) activity in rat brain tissue after 40 days of exposure, but it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents [31].

Of note, the melatonin production of infants in isolettes in neonatal intensive care units appears to be impacted by the high ELF-EMF environment, in that when infants were removed from those exposures they showed an increase in melatonin levels [32]. There is an increased prevalence of ASCs in children who were born prematurely [33–43]. There are many potential prematurity-associated factors that could contribute to increased risk for ASCs, but proper melatonin regulation warrants EMF/RFR controls in the newborns' environment.

2.1.2.3. Melatonin and autism. Regarding melatonin status in people with ASCs, a recent meta-analysis summarized the current findings as indicating that "*(1) Physiological levels of melatonin and/or melatonin derivatives are commonly below average in ASC and correlate with autistic behavior, (2) Abnormalities in melatonin-related genes may be a cause of low melatonin levels in ASD, and (3) . . . treatment with melatonin significantly improves sleep duration and sleep onset latency in ASD.*" [44].

The meta-analysis also showed that polymorphisms in melatonin-related genes in ASC could contribute to lower melatonin concentrations or an altered response to melatonin, but only in a small percentage of individuals, since pertinent genes were found in only a small minority of those screened.

Based on the common presence of both sleep disorders and low melatonin levels, Bourgeron [45] proposed that synaptic and clock genes are important in ASCs, and that future studies should investigate the circadian modulation of synaptic function [45]. A number of melatonin-related genetic variants have been identified as associated with ASCs. Polymorphisms and deletions in the ASMT gene, which encodes the last enzyme of melatonin synthesis, have been found [46–48], and variations have been found as well for melatonin receptor genes [46,47,49]. CYP1A2 polymorphisms have been found in slow melatonin metabolisers, in whom melatonin levels are aberrant and initial response to melatonin for sleep disappeared in a few weeks [50].

2.1.2.4. Autism AND melatonin AND glutathione. Whereas PubMed searches for "autism AND melatonin" and "autism AND glutathione" each coincidentally yielded 72 citations, and "melatonin AND glutathione" yielded 803 citations, the search for "autism AND melatonin AND glutathione" yielded zero citations. This is interesting given the strong connection of melatonin and glutathione metabolically, as discussed above, alongside of the strongly established interest in both glutathione and melatonin in ASC research and increasingly in clinical practice. Hopefully one contribution of an investigation of EMF/RFR links to ASCs will be to help bring attention to this relationship, which may help identify potential environmental and physiological causes for low melatonin in those without pertinent mutations. Of pertinence, tryptophan hydroxylase (TPH2) – the rate limiting enzyme in the synthesis of serotonin, from which melatonin is derived – is extremely vulnerable to oxidation, and tends to misfold when its cysteine residues are oxidized, with the enzyme being converted to a redox-cycling quinoprotein [51–54].

2.1.3. Disturbed immune function

There is by now a broad appreciation of the presence of immune disturbances in ASCs, to the point where there is an emerging discussion of ASCs as neuroimmune disorders [55,56]. Research identifying immune features in ASCs spans from genetics where risk genes have been identified to epigenetics where altered expression of immune genes is being reported as prominent in ASC epigenetics [57–59], and also includes prenatal infectious and immune disturbances as risk factors for autism as well as other neurodevelopmental and neuropsychiatric diseases as well as other conditions such as asthma [60–62]. Immune disturbances in infants and children with ASC are heterogeneous, with some but not all manifesting autoimmunity [63,64]. Anecdotally, recurrent infection is common while on the other hand some get sick less often than their peers. It is common for people with autism to have family members with immune or autoimmune diseases [65]. The immune system is turning out to have an important role in brain development [66–68]. As mentioned, glial activation associated with brain immune response has been identified in a growing number of studies. Whether or not EMF/RFR contributes to these features of ASCs causally, based on the evidence below regarding immune impacts of EMF/RFR exposure [69], it is certainly plausible that such exposures could serve as aggravating factors.

2.1.3.1. Low-intensity exposures. The body's immune defense system is now known to respond to very low-intensity exposures [70]. Chronic exposure to factors that increase allergic and inflammatory responses on a continuing basis is likely to be harmful to health, since the resultant chronic inflammatory responses can lead to cellular, tissue and organ damage over time. Many chronic diseases are related to chronic immune system dysfunction. Disturbance of the immune system by very low-intensity electromagnetic field exposure is discussed as a potential underlying cause for cellular damage and impaired healing (tissue repair), which could lead to disease and physiological impairment [71,72]. Both human and animal studies report that exposures to EMF and RFR at environmental levels associated with new technologies can be associated with large immunohistological changes in mast cells as well as other measures of immune dysfunction and dysregulation. Mast cells not only can degranulate and release irritating chemicals leading to allergic symptoms; they are also widely distributed in the body, including in the brain and the heart, which might relate to some of the symptoms commonly reported in relation to EMF/RFR exposure (such as headache, painful light sensitivity, and cardiac rhythm and palpitation problems).

2.1.3.2. Consequences of immune challenges during pregnancy. As mentioned, infection in pregnancy can also increase the risk of autism and other neurodevelopmental and neuropsychiatric disorders via maternal immune activation (MIA). Viral, bacterial and parasitic infections during pregnancy are thought to contribute to at least 30% of cases of schizophrenia [73]. The connection of maternal infection to autism is supported epidemiologically, including in a Kaiser study where risk was associated with psoriasis and with asthma and allergy in the second trimester [65], and in a large study of autism cases in the Danish Medical registry [74] with infection at any point in pregnancy yielding an adjusted hazard ration of 1.14 (CI: $0.96-1.34$) and when infection occurred during second trimester the odds ratio was 2.98 (CI: $1.29-7.15$). In animal models, while there is much variation in study design, mediators of the immune impact include oxidative stress, interleukin-6 and increased placental cytokines [61,68,75]. Garbett et al. [76] commented on several mouse models of the effects of MIA on the fetal brain that "The overall gene expression changes suggest that the response to MIA is a neuroprotective attempt by the

developing brain to counteract environmental stress, but at a cost of disrupting typical neuronal differentiation and axonal growth." [76]. Maternal fetal brain-reactive autoantibodies have also been identified in some cases [62,77–82].

Although we have evidence of immune impacts of EMF/RFR, the impact of repeated or chronic exposure to EMF and RFR during pregnancy is poorly studied; could this trigger similar immune responses (cytokine production) and stress protein responses, which in turn would have effects on the fetus? Although this has been poorly studied, we do have data that very low cell phone radiation exposures during both human and mouse pregnancies have resulted in altered fetal brain development leading to memory, learning, and attention problems and behavioral problems [83].

2.1.3.3. Potential immune contributions to reactivity and variability in ASCs. Immune changes in ASCs appear to be associated with behavioral change [84–88], but the mechanisms are complex and to date poorly understood [89] and likely will need to be elucidated through systems biology methods that capture multisystem influences on the interactions across behavior, brain and immune regulation [90], including electrophysiology.

Two of the particularly difficult parts of ASCs are the intense reactivity and the variability in assorted symptoms such as tantrums and other difficult behaviors. Children with ASCs who also have gastrointestinal symptoms and marked fluctuation of behavioral symptoms have been shown to exhibit distinct innate immune abnormalities and transcriptional profiles of peripheral blood monocytes [91]. It is worth considering EMF/RFR exposures could be operating through related mechanisms so as to add to 'allostatic loading' in ways that exacerbate behavior. In Johansson 2006 and 2007 a foundation is provided for understanding how chronic EMF/RFR exposure can compromise immune function and sensitize a person to even small exposures in the future [72,92]. Johansson discusses alterations of immune function at environmental levels resulting in loss of memory and concentration, skin redness and inflammation, eczema, headache, and fatigue. Mast cells that degranulate under EMF and RFR exposures and substances secreted by them (histamine, heparin and serotonin) may contribute to features of this sensitivity to electromagnetic fields [92]. Theoharides and colleagues have argued that environmental and stress related triggers might activate mast cells, causing inflammatory compromise and leading to gut–blood–brain barrier compromise, seizures and other ASC ASC symptoms [93,94], and that this cascade of immune response and its consequences might also be triggered in the absence of infection by mitochondrial fragments that can be released from cells in response to stimulation by IgE/anti-IgE or by the proinflammatory peptide substance P [95].

Seitz et al. [96] reviewed an extensive literature on electromagnetic hypersensitivity conditions reported to include sleep quality, dizziness, headache, skin rashes, memory and concentration impairments related to EMF and RFR [96]. Some of these symptoms are common in ASCs, whether or not they are due to EMF/RFR exposure, and the experience of discomfort may be hard to document due to difficulties with self-reporting in many people with ASCs.

Johansson [72] also reports that benchmark indicators of immune system allergic and inflammatory reactions occur under exposure conditions of low-intensity non-ionizing radiation (immune cell alterations, mast cell degranulation histamine-positive mast cells in biopsies and immunoreactive dendritic immune cells) [71,72]. In facial skin samples of electro-hypersensitive persons, the most common finding is a profound increase in mast cells as monitored by various mast cell markers, such as histamine, chymase and tryptase [97]. In ASCs, infant and childhood rashes, eczema and psoriasis are common, and they are common in family members as well [98].

2.1.4. Alteration of and damage to cells in the brain

Brain cells have a variety of ways of reacting to environmental stressors, such as shape changes, metabolic alterations, upregulation or downregulation of neurotransmitters and receptors, other altered functionality, structural damage, production of un-metabolizable misfolded proteins and other cellular debris, and apoptosis; these range along a spectrum from adaptation to damage and cell death. These types of alterations can be looked at in animals under controlled conditions, but in human beings direct cellular examination can only be done on surgical biopsy tissue – which is hardly ever available in people with ASCs – or after death, at which point there has been a whole lifetime of exposures that are generally impossible to tease apart if there were even motivation to do so. This complicates the comparison of brain cell and tissue-related pathophysiology between what is seen in ASCs and what is associated with EMF/RFR exposures.

2.1.4.1. Brain cells. Impact of EMF/RFR on cells in the brain has been documented by some of the studies that have examined brain tissue after exposure, although the interpretation of inconsistencies across studies is complicated by sometimes major differences in impact attributable to differences in frequencies and duration of exposure, as well as to differences in resonance properties of tissues and other poorly understood constraints on cellular response. These studies and methodological considerations have been reviewed in depth in several sections of the 2012 BioInitiative Report [11,99]. A few examples of observations after exposure have included dark neurons (an indicator of neuronal damage), as well as alteration of neuronal firing rate [100], and upregulation of genes related to cell death pathways in both neurons and astrocytes [101]. Astrocytic changes included increased GFAP and increased glial reactivity [102–105], as well as astrocyte-pertinent protein expression changes detected by Fragopoulou et al. [322] as mentioned above. Also observed has been a marked protein downregulation of the nerve growth factor glial maturation factor beta (GMF) which is

considered as an intracellular signal transduction regulator in astrocytes, which could have significant impact on neuronal-glial interactions as well as brain cell differentiation and tumor development. Diminution of Purkinje cell number and density has also been observed, [106] including in two studies of the impacts of perinatal exposure [107,108]. Promotion of pro-inflammatory responses in EMF-stimulated microglial cells has also been documented [109].

Neuropathology findings in ASCs have been varied and have been interpreted according to various frameworks ranging from a regionalized approach oriented to identifying potential brain relationships to ASC's behavioral features [110] to identifying receptor, neurotransmitter and interneuron abnormalities that could account for an increased excitation/inhibition ratio [111–115]. Studies have documented a range of abnormalities in neurons, including altered cellular packing in the limbic system, reduced dendritic arborization, and reductions in limbic GABAergic systems [116]. Over the past decade a shift has occurred from presuming that all pertinent brain changes occurred prior to birth, to an acknowledgement that ongoing cellular processes appear to be occurring not only after birth but well into adulthood [117]. One of the reasons for this shift was the observation that head size (as well as brain weight and size) was on average larger in children with autism, and the head sizes of children who became diagnosed with autism increased in percentile after birth [118].

2.1.4.2. Neuroinflammation, glial activation and excitotoxicity. Although much attention has been paid in ASC brain literature to specific regions manifesting differences in size and activity in comparison to those without ASCs, there are other observations that are not strictly regional in nature, such as more widely distributed scaling differences (e.g. larger brains, wider brains, increased white matter volume, along with altered functional connectivity and coherence to be discussed below). Recently more studies have appeared identifying pathophysiological abnormalities such as neuroinflammation, mitochondrial dysfunction and glutathione depletion in brain tissue. Neuroinflammation was first identified in a study of postmortem samples from eleven individuals aged 5–44 who had died carrying an ASC diagnosis, in which activated astrocytes and microglial cells as well as abnormal cytokines and chemokines were found. Other research has identified further astrocyte abnormalities such as altered expression of astrocyte markers GFAP abnormalities, with elevation, antibodies, and altered signaling having been documented [119–121]. Increased microglia activation and density as well as increased myeloid dendritic cell frequencies have also been documented [87,122,123], as has abnormal microglial-neuronal interactions [124]. Recently, through use of the PET ligand PK11105, microglial activation was found to be significantly higher in multiple brain regions in young adults with ASCs [125]. Genes associated with glial activation have been documented as upregulated. Garbett et al measured increased transcript levels of many immune genes, as well as changes in transcripts related to cell communication, differentiation, cell cycle regulation and chaperone systems [126]. Voineaugu and colleagues performed transcriptomic analysis of autistic brain and found a neuronal module of co-expressed genes which was enriched with genetically associated variants; an immune-glial module which showed no such enrichment for autism GWAS signals was interpreted as secondary [127], but this seems to involve circular thinking, since it implies that the primary cause must be genetic, which is an assumption deriving from a dominant model, but is not a proven fact.

Neuroinflammation also does not appear to be strictly localized in a function-specific fashion, and it may contribute both to more broadly distributed and more focal features for tissue-based reasons. It may be that brain regions with particular prominence in ASCs may have distinctive cellular characteristics—e.g. the amygdala [128–138], which may have a larger or more reactive population of astrocytes [139] or the basal ganglia which may have greater sensitivity to even subtle hypoxia or perfusion abnormalities. In this case it may be the histology of these areas that makes them vulnerable to environmental irritants, and this may contribute to how environmental factors such as EMF/RFR might trigger or aggravate some of ASC's features. More widely distributed brain tissue pathology be part of what leads to differences in ASCs in brain connectivity. However these types of tissue-function relationships have been poorly investigated. Belyaev has intensively reviewed physical considerations including the contribution of tissue differences to variability in measured EMF/RFR impacts [11].

Various signs of mitochondrial dysfunction and oxidative stress have also been identified in the brain. Findings include downregulation of expression of mitochondrial electron transport genes [140] or deficit of mitochondrial electron transport chain complexes [141], brain region specific glutathione redox imbalance [142], and evidence of oxidative damage and inflammation associated with low glutathione redox status [143]. Oxidative stress markers were measured as increased in cerebellum [144].

Additional support for the presence of tissue pathophysiology-based changes in brains of people with ASCs comes from the various studies documenting reduction in Purkinje cell numbers [117,145–150], possibly due to oxidative stress and an increased excitation/inhibition ratio that could potentially be acquired [150]. Also of note are changes in the glutamatergic and GABAergic systems, which when imbalanced can disturb the excitation/inhibition ratio and contribute to seizure disorders; reductions in GABA receptors as well as in GAD 65 and 67 proteins that catalyse the conversion of glutamate into GABA have been measured [151–153]. A consensus statement on the cerebellum in ASCs stated that, *"Points of consensus include presence of abnormal cerebellar anatomy, abnormal neurotransmitter systems, oxidative stress, cerebellar motor and cognitive deficits, and neuroinflammation in subjects with autism*" [150].

Some indirect corroboration for these findings has come from neuroimaging, where the initial hypothesis regarding the tissue basis of the larger size of brains in so many people with autism – that it was due to a higher density of neurons and more tightly packed axons – came under question with the emergence of contradictory findings, well reviewed a few years ago by Dager and colleagues [154]. These include reduced rather than increased density of NAA (*n*-acetylaspartate, a marker of neuronal integrity and density that is produced in the mitochondria), reduced rather than increased fractional anisotropy suggesting less tightly packed axonal bundles [155–161] and greater rather than lower diffusivity, all of which may be more consistent with lower density of tissue and tissue metabolites and more fluid, which could be consistent with neuroinflammation and/or oxidative stress. The early postnatal development of such lower fractional anisotropy and increased diffusivity was measured in the process of occurring recently, in the first large prospective longitudinal imaging study of infants, who trended from 6 months to 2 years in the direction of these findings becoming more pronounced—but still with substantial overlap with those infants who did not develop autism [160]. This trend was consistent with prior studies showing increase in head size after birth, and added some information about what was happening in the brain to drive this size increase, although due to its methods it could only indirectly address the possibility that emergence during the first few years of life of tissue pathophysiology disturbances such as neuroinflammation might be contributing to these trends [162].

There is also substantial variability across many different types of brain findings. Of interest is that a number of functional brain imaging and electrophysiology studies have identified greater heterogeneity in response to stimuli between individuals in the ASC group than individuals in the neurotypical control group [163,164]. This may make more sense from the point of view of non-linear response—i.e. a disproportionality between output and input (as well as state and context sensitivity), in a pathophysiologically perturbed brain system. Nonlinearity has also been a significant methodological issue in EMF/RFR research because linear methods of study design and data analysis have often been insensitive to effects, whereas nonlinear methods have been argued to show greater sensitivity [165–175].

It is important to entertain how environmental agents could contribute individually and synergistically to brain changes in ASCs, how different exposures may disturb physiology similarly or differently, and how these changes may develop over progress over time after the earliest periods in brain development. EMF/RFR exposures could be preconceptional, prenatal or postnatal—or all of the above; it is conceivable that this could be the case in ASCs as well.

2.1.4.3. Altered development. There is some evidence for altered brain and organism development in relation to EMF/RFR exposure. Aldad et al. [83] exposed mice in-utero to cellular telephones, with resultant aberrant miniature excitatory postsynaptic currents, and dose-responsive impaired glutamatergic synaptic transmission onto layer V pyramidal neurons of the prefrontal cortex [83]. Lahijani exposed preincubated chicken embryos to 50 Hz EMFs, and made the following morphological observations: "*exencephalic embryos, embryos with asymmetrical faces, crossed beak, shorter upper beak, deformed hind limbs, gastroschesis, anophthalmia, and microphthalmia. H&E and reticulin stainings, TEMS, and SEMs studies indicated EMFs would create hepatocytes with fibrotic bands, severe steatohepatitis, vacuolizations, swollen and extremely electron-dense mitochondria, reduced invisible cristae, crystalized mitochondria with degenerated cristae, myelin-like figures, macrophages engulfing adjacent cells, dentated nuclei, nuclei with irregular envelopes, degenerated hepatocytes, abnormal lipid accumulations, lipid droplets pushing hepatocytes' nuclei to the corner of the cells, abundant cellular infiltrations cellular infiltrations inside sinusoid and around central veins, disrupted reticulin plexus, and release of chromatin into cytosol, with partially regular water layers, and attributed cell damage to elevated free radical induced cell membrane disruptions*" [5].

Although it is of great interest to characterize the changes in development associated with ASCs, it is also difficult to do in human beings because at present diagnosis is not possible until at least 2–3 years after birth. By now there have been a lot of prospective studies of infants at high risk for autism, but the in vivo brain imaging and electrophysiology data from these studies is only starting to be published, and so the for now the main sources of information are still inference backwards from post-mortem or imaging data, and animal models, both of which have clear limitations. Thus it is impossible to seek precise parallels here between what we know about the development of ASCs compared with the impacts of EMF/RFR exposures.

Nevertheless it is of real concern that such exposures have elicited some of the brain tissue changes that have been documented in ASCs, both in early development and subsequently. Already noted above is the question of whether high exposures of neonates to monitoring equipment may affect the melatonin levels of neonates [32]; these exposures also impact heart rate variability [258]. There are no studies yet on infants exposed to baby surveillance monitors or DECT wireless phones. However there are good laboratory testing studies yielding actual measurements of these devices that conclude: "*Maximum incident field exposures at 1 m can significantly exceed those of base stations (typically 0.1–1 V/m). At very close distances the derived or reference exposure limits are violated for baby surveillance monitors and DECT phones. Further, the authors conclude that, based on very strictly controlled laboratory testing of everyday devices like baby monitors and some cordless phones (W)orse case peak spatial SAR values are close to the limit for the public or uncontrolled environments, e.g., IEEE 802.11b and Bluetooth Class I*" [176].

Even exposure of the fetus to laptop computer wireless emissions through the pregnant mother's use of this device on her lap may involve induction of strong intracorporeal electric current densities from the power supply possibly even more than the device itself [177].

2.1.4.4. Brain blood flow and metabolism. Cerebral perfusion and metabolism abnormalities have been identified in close to two dozen papers studying autistic cohorts. Cerebral perfusion refers to the quantity of blood flow in the brain. Abnormal regulation of cerebral perfusion is found in a range of severe medical conditions including tumors, vascular disease and epilepsy. Cerebral hypoperfusion has also been found in a range of psychiatric disorders [178]. Neurocognitive hypotheses and conclusions, as well as localization of perfusion changes, have been heterogeneous across these papers. Hypoperfusion or diminished metabolism has been identified in frontal regions [179–184], temporal lobes [179,181,183–190], as well as a variety of subcortical regions including basal ganglia [181,188,189], cerebellum [188], limbic structures [184,191] and thalamus [188,189,191]—i.e. in a widely distributed set of brain regions. Possibly because virtually all of these studies were oriented toward testing neuropsychological rather than pathophysiological hypotheses, there were no probes or tests reported to unearth the tissue level alterations that might be underlying these reductions in blood flow in these brains.

While a large number of animal studies have documented blood–brain barrier (BBB) abnormalities from EMF/RFR exposures, only a few PET studies have been performed evaluating EMF exposure effects upon brain glucose metabolism. Volkow et al. performed PET scans both with and without EMF exposure (50 min of GSM-900 with maximum SAR of 0.901 W/kg), and the participants were blinded to the exposure situation [192]. A 7% increase in metabolism in the exposure situation compared to controls was identified regionally on the same side of the head as where the mobile phone was placed. The strength of the E-field from the phones correlated positively with the brain activation, which the authors hypothesized was from an increase in brain neuron excitability. A subsequent smaller study by Kwon et al. demonstrated not increased but decreased brain ^{18}FDG uptake after GSM-900 exposure [193].

Many possible mechanisms could be involved in the metabolic and perfusion abnormalities identified, ranging from altered neuronal activity that was hypothesized in the Volkow et al. [192] ^{8}FDG PET study to narrowing of vascular lumen in the setting of reduced perfusion. Underlying tissue pathophysiology-based phenomena could influence the measurable metabolism and perfusion abnormalities, via mechanisms such as excitotoxicity, cell stress response, constriction of capillary lumen by activated astrocytes, volume effects of vascular extravasation, subtle alterations in blood viscosity due to immune or oxidative stress-associated blood chemical changes, with other possibilities as well. Differences in findings between papers could relate at least in part to study design and nonlinearity issues.

2.1.5. Electrophysiology perturbations

At this stage the argument we hit a key pivot point, where we look at how the alterations in molecular, cellular and systems physiological function, which occur in the brain as well as in the body, impact the transduction into the electrical signaling activities of the brain and nervous system. Certainly the cells and tissues whose physiological challenges we have already discussed provide the material substrate for the electrical activity. Although ASC behaviors are influenced by many factors, they must in principle be mediated through nervous system electrophysiology.

If the cells responsible for generating synapses and oscillatory signaling are laboring under cellular and oxidative stress, lipid peroxidation, impaired calcium and other signaling system abnormalities, then mitochondrial metabolism will fall short, all the more so because of the challenges from the immune system which in turn be triggered to a major extent by environment. How well will synaptic signals be generated? How well will immune-activated and thereby distracted glial cells be able to modulate synaptic and network activity? [194–197].

At present we are in the early stages of being able to formulate these questions well enough to address them empirically. We do know that microglial activation can impact excitatory neurotransmission mediated by astrocytes [198]. We do know that the cortical innate immune response increases local neuronal excitability and can lead to seizures [199,200]. We do know that inflammation can play an important role in epilepsy [201]. We know less about lower levels of chronic or acute pathophysiological dysfunction and how they may modulate and alter the brain's electrophysiology.

2.1.5.1. Seizures and epilepsy. EEG signals in ASCs are abnormal on a variety of levels. At the most severe level, EEGs show seizure activity. Although less than 50% of people with ASCs clearly have seizures or epilepsy a much larger number have indications of epileptiform activity, and an even larger percent have subclinical features that can be noted by a clinical epileptologist though not necessarily flagged as of clinical concern. In addition to the association of some severe epilepsy syndromes (e.g. Landau Kleffner, tuberous sclerosis) with autism, the risk of epilepsy is substantially higher in people with ASCs than in the general population, with a large subset of these individuals experiencing seizure onset around puberty, likely in relation to aberrations in the dramatic and brain-impactful hormonal shifts of that phase of life. Epileptic seizures can be both caused by and cause oxidative stress and mitochondrial dysfunction. Seizures can cause extravasation of plasma into brain parenchyma [202–206] which can trigger a vicious circle of tissue damage from albumin and greater irritability, as discussed above. Evidence suggests that if a BBB is already disrupted, there

will be greater sensitivity to EMF/RFR exposure than if the BBB were intact [207,208], suggesting that such exposures can further exacerbate vicious circles already underway.

The combination of pathophysiological and electrophysiological vulnerabilities has been explored in relation to the impact of EMF/RFR on people with epilepsy EMF/RFR exposures from mobile phone emissions have been shown to modulate brain excitability and to increase interhemispheric functional coupling [209,210]. In a rat model the combination of picrotoxin and microwave exposure at mobile phone-like intensities led to a progressive increase in neuronal activation and glial reactivity, with regional variability in the fall-off of these responses three days after picrotoxin treatment [211], suggesting a potential for interaction between a hyperexcitable brain and EMF/RFR exposure.

One critical issue here is nonlinearity and context and parameter sensitivity of impact. In one study, rat brain slices exposed to EMF/RFR showed reduced synaptic activity and diminution of amplitude of evoked potentials, while whole body exposure to rats led to synaptic facilitation and increased seizure susceptibility in the subsequent analysis of neocortical slices [212]. Another study unexpectedly identified enhanced rat pup post-seizure mortality after perinatal exposure to a specific frequency and intensity of exposure, and concluded that apparently innocuous exposures during early development might lead to vulnerability to stimuli presented later in development [213].

2.1.5.2. Sleep. Sleep involves a profound change in brain electrophysiological activity, and EEG abnormalities including disrupted sleep architecture figure in sleep challenges in ASCs. Sleep symptoms include bedtime resistance, sleep onset delay, sleep duration and night wakings; and sleep architecture can involve significantly less efficient sleep, less total sleep time, prolonged sleep latency, and prolonged REM latency [214,215], with these sleep problems being worse in children with ASCs who regressed than in those who did not regress into their autism [215]. EEG abnormalities have also been associated with EMF/RFR exposure, including disrupted sleep architecture as well as changes in sleep spindles and in the coherence and correlation across sleep stages and power bands during sleep [216,217].

Sleep disturbance symptoms are also common in both situations. Insomnia is commonly reported in people who are chronically exposed to low-level wireless antenna emissions. Mann and Rosch reported an 18% reduction in REM sleep, which is key to memory and learning functions in humans [321]. In ASCs sleep difficulties are highly pervasive and disruptive not only to the affected individual but also to their whole family due to the associated problems such as noise (e.g. screaming at night) and the need for vigilance.

The multileveled interconnections involved in the modulation of sleep exemplify the interconnectedness of the many levels of pathophysiology reviewed here: "*Extracellular ATP associated with neuro- and glio-transmission, acting via purine type 2 receptors, e.g., the P2X7 receptor, has a role in glia release of IL1 and TNF. These substances in turn act on neurons to change their intrinsic membrane properties and sensitivities to neurotransmitters and neuromodulators such as adenosine, glutamate and GABA. These actions change the network input-output properties, i.e., a state shift for the network*" [218]. With disturbance simultaneously at so many of these levels, it is not surprising that sleep dysregulation is nearly universal in ASCs, and common in the setting of EMF/RFR exposures.

2.1.5.3. Quantitative electrophysiology. While clinical reading of EEG studies is done visually, a growing number of studies are examining EEG and MEG data using digital signal processing analysis to find not only epilepsy, but also abnormalities in the power spectrum, i.e. the distribution of power over the different frequencies present, with some studies showing impaired or reduced gamma-and activity [219–221] and others showing reduction of spectral power across all bands [222] while still others showed increased high-frequency oscillations [223]. Abnormalities in coherence and synchronization between various parts of the brain have been found [224–226], comparable to abnormal functional connectivity measured by fMRI [227] but measurable with higher temporal resolution using EEG or MEG [228–232]. Several studies have identified reduced complexity and increased randomness in EEGs of people with ASCs [233,234], as well as an increase in power but a reduction in coherence [229,235]. Some electrophysiological metrics are emerging as potential discriminators between brain signal from individuals with ASCs and those who are neurotypical, such as a wavelet-chaos-neural network methodology applied to EEG signal [236] and reduced cross-frequency coupling [237].

EMF/RFR also has impacts at levels of brain function measurable by these techniques. At various frequencies and durations of exposure it has been noted to impact alpha and beta rhythms [238], to increase randomness [170,239], to alter power, to modulate interhemispheric synchronization [240], to alter electrical activity in brain slices [241] and to alter the patterns of coordination (spectral power coherence) across the major power bands [242]. Bachman et al. [243] showed statistically significant changes in EEG rhythms and dynamics occurred in between 12% and 20% of healthy volunteers [243]. In children, exposures to cell phone radiation have resulted in changes in brain oscillatory activity during some memory tasks [97,102].

2.1.5.4. Sensory processing. Symptomatic level issues with sensory processing are highly prevalent in ASCs and can include hypersensitivity to external stimuli, hyposensitivity to internal sensations and difficulty localizing sensation including pain, and difficulty processing more than one sensory channel at one time [244–246]. There is now electrophysiological evidence of abnormalities at early (brainstem) stages of sensory processing, as well as in later stages of processing that occur in the cortex [247]. Some studies have

shown lower and some longer latencies of response to an auditory stimulus [247]. Domains of perception where the performance of people with ASCs is superior to that of neurotypical individuals have been identified [248]. "*It is . . . probable that several mechanisms and neuronal abnormalities, most likely at multiple levels (from single neurons through to inter-area connections), all contribute to varying degrees to the abnormal sensory processing observed in ASD. It is also likely that no single mechanism is unique to one sensory modality, which is why we see such a widely distributed range of abnormalities across modalities*" [247].

It is also possible that the mechanisms may not simply be neural—they may also be modulated by glial, metabolic, immune, perfusional and other physiological processes by common underlying cellular abnormalities, and by physical properties as well. Yet there are few studies focusing upon the interface of tissue pathophysiology with electrophysiology.

Kenet et al. demonstrated environmental vulnerability of sensory processing in the brain by the exposure of rat dams to noncoplanar polychlorinated biphenyls (PCBs), during gestation and for three subsequent weeks of nursing [247]. The rat pups showed normal hearing sensitivity and brainstem auditory responses, but their tonotopic development of the primary auditory cortex was grossly distorted [249]. This study may be particularly relevant for EMF/RFR exposures, as Pessah, a co-author on this Kenet et al. [249] paper, was cited earlier as documenting how the noncoplanar PCBs used in this experiment target calcium signaling as do EMF/RFR exposures—i.e. they both converge upon a common particularly critical cellular mechanism [250,251].

2.1.5.5. Autonomic dysregulation. Although there are a fair number of negative studies regarding the impact of EMF/RFR exposure on the autonomic nervous system, increased HRV and autonomic disturbances have been documented [252–256]. Buchner and Eger [257], in a study in rural Germany of the health impacts of exposures from a new base station yielding novel exposure to EMF/RFR, saw a significant elevation of the stress hormones adrenaline and noradrenaline during the first six months with a concomitant drop in dopamine, with a failure to restore the prior levels after a year and a half. These impacts were felt by the young, the old and the chronically ill, but not by healthy adults [257].

Neonate vulnerability was documented by Bellieni et al. [258] who found that heart rate variability is adversely affected in infants hospitalized in isolettes or incubators where ELF-EMF levels are in the 0.8 to 0.9 μT range (8 to 9 mG). Infants suffer adverse changes in heart rate variability, similar to adults [258]. This electromagnetic stress may have lifelong developmental impacts, based on a study showing that in-utero beta 2 agonist exposure can potentially induce a permanent shift in the balance of sympathetic-to-parasympathetic tone [259].

Meanwhile clinical observation and a growing body of literature support a major role for stress in ASCs [260–263], with variability amongst individuals in the severity of the stress response but a tendency to have high tonic sympathetic arousal at baseline [264–269].

The impact of EMF/RFR exposure can also be greatly influenced by the stress system status of the individual being exposed. Tore et al. sympathecotomized some of his rats before exposure to GSM, to simulate cell phone exposure [207,208]. Sympathectomized rats, which were in a chronic inflammation-prone state, had more prominent albumin leakage than sham-exposed rats. However in the sympathecotmized rats who were exposed to GSM, albumin leakage was greatly increased, to levels resembling those observed in positive controls after osmotic shock. Salford et al. [99] suggest that "*. . .more attention should be paid to this finding, since it implicates that the sensitivity to EMF-induced BBB permeability depends not only on power densities and exposure modulations, but also on the initial state of health of the exposed subject*" [99].

The interconnection between stress and brain connectivity (or coherence) in ASCs is brought out by Narayanan et al. in a pilot study testing the impact of the beta blocker propranolol on brain functional connectivity measured using functional MRI [270]. A fairly immediate increase in functional connectivity was noted from propranolol—but not from nadolol which has the same vascular effects but does not cross the BBB. Propranolol decreases the burden of norepinephrine, thereby reducing the impact of stress systems on brain processing, and the authors interpreted these effects as creating an improvement of the brain's signal-to-noise ratio [271], allowing it to utilize and coordinate more remote parts of its networks. This suggests that stressors such as EMF/RFR, by adding biologically non-meaningful noise to the system, might have the opposite effects, degrading coherent integration.

2.2. De-tuning of the brain and organism

2.2.1. Electromagnetic signaling, oscillation and synchrony are fundamental, and vulnerable

While electrophysiological activity is an intrinsic property of the nervous system, electromagnetic signaling is a vital aspect of every cell and of molecular structure.

All life on earth has evolved in a sea of natural low-frequency electromagnetic (EM) fields. They originate in terrestrial and extraterrestrial sources. The ever-growing use of electric power over the last century has sharply modified this natural environment in urban settings. Exposure to power-frequency fields far stronger than the natural environment is now universal in civilized society. [272]

Adey published some of the earliest scientific studies on the "cooperativity" actions of cells in communication. Studies showing us that the flux of calcium in brain tissue and immune cells is sensitive to ELF-modulated radiofrequency fields is actually telling us that some of the most fundamental properties of cells and thus of our existence can be modulated by EMF/RFR. "*. . .in first detection of environmental*

EM fields in tissues, there appears to be a general consensus that the site of field action is at cell membranes. Strands of protein are strategically located on the surface of cells in tissue, where they act as detectors of electrical and chemical messages arriving at cell surfaces, transducing them and transmitting them to the cell interior. The structural basis for this transductive coupling by these protein strands is well known. Through them, cell membranes perform a triple role, in ***signal detection, signal amplification, and signal transduction to the cell interior***" [272].

Oscillation is also a universal phenomenon, and biological systems of the heart, brain and gut are dependent on the cooperative actions of cells that function according to principles of non-linear, coupled biological oscillations for their synchrony, and are dependent on exquisitely timed cues from the environment at vanishingly small levels [273,274]. The key to synchronization is the joint actions of cells that co-operate electrically - linking populations of biological oscillators that couple together in large arrays and synchronize spontaneously according to the mathematics described for Josephson junctions (Brian Josephson, the 1993 Nobel prize winner for this concept). This concept has been professionally presented in journal articles and also popularized in a book by Prof. Steven Strogatz, a mathematician at Cornell University who has written about 'sync' as a fundamental organizing principle for biological systems [274,275]. "*Organisms are biochemically dynamic. They are continuously subjected to time-varying conditions in the form of both extrinsic driving from the environment and intrinsic rhythms generated by specialized cellular clocks within the organism itself. Relevant examples of the latter are the cardiac pacemaker located at the sinoatrial node in mammalian hearts and the circadian clock residing at the suprachiasmatic nuclei in mammalian brains. These rhythm generators are composed of thousands of clock cells that are intrinsically diverse but nevertheless manage to function in a coherent oscillatory state. This is the case, for instance, of the circadian oscillations exhibited by the suprachiasmatic nuclei, the period of which is known to be determined by the mean period of the individual neurons making up the circadian clock. The mechanisms by which this collective behavior arises remain to be understood*" [274].

The brain contains a population of oscillators with distributed natural frequencies, which pull one another into synchrony (the circadian pacemaker cells). Strogatz has addressed the unifying mathematics of biological cycles and external factors disrupt these cycles. Others have discussed how this also applies to mitochondria: "*Organisation of mitochondrial metabolism is a quintessential example of a complex dissipative system which can display dynamic instabilities. Several findings have indicated that the conditions inducing instabilities are within the physiological range and that mild perturbations could elicit oscillations. Different mathematical models have been put forth in order to explain the genesis of oscillations in energy metabolism. One model considers mitochondria as an organised network of oscillators and indicates that communication between mitochondria involves mitochondrial reactive oxygen species (ROS) production acting as synchronisers of the energy status of the whole population of mitochondria. An alternative model proposes that extramitochondrial pH variations could lead to mitochondrial oscillations*" [276].

Mitochondrial dysfunction is important in ASCs but is usually conceptualized in purely biochemical terms without mentioning any oscillatory dimension to mitochondrial activity; it is conceivable that the interplay between biochemistry and oscillation could figure significantly in the mechanisms of impact of EMF/RFR in ASCs.

The field of bioelectromagnetics has studied exposure to very low levels of electromagnetic frequencies. Exposures can alter the magnetokinetics of the formation of a chemical bond, shifting the rate and amount of product produced [272].

Not just chemical reactions but synchronous biological oscillations in cells (pacemaker cells) can be disturbed and disrupted by artificial, exogenous environmental signals, which can lead to desynchronization of neural activity that regulates critical functions (including metabolism) in the brain, gut and heart and circadian rhythms governing sleep and hormone cycles [277]. Buzsaki in his book *Rhythms of the Brain* says "*rhythms can be altered by a wide variety of agents and that these perturbations must seriously alter brain performance*." [273].

Disturbance can get increasingly disruptive as more damage occurs and more systems are thrown out of kilter and out of cooperativity. One can think of the kindling model in which repeated induction of seizures leads to longer and more severe seizures and greater behavioral involvement. The combination of disruptive and stimulatory effects of biologically inappropriate EMF/RFR exposures could contribute to disruption of synchronized oscillation and cooperativity at a myriad of levels but particularly in the brain, and this may contribute to the loss of coherence and complexity in the brain in autism, as well as dysregulation of multiple other bodily systems. Strogatz points out that there are many more ways of being desynchronized than of being synchronized [274] (which may relate to ASC's great heterogeneity). It has even been suggested that autism itself could be due to brain desynchronization [278].

2.2.2. *Behavior as an "emergent property"*

From a pathophysiological point of view one might hypothesize that a brain with greater indications of oxidative stress along with immune activation and mitochondrial dysfunction might generate different oscillatory activity than a brain in which those pathophysiological features were absent. From this vantage point it would make sense to propose that the compromised whole body health status of at least many with ASCs would make it harder for them to maintain the resilience of their brain cells and brain activities in the face of potentially disruptive exposures. Yet the investigation of how this might occur remains a largely unexplored frontier. But

from the point of view of making sense of the brain impact of environmental challenges – including but not limited to EMF-RFR – this investigation is crucial.

The pathophysiological perspective that guides this review would suggest a move away from considering the behavioral manifestations of ASCs as core, intrinsic, 'hard-wired traits.' *Instead behaviors may be better understood as 'outputs' or emergent properties – what the brain and body produce – when their physiological attributes are altered* in these fashions for whatever reasons—be they genetic, environmental or many combinations of both [279–284]. Sleep and consciousness have also been considered 'emergent properties' [285,286]. Brain oscillatory activity is critical for organizing behavior, and it arises from cells and subcellular features that are shaped by the environment and can act differently based on their functional status as well as on account of external sensory or psychosocial stimuli.

In particular, (a) brain oscillatory activity is intimately connected with underlying cellular, metabolic and immune status, (b) EMF/RFR is capable of perpetrating changes at each of these levels, and (c) problems at each of these levels can make other problems worse. And as mentioned earlier, EMF/RFR and various toxicants can co-potentiate damage [287–294], amplifying 'allostatic load'.

Put together, all of this implies that the combination of these EMF/RFR impacts may quite plausibly significantly contribute both to how ASCs happen in individuals and to why there are more reported cases of ASCs than ever before (1200–1500% increase in reported cases over the past 15–20 years, with studies showing that a substantial portion of this increase (45–65%) cannot be written off as artifact and may well represent true increases [295,296]).

The hopeful side of this framing of the problem comes from moving beyond the increasingly anachronistic idea that autism is determined overwhelmingly by genetic code about which we can do little or nothing. An emerging model that explains much more of what we now know frames ASCs as the dynamic, active outcomes of perturbed physiological processes – again, more like a chronic but changeable 'state' than a 'trait.' In the latter model, one is empowered – and motivated – to strongly reduce exposures and to make aggressive constructive environmental changes – particularly in diet and nutrition, given their protective potency discussed above [297]. In this way 'allostatic load' can be reduced, physiological damage can be repaired, homeostasis can be restored and resilience and optimal function can be promoted.

3. Implications

3.1. Exposures and their implications

Several thousand scientific studies over four decades point to serious biological effects and health harm from EMF and RFR [298,299]. These studies report genotoxicity, single-and double-strand DNA damage, chromatin condensation, loss of DNA repair capacity in human stem cells, reduction in free-radical scavengers (particularly melatonin), abnormal gene transcription, neurotoxicity, carcinogenicity, damage to sperm morphology and function, effects on behavior, and effects on brain development in the fetus of human mothers that use cell phones during pregnancy. Cell phone exposure has been linked to altered fetal brain development and ADHD-like behavior in the offspring of pregnant mice [83].

3.1.1. Exposures have outpaced precautions

There is no question that huge new exposures to EMF/RFRs have occurred over the past few decades. As discussed extensively in the BioInitiative 2012 update [299], there is much concern that regulations to date have been based on a very limited sense of the pertinent biology, and particularly that limiting concern to thermal impacts is no longer valid since there is a wealth of evidence by now that non-thermal impacts can be biologically very powerful. Only in the last two decades have exposures to RFR and wireless technologies become so widespread as to affect virtually every living space, and affect every member of societies around the world. Even as some disease patterns like brain tumors from cell phone use have become 'epidemiologically visible', there are no comprehensive and systematic global health surveillance programs that really keep up to report EMF/RFR health trends [300].

The deployment of new technologies is running ahead of any reasonable estimation of possible health impacts and estimates of probabilities, let alone a solid assessment of risk. However, what has been missing with regard to EMF/RFR has been an acknowledgement of the risk that is demonstrated by the scientific studies. There is clear evidence of risk, although the magnitude of the risk is uncertain, and the magnitude of doing nothing on the health effects cost to society is similarly uncertain. This situation is very similar to our history of dealing with the hazards of smoking decades ago, where the power of the industry to influence governments and even conflicts of interest within the public health community delayed action for more than a generation, with consequent loss of life and enormous extra health care costs to society. [301].

3.1.2. The population's exposure has increased

The very rapid global deployment of both old and new forms of emerging wireless technologies in the last two decades needs aggressive evaluation from a public health perspective, given the range of physiological impacts described in Section 2.

In the United States, the deployment of wireless infrastructure (cell tower sites) to support cell phone use has accelerated greatly in the last decades. The Cellular Telephone Institute of America (CTIA) estimated that in 1997 there were only 36,650 cell sites in the US; but increased rapidly to 131,350 in June 2002; 210,350 in June 2007 and 265,561 in June 2012 [302,303]. About 220,500 cell sites existed in 2008 [303–305]. These wireless facilities for cellular phone voice

and data transmission produce RFR over broad areas in communities and are an involuntary and unavoidable source of whole-body radiofrequency radiation exposure. Other new RFR exposures that did not exist before are from WI-FI access points (hotspots) that radiate 24/7 in cafes, stores, libraries, classrooms, on buses and trains, and from personal WI-FI enabled devices (iPads, tablets, PDAs, etc).

Not surprisingly, the use of cell phones has a parallel growth trend. In the late 1980s and early 1990's, only a few percent of the US population were cell phone users. By 2008, eighty-four percent (84%) of the population of the US owned cell phones. CTIA reports that wireless subscriber connections in the US increased from 49 million in June 1997 to 135 million in June 2002 to 243 million in June 2007 to 322 million in June 2012 [302,303]. This represents more than a 100% penetration rate in the US consumer market, up from just a few percent in the early 1990's. The number of wireless subscribers in June 1997 was 18%; in June 2002 it was 47%; in June 2007 it was 81% and in June 2012 it was 101%.

The annualized use of cell phones in the US was estimated to be 2.23 trillion minutes in 2008 and 2.296 trillion minutes in 2010 [303]. There are 6 billion users of cell phones worldwide in 2011 up from 2.2 billion in 2008 and many million more users of cordless phones.

The number of US homes with *only* wireless cell phones has risen from 10.5% in 2007 to 31.6% in June of 2012 [302,303]. There are no statistics for June 1997 nor for June 2002, since landline (non-wireless) phone use predominated. The shift to wireless communications, more minutes of use, and reliance on cell and cordless phones rather than corded phones is an extremely revealing measure of new EMF and RFR exposures for both adults and children.

The prevalence of autism has risen in parallel from one (1) in 5000 (1975) to 1 in 2500 (1985) to 1 in 500 (1995) to 1 in 250 (∼2001) to 1 in 166 (∼2004) to 1 in 88 (∼2008) to 1 in 50 (∼2013). All reflected birth cohorts born earlier[1,2]. Further research into autism prevalence studies have debunked the initial contention that higher numbers could be explained away by better diagnosis and broadening of diagnostic criteria[3-6].

3.1.3. Infants, children and childbearing families are highly exposed and vulnerable

The spread of cell towers in communities, often placed on pre-school, church day-care, and school campuses, means that young children may have hundreds of thousands of times higher RFR exposures in home and school environments than existed even 20–25 years ago. In addition, the nearly universal switch to cordless and cell phones, and away from corded landline phones, means that people are experiencing close and repetitive exposures to both EMF and RFR in the home [306]. Wireless laptops and wireless internet in schools, and home offices and for homework mean even more chronic exposures to RFR, a designated IARC 2B Possible Human Carcinogen [307,308]. The great utility of handheld devices as communication aids and engaging sources of information and satisfaction for people on the autism spectrum may come with a concerning biologically harmful underbelly.

Exposures prior to conception or during pregnancy and infancy can come from faulty wiring, proximity to power lines, or high-frequency transients from a proximate transformer on a utility pole. Sources of pulsed RFR inside the home include an electronic baby monitor in the crib, a wireless router in the next room, a DECT phone that pulses high emissions of RFR on a continuous basis 24/7, or conversion to all compact fluorescent bulbs that produce significant 'dirty electricity' for occupants due to low-kilohertz frequency fields on electrical wiring and in ambient space. Sick and vulnerable infants in neonatal intensive care units are heavily exposed from being surrounded by equipment, with negative metabolic and autonomic consequences documented [32,258].

Wireless phones and laptops exposures produce extremely low frequency pulses from the battery of the wireless device [301,306,309] and the exposures to pulsed radiofrequency microwave radiation when the wireless device is transmitting or receiving calls and emails.

Especially since EMF/RFR exposures are already classified as IARC 2B Possible Human Carcinogens, we should be actively investigating these sources of damage to DNA that could reasonably result in 'de novo mutations' but also be aware that common environmental exposures from EMF and RFR might play a role in the higher rates of concordance for autism (ASD) among twins and siblings.

Researchers also should be aware that common environmental exposures from EMF and RFR might play a role in the higher rates of autism (ASD) among twins and siblings, not solely because of maternal use of wireless devices during pregnancy and paternal sperm exposure to wireless devices peri-conception; but also because such oxidative damage to DNA can occur at levels introduced into the world of the fetus, and young developing infant and child via baby surveillance monitoring devices in the crib and wireless devices in the home. The deployment of technologies poses risks to human fertility and reproduction capacity, to the fetus, to children and adults [301].

3.1.4. ASC risk and genomic damage to future generations

Barouki and Grandjean make a persuasive case that public health interventions are critically needed in early childhood development to prevent adult diseases that appear decades later [310]. Although they do not include EMF or RFR but only chemicals, they do say that physiological stressors, which EMF and RFR certainly have been established, should be reduced during critical development windows. They say: "*The current pandemic of non-communicable diseases and the increased prevalence of important dysfunctions demand an open interrogation of why current interventions appear insufficient. We now know that disease risk can be induced very early in the life course and that it is modifiable by*

nutrients and environmental chemical exposures (along with drugs. infections, and other types of stresses)" [310].

Public health interventions are warranted now to protect the genetic heritage of humans, as well as the other stocks of genetic material in wildlife and plants in the face of what appears to be on-going impairment of these genomes. The risk of genomic damage for future generations is sufficiently documented to warrant strong preventative action and new public safety limits that observe EMF/RFR levels shown to cause adverse effects.

3.1.5. De-tuning the organism

Genetic mutations may lead to cancer and other diseases in the present and future generations, but the exposures that are capable of creating genotoxic impacts also compromise physiological function. Even genotoxicity can have not only specific but also non-specific effects due to molecular inefficiencies, misfolded proteins, and cellular debris [311,312].

In the setting of autism, a baby gestated or developing as a neonate in a milieu with excessively elevated EMF/RFR exposures is vulnerable to interference with the normal development processes, including the organization of information and experience in the brain. This baby's environment also often includes nutritional insufficiencies (processed denatured pesticide-laden food low in antioxidants, minerals and essential fatty acids essential to cellular protection). The baby's gestational period may have been complicated by the mother's own health issues such as conditions like obesity and diabetes [313] which converge upon on inflammation, oxidative stress and other common forms of physiological dysregulation. The exquisite 'tuning up' of the brain and body as it develops will integrate and respond to the environmental inputs it receives, and is particularly sensitive to environmental miscues (whether chemical like endocrine disruptors, EMF/RFR which can be both chemically and electromagnetically disruptive, or other environmental conditions whether hostile or nurturing). To the extent that the baby is burdened with more disorganized or hostile cues than nurturing and organizing cues, that baby may lose resiliency and become more physiologically vulnerable –perhaps approaching a tipping point into decompensation such as autistic regression or development of other chronic disease processes.

From a systems point of view, the phenomenon of 'autistic regression' can be understood as occurring after an accumulation of multisystem signaling interference leading to a tipping point of loss of some vital systems synchronization and increase in randomization. EMF/RFR exposures could plausibly contribute both to this vulnerability and to the decompensation/desynchronization process – as could other stressors such as infection, toxicity, acute stress. The vulnerability, then, is the 'allostatic load' – the total burden of stressors pressing toward disorganization. The tipping point may come in a variety of ways; but upon investigation one is likely to find that unless a stressor is severe, the trigger most proximally associated with the decompensation is likely to be the 'straw that breaks the camel's back' laid atop a prior accumulation of 'allostatic load.'

3.2. Conclusions and recommendations

The case has been made that ASCs involve physiological challenges at multiple levels, and that these challenges are paralleled in the physiological impacts of EMF/RFR exposure. Evidence has also been presented to suggest that the many levels of damage and degradation of physiological and functional integrity are profoundly related to each other. Although autism spectrum conditions (ASCs) are defined by problems with behavior, communication, social interaction and sensory processing, under the surface they also involve a range of disturbances of underlying biology that find striking parallels in the physiological impacts of electromagnetic frequency and radiofrequency radiation exposures (EMF/RFR). At the cellular and molecular level many studies of people with ASCs have identified oxidative stress and evidence of free radical damage, evidence of cellular stress proteins, as well as deficiencies of antioxidants such as glutathione. Elevated intracellular calcium in ASCs can be associated with genetic mutations but more often may be downstream of inflammation or chemical exposures. Cell membrane lipids may be peroxidized, mitochondria may function poorly, and immune system disturbances of various kinds are common. Brain oxidative stress and inflammation as well as measures consistent with blood–brain barrier and brain perfusion compromise have been documented. Changes in brain and autonomic nervous system electrophysiology can be measured and seizures are far more common than in the population at large. Sleep disruption and high levels of stress are close to universal. In parallel, all of these phenomena have also been documented to result from or be modulated by EMF/RFR exposure. Moreover, some people with ASCs have de novo mutations (that their parents do not have), and EMF/RFR exposures could contribute to this due to their potential genotoxicity. EMF/RFR exposure during pregnancy may send spurious signals to developing brain cells during pregnancy, altering brain development during critical periods, and may increase oxidative stress and immune reactivity that can increase risk for later developmental impairments, with further disruption later in development increasing risk, physiological dysregulation and severity of outcome.

All of this does not prove that EMF/RFR exposures cause autism, but it does raise concerns that they could contribute by increasing risk, and by making challenging biological problems and symptoms worse in these vulnerable individuals. Placed alongside the dramatic rise in reported cases of ASCs [333], that parallels the dramatic rise in deployment of wireless technologies, a strong case can be made for aggressively investigating links between ASCs and EMR/RFR, and minimizing exposures for people with autism as well as families preconceptionally, during pregnancy, and around infants and children at home, at school, and in health care centers and hospitals.

These arguments have implications for how we understand what ASCs 'are' and how they work, including an appreciation that it may be the physiological disturbance is what actually generates the 'autism' on a moment-to-moment basis—and that these physiological disturbances are profoundly driven by environmental insults. These implications call upon us to take the environmental contribution very seriously, which involves on the one hand a sobering appreciation of the vast array of exposures that can contribute to risk via perturbed development and physiological degradation, and on the other hand a sense that there are powerful things we can do to reduce risk and improve the situation.

3.2.1. Change our deployment of EMF/RFR

The deployment of RFR from wireless technologies has incredible momentum, and it has made many things easier and many other things possible for the first time. On the other hand this momentum can interfere with setting up the technology in a fashion truly respectful of biological tolerances. "*There is no question that global implementation of the safety standards proposed in the Bioinitiative (2007) Report, if implemented abruptly and without careful planning, have the potential to not only be very expensive but also disruptive of life and the economy as we know it. Action must be a balance of risk to cost to benefit. The major risk from maintaining the status quo is an increasing number of cancer cases, especially in young people, as well as neurobehavioral problems at increasing frequencies. The benefits of the status quo are expansion and continued development of communication technologies. But we suspect that the true costs of even existing technologies will only become much more apparent with time. Whether the costs of remedial action are worth the societal benefits is a formula that should reward precautionary behavior*" [301].

3.2.2. Encourage precautions right now based on present knowledge

Physicians and health care workers should raise the visibility of EMF/RFR as a plausible environmental factor in clinical evaluations and treatment protocols. Reducing or removing EMF and wireless RFR stressors from the environment is a reasonable precautionary action given the overall weight of evidence.

- Children with existing neurological problems that include cognitive, learning, attention, memory, or behavioral problems should as much as possible be provided with wired (not wireless) learning, living and sleeping environments,
- Special education classrooms should aim for 'no wireless' conditions to reduce avoidable stressors that may impede social, academic and behavioral progress.
- Adaptations to preserve the attractive design innovations of technologies such as tablet computers in a 'no wireless' environment should be developed.
- All children should reasonably be protected from the physiological stressor of significantly elevated EMF/RFR (wireless in classrooms, or home environments).
- School districts that are now considering all-wireless learning environments should be strongly cautioned that wired environments are likely to provide better learning and teaching environments, and prevent possible adverse health consequences for both students and faculty in the long-term.
- Monitoring of the impacts of wireless technology in learning and care environments should be performed with sophisticated measurement and data analysis techniques that are cognizant of the non-linear impacts of EMF/RFR and of data techniques most appropriate for discerning these impacts.
- There is sufficient scientific evidence to warrant the selection of wired internet, wired classrooms and wired learning devices, rather than making an expensive and potentially health-harming commitment to wireless devices that may have to be substituted out later, and
- Wired classrooms should reasonably be provided to all students who opt-out of wireless environments.

Broader recommendations also apply, related to reducing the physiological vulnerability to exposures, reduce 'allostatic load' and build physiological resiliency through high quality nutrition, reducing exposure to toxicants and infectious agents, and reducing stress [297], all of which can be implemented safely based upon presently available knowledge.

3.2.3. Build an environmentally physiologically centered research program in ASCs as a platform for investigating the EMR/RFR-ASC linkage

This review has been structured around the physiological parallels between ASCs and the impacts of EMF/RFR. What is missing from the autism research agenda is some cross-study of these two bodies of research evidence. To do this we will need both a recognition of the importance of these risks, and a collaborative multi-site research program centered around a "middle-out" physiological approach [314] that can transcend the limits of the gene-brain-behavior agenda that has dominated ASC research, by incorporating this now clearly limited approach into a broader framework [315]. This still dominant gene-brain-behavior approach has been based on an expectation of linear mapping across the levels on which it focuses, but instead the systems involved appear to be much more complex. The middle-out approach is an emerging more inclusive framework in systems biology that can incorporate complexity and nonlinear, multi-scale modeling [316–320]. The physiological levels largely left out in the gene-only approach are critically important to helping people with ASCs because they will help not only with understanding how environment impacts function but also with identifying leverage points.

3.2.4. Take the evidence as a call to action

Both EMF and RFR exposures are already classified as IARC Group 2B Possible Human Carcinogens. The substantial scientific literature on EMF and RFR effects on DNA, on immune and blood–brain barrier disruption, on stress proteins, on circadian rhythms and hormone disregulation, and on cognition, sleep, disruption of neural control and altered brainwave activity all argue for reduction of exposures now, and better coordinated research in these areas. The evidence is sufficiently documented to warrant strong preventative action and new public safety limits that observe EMF/RFR levels shown to cause adverse effects.

All relevant environmental conditions should be given weight in defining and implementing prudent, precautionary actions to protect public health, including EMF and RFR. Evidence is sufficient to add EMF/RFR prominently to the list of exposures that can degrade the human genome, and impair normal development, health and quality of our physiology. With the rising numbers people with ASCs and other childhood health and developmental disorders, we cannot afford to ignore this component of risk to our children and vulnerable populations. When the risk factors are largely avoidable or preventable, ignoring clear evidence of large-scale health risks to global populations poses unnecessary and unacceptable risks. Taking this evidence as a call to action will be challenging and disruptive in the short term, but constructive in the longer term as we learn to use EMF/RFR in healthier ways.

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