SECTION 20

Findings in Autism (ASD) Consistent with Electromagnetic Fields (EMF) and Radiofrequency Radiation (RFR)

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Part 1 - INTRODUCTION

The premise of this review is that although scant attention has been paid to possible links between electromagnetic fields and radiofrequency exposures (EMF/RFR) and Autism Spectrum Disorders (ASDs), 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 ASDs have remarkable similarities. Additional support may be found in the parallels between the rise in reported cases of ASDs and the remarkable increases in EMF/RFR exposures over the past few decades. Reviewing these similarities does not prove that these parallels imply causality – that kind of research has not been done. Moreover, the physiological processes affected by EMF/RFR are also impacted by other environmental factors. Yet EMF/RFR does not need to be a unique contributor to ASDs to add significantly to system overload ('allostatic load') and dysfunction. Even so these pathophysiological overlaps do suggest that the potential for an EMF/RFR-ASD connection should be taken seriously, and that their vulnerable biological features may make many with ASDs more likely to experience adverse EMF/RFR impacts. This is a sufficient basis to recommend that precautionary measures should be implemented and respected, 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 ASDs better and find more ways to improve the lives of people with ASDs and of so many others.

A. How are biology and behavior related?

Considering a potential link between ASDs and EMF/RFR (or indeed of any potential contributor to incidence or pathogenesis) requires taking account of the evolution that has been occurring in our understanding of the relationship between ASD's behavioral and biological features. ASDs 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, characteristic of all 11 of the children in his first case series (Kanner 1943). Although in the seven decades since this condition was first constructed as a category there has been some modification of the way these behavioral features have been characterized, ASDs 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) (American Psychiatric Association 2000, 2013, May).

1. Transduction is fundamental but poorly understood

Yet in considering how an environmental factor such as EMF/RFR could lead to autism and/or influence its severity or incidence, we need to think about how underlying biology is transduced into changes in nervous system electrical activity, and how these in turn generate the set of behaviors we have categorized as 'autism.' {Herbert, 2005 #757} 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. More than brain

Although 'autism' has long been considered to be a psychiatric or neurological brain-based disorder (Rapin and Katzman 1998; Polleux and Lauder 2004), it has become undeniable that people diagnosed with ASDs often also have a multitude of biological features – including systemic pathophysiological disturbances (such as oxidative stress, mitochondrial dysfunction and metabolic and immune abnormalities) (Ming et al. 2012; Tsaluchidu et al. 2008; Pieczenik and Neustadt 2007; Gonzalez et al. 2011) as well as symptomatic medical comorbidities (such as gastrointestinal distress, recurrent infections, epilepsy, autonomic dysregulation and sleep disruption) (Nikolov et al. 2009; Kotagal and Broomall 2012; Kaartinen et al. 2012; Daluwatte et al. 2012; Tuchman and Cuccaro 2011; Canitano 2007; Malow 2004; Kang and Barnes 2013; Jyonouchi et al. 2011) – in addition to the core defining behaviors – and many of these occur commonly (Kohane et al. 2012). The problem has been that no one such biological feature has turned out to be present in every single person carrying an ASD diagnosis – and they are not specific to ASDs, either. Moreover there has been much variability in many of the features of autism – not only between individuals but in many cases within individuals at different points in time or under different circumstances. Because of this variability, the relevance of many of these biological features has been dismissed as secondary and not intrinsically related to the 'autism.' Instead, many have considered the behavioral features as fundamental not only to how autism manifests and is definedbut also to the core intrinsic nature of ASDs, even though the biological basis of these behaviors has by no means been established.

3. Heterogeneity: More Genetic and Environmental than Physiological

It is not as if this variability is unique to the 'environmental side.' At the present time over 800 genes have been associated with ASDs, and over 100 different rare genetic syndromes are frequently accompanied by ASD, with no clear specific unifying mechanism uniting this remarkable heterogeneity (Trikalinos et al. 2006; Ring et al. 2008; Pelphrey et al. 2011; Mandell 2011; Hall et al. 2012; Bill and Geschwind 2009).

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 (Whitehouse et al. 2012; Kocovska et al. 2012; Schmidt et al. 2011; Landrigan 2010; Roberts et al. 2007; Shelton, Hertz-Picciotto, and Pessah 2012; Becerra et al. 2012; Volk et al. 2011). Yet at the physiological level a smaller set of disturbances are showing up as common across substantial numbers of people with ASDs – and in fact not uniquely to ASDs but also in myriad other chronic conditions whose prevalence also appears to be increasing (Bilbo, Jones, and Parker 2012; Knox 2010). Prominent among these are immune disturbances including inflammation, mitochondrial dysfunction, and oxidative stress, as well as toxic body burden. Vulnerability to all of these can be increased mildly or substantially by a variety of often common genetic mutations, but may remain latent without the overlay of environmental triggers. Conversely, with substantial enough environmental input, genetic vulnerability may not be necessary.

4. Mechanism is more than correlation

Just HOW biological features might be related to the behavioral features that have up until now defined ASDs has not been clarified; until recently the main research effort regarding pathophysiology in ASDs has been to establish the presence of these phenomena in the first place. Even so, some correlations between biological and behavioral features have been identified – e.g. a higher level of immune abnormalities correlates with more aberrant behaviors (Wei et al. 2012; Careaga and Ashwood 2012; Jyonouchi et al. 2011; Ashwood et al. 2011; Heuer et al. 2008; Zerrate et al. 2007; Curran et al. 2007). Still, such correlations in themselves do not explain the *mechanisms* by which the *transduction of pathophysiology into behavior* might actually occur. In order to do that, an important component would be to study the relationship between systemic pathophysiology and nervous system electrophysiology.

5. EMF/RFR research may help us understand how ASDs 'work'

Assessing the potential contribution of EMF/RFR to ASDs puts this question of the nature of the pathophysiology-behavior transduction into an interesting and provocative light since 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 ASD research has largely been on 'structure-function' relationships that have been anatomy-centered. This research has generated correlations between brain structures and behaviors, and has found some genetic correlates as well, but it has made assumptions that these phenomena are rooted in genetics and genetically perturbed molecular structures and substances. This leads to

targeting the molecular level with pharmaceuticals, but not to the broader agenda of understanding environmental or physiological contributions or dynamic features of brain and behavior. Thus, exploring how EMF/RFR impacts ASDs may help to force the question of how these pathophysiological and electrophysiological/information processing levels actually interact, and how anatomy may in many ways be a product rather than a cause of physiology.

B. Time courses of mechanisms

For the most part, researchers have 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 ASDs may in many respects be more state-like and variable than trait-like and fixed.

1. Plasticity

One of the remarkable shifts in conceptual thinking about ASDs is an appreciation of its brain plasticity (Helt et al. 2008). 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 (Cobb, Guy, and Bird 2010; Ehninger et al. 2008; Goebel-Goody et al. 2012; Henderson et al. 2012; Kaphzan et al. 2012; Liu, Huang, and Smith 2012; Mehta, Gandal, and Siegel 2011; Paylor et al. 2008; Rotschafer et al. 2012; Sato et al. 2012; Suvrathan et al. 2010), short-term pharmaceutically induced improvement in brain connectivity (Narayanan et al. 2010), and transient reversal or abeyance of symptomatology under various circumstances (including fever, fluid-only diet, and certain antibiotic treatments (Sandler et al. 2000; Curran et al. 2007)) – all of these throw into question the long-standing assumption that we are simply dealing with a 'broken brain.' Indeed, how could a 'broken brain' produce markedly improved function with such a short turnaround time? (Herbert 2009) Such a time frame cannot possibly be accounted for by remodeling of the brain's anatomical substrate. 'Brain waves' and their synchronization, on the other hand, could easily vary over short time periods. Looking into physiological and environmental modulators not only of brain development but also of everyday brain function becomes increasingly imperative.

In addition, documentation of average to superior intelligence in most people with autism (Edelson 2006; Dawson et al. 2007), as well as of domains of perceptual superiority (Soulieres, Zeffiro, et al. 2011; Soulieres, Dawson, et al. 2011; Samson et al. 2011; Soulieres et al. 2010; Soulieres et al. 2009; Mottron et al. 2006; Mottron 2004; Bertone et al. 2005; Perreault et al. 2011), call into question the long-standing assumption that ASDs are intrinsically or for the most part associated with cognitive deficits – another strike against the outdated 'deficit' or 'broken brain' model.

2. Mechanisms that operate actively throughout the lifecourse

One particularly valuable lesson about ASDs that can be learned from looking at how EMF/RFR affects underlying biology is that these impacts are by no means confined to early development. We already have 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 (Korson 2007). These children with their vulnerable, barely compensated mitochondria seem to be teetering right at the brink of the interface of metabolic and electrophysiological dysfunction, tipping back and forth on this knife edge. It makes one wonder what everyday exposures – allergens, infection, pesticide on the school playground, even perchance EMF/RFR – might contribute to the bad days (with their loss of electrophysiological optimization, probably on account of insufficient energy to drive fully integrated brain function), and conversely how many choices exist in everyday life that could tilt things in the direction of more good days (by helping to stabilize more optimal nervous system performance) (Herbert and Weintraub 2012).

The short time course needed for biologically effective EMF/RFR 'doses' to lead to observable impacts reflects that these exposures can affect cells without obstruction (unlike many chemical agents), and create impacts within minutes. This type of mechanism may also give us fresh and important ways of understanding the short-term variability – the good days and the bad days – that are so common in ASD even in those who do not have a formal diagnosis of mitochondrial disease.

3. Pathophysiology and Allostatic Load

Based on these considerations, the strategy to be pursued in this examination of a potential EMF/RFR - ASD link is to review the many parallels between underlying biology, or pathophysiology, in ASDs and the impacts of EMF/RFR on living organisms. EMF/RFR exposures have demonstrated impacts at just about every level at which biology and physiology have been shown to be disrupted in ASDs. EMF/RFR has been shown to potentiate the impact of various toxicants when both exposures occur together (Juutilainen, Kumlin, and Naarala 2006); this may be additive or more than additive. This suggests that EMF/RFR may synergize with other contributors and make things worse. With many different environmental factors piling on to a much smaller number of environmentally vulnerable physiological mechanisms (Herbert 2010), one must consider that the model of 'allostatic load' – the sum total of stressors and burdens – 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. A cascade of exposures interacting with vulnerabilities can potentially lead to a tipping point for an individual, such as the phenomenon of autistic regression experienced by a substantial subset of people with ASDs. When exposures increase at the population

level, we are likely to see trends of increase in the number of people passing that tipping point and getting diagnosed. EMF/RFR exposures have increased several thousand-fold or more in the past two decades from wireless technology innovations that have unplanned side effects from pulsed RFR, a newly classified human carcinogen (Baan et al, 2011). Nearly six billion people globally own wireless phones, for example. Many hundreds of thousands more are exposed to wireless whole-body transmissions from wireless antenna facilities (Sage and Carpenter, BioInitiative 2012 Report, Section 24). For this as well as for physiological reasons allostatic loading as a viable concept for the study of ASDs should reasonably address EMF/RFR as one of the collection of 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 lifecourse.

In an article entitled "Unrelenting Stress is Toxic,: The New Scientist (28 July 2012) describes stress in an eloquent way:

> "*Unrelenting stress is toxic because it can turn the body's defense system against itself. Neuroendocrinologist Bruce McEwen at Rockefeller University in New York says the stress response that evolved to protect us from harm can be hijacked and actually cause harm when the stress level never abates. In a normal situation, the introduction of stress causes the body to deliver a boost of energy – by sending a surge of glucose to the muscles – and to increase heart rate, blood pressure and breathing to get oxygen to the muscles in hurry. At the same time, blood vessels constrict and clotting factors increase – ready to slow bleeding in case you are wounded. These responses are a part of a fight-or-flight survival kit, and once the stress has passed, these should subside. But for people under unrelenting stress, this response never quite switches off – leaving sugar levels unregulated, high blood pressure, increate risk of blood clots, depressed sex drive and an immune system buckling under the strain. Prolonged exposure to stress hormones can have other effects as well, including affecting the brain by altering the structure of the neurons and their connections, which in turn can influence behaviour and hormonal processes."*

This passage refers to effects on the hypothalamo-pituitary-adrenal axis {Aldad, 2012 #2034}, but as will be discussed in the Part II, equally important is cellular stress from stress proteins (heat shock protein HSP) and from oxidative stress generated at very low-intensity EMF and RFR levels as detailed in the BioInitiative 2012 Update, Section 7 by Martin Blank, PhD) {Blank, 2012 #2467}. Both are significant kinds of stress that can add body-burdens via allostatic loading.

Part II - PARALLELS IN PATHOPHYSIOLOGY

This section will review parallels in pathophysiology between ASDs and impacts of EMF/RFR. It will begin with a review of mechanisms of direct impact 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, immune function and nervous system physiology. The review of parallels will conclude with a discussion of electromagnetic signaling and synchronized oscillation from membranes to nervous system, treating 'aberrant' neural systems and somatic function and behaviors as consequences or 'outputs' of disturbed underlying physiology to which EMF/RFR is a plausible contributor.

A. DAMAGE: MEANS AND DOMAINS

ASDs 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 ASDs has to do with differences in the way it was formed. 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. This chapter begins the work to systematically rectify the omission of EMF/RFR as one environmental contributor in ASDs.

However the influence of the environment on neurodevelopmental conditions such as ASDs 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 (Lintas, Sacco, and Persico 2012).In a study of gene expression in ASDs, Down syndrome and Rett syndrome, these authors state, *"Our 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 ASD (Kong et al. 2012; Jung, Kohane, and Wall 2011; Voineagu et al. 2011; Waly et al. 2012). 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. Evidence for pathophysiological dysfunction in ASDs increasingly abounds. In particular, a growing body of 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.

1. Cellular Stress

Oxidative Stress

Autism (ASD) 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 ASDs 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 (Kanthasamy et al. 2012; Roberts et al. 2010; Knox 2010; Rose, Melnyk, Trusty, et al. 2012; Rose, Melnyk, Pavliv, et al. 2012; Ghanizadeh et al. 2012; Frustaci et al. 2012; Rossignol and Frye 2011; Adams et al. 2011, 2011; Mostafa et al. 2010; Zecavati and Spence 2009; Yao et al. 2006; Naviaux 2012; Chauhan and Chauhan 2006; Chauhan, Chauhan, and Brown 2009).

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 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 ASD 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 in Section 6 (Genotoxicity) of this BioInitiative 2012 Report and in the BioInitiative Report (2007),

both by Henry Lai, PhD {Lai, 2012 #2548}{Lai, 2007 #2549}. 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 (Lai and Singh 2004; De Iuliis et al. 2009) particularly via the Fenton reaction, and prolonging the effect 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 (Lai, in the BioInitiative Report 2007) {Lai, 2007 #2549}. 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 ASDs (Bristot Silvestrin et al. 2012; Brown et al. 2012; Choudhury, Lahiri, and Rajamma 2012; Essa et al. 2012; Oberman 2012; Yang and Pan 2012; Chauhan, Audhya, and Chauhan 2012; Frustaci et al. 2012; Main et al. 2012; Pecorelli et al. 2012; Rose, Melnyk, Pavliv, et al. 2012; Rose, Melnyk, Trusty, et al. 2012; Waly et al. 2012; Banerjee et al. 2012; Coghlan et al. 2012; Enticott et al. 2012; Kang and Barnes 2013; Mendez et al. 2012; Piton et al. 2012; Anitha, Nakamura, Thanseem, Matsuzaki, et al. 2012; Anitha, Nakamura, Thanseem, Yamada, et al. 2012; Gargus 2008; Giulivi et al. 2010; Hadjixenofontos et al. 2013; Napolioni et al. 2011; Rossignol and Frye 2011). 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 (Campisi et al. 2010).

Fragopoulou et al (2012) conducted proteomics analysis of proteins involved in brain regulation in mice as a consequence of prolonged exposure to EMF(Fragopoulou et al. 2012). 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 ASDs, 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 (Shapiro et al. 2012; Ozgur, Guler, and Seyhan 2010; Ozguner et al. 2005; Moustafa et al. 2001; Kesari, Kumar, and Behari 2011; Jelodar, Akbari, and Nazifi 2012; Hoyto et al. 2008; Guney et al. 2007; Esmekaya, Ozer, and Seyhan 2011; Atasoy et al. 2012){Al-Demegh, 2012 #2624}{Kumaf, 2010 December #2619}{Meral, 2007 #2627}{Oktem, 2005 #2074}{Ozguner, 2006 #2625} 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 (Lee, Jacobs, and Porta 2009), 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 900MHz EMR exposure (Guney et al. 2007). Gingko bioloba 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 xanthin oxidase and adenosine deaminase activities, and treated rats were spared the histopathological cell injury found in the untreated rats (Ilhan et al. 2004). Substantial further literature on antioxidants and radical scavengers is reviewed in Section 15 in Belyaev's contribution to the Bioinitiative 2012 Report (Belyaev 2012).

Stress Protein (Heat Shock Protein) Responses

Another well-documented effect of exposure to low- intensity ELF and RFR is the creation of stress proteins (heat shock proteins) that signal a cell is being placed under physiological stress) (Weisbrot et al. 2003; Velizarov, Raskmark, and Kwee 1999; Leszczynski et al. 2004; Leszczynski et al. 2002; de Pomerai et al. 2000; Daniells et al. 1998; Blank and Goodman 2004). Heat shock proteins are in a family of inducible proteins that are initiated when any increased need for protection from stray electrons occurs (Padmini 2010; Bottoni, Giardina, and Scatena 2009). 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 (George et al. 2008). Another concomitant impact of cellular stress can be protein misfolding, which has been documented in association with exposure to EMF/RFR. (Bohr and Bohr 2000; Mancinelli et al. 2004)

Although a number of papers have demonstrated increases in HSPs in people with ASDs (El-Ansary and Al-Ayadhi 2012; Evers, Cunningham-Rundles, and Hollander 2002; El-Ansary, Ben Bacha, and Kotb 2012; Walker, Segal, and Aschner 2006; Vojdani et al. 2004), it has been investigated far less often than oxidative stress. Part of the research needed to study possible influences of EMF/RFR on ASDs would be to study this more carefully.

2. Membranes and Channels

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. 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 (Mironova et al. 1994), hormones (Liburdy 1995; Ishido, Nitta, and Kabuto 2001), growth- regulating enzyme expression (Byus, Pieper, and Adey 1987; Chen et al. 2000; Litovitz et al. 1993) (Penafiel et al. 1997), and cancer-promoting chemicals (Cain, Thomas, and Adey 1993; Mevissen, Haussler, and Loscher 1999). In none of these studies does tissue heating appear involved causally in the responses. Physicists and engineers have continued to offer microthermal, rather than athermal, models for these phenomena (Barnes 1996; Astumian, Weaver, and Adair 1995), with views that exclude consideration of cooperative organization and coherent charge states, but it is difficult to reconcile experimental evidence for factors such as modulation frequency-dependence and required duration of an amplitude-modulated signal to elicit a response (coherence time) (Litovitz et al. 1993) with models based on the equilibrium dynamics of tissue heating."* (Adey 2002)

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 brain tissue. Lipid peroxidation of membranes has been identified as an effect of EMF/RFR in multiple studies (Desai, Kesari, and Agarwal 2009; Phelan et al. 1992). 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 nonthermal effects of microwave radiation (Beneduci et al., 2012). Membrane potential and currents may also be impacted by pulsed radiofrequency fields (Linz et al., 1999). 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 (Cammaerts et al (2011) 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 ASDs, including malonaldehyde and isoprostanes, as well as alteration of membrane phospholipids and prostaglandins (Pecorelli et al. 2012; El-Ansary et al. 2010; El-Ansary, Ben Bacha, and Kotb 2012; Zhang, Sun, et al. 2012; Yao et al. 2006; Al-Gadani et al. 2009; Chauhan and Chauhan 2006; Ming, Stein, et al. 2005; Zoroglu et al. 2004) In one study the iosoprostane levels showed a biomodal distribution with the majority of ASD subjects showing moderate increase but a smaller group showing dramatic increases (Ming, Stein, et al. 2005). Thromboxane, reflecting platelet activation, was also elevated in one study (Yao et al. 2006). Given that this phenomenon has been identified in many people with ASDs, it is plausible that such individuals will likely be more vulnerable to having such cellular injuries caused, worsened or both by EMF/RFR exposures.

Calcium channels

Of particular prominence in the EMF/RFR physiological impact literature is the impact on calcium channels and signaling. Calcium signaling is ubiquitous in biological systems ranging from single-celled organisms to the most sophisticated functioning of our nervous and immune systems. This signaling takes place through a myriad of mechanisms within and between cells. The exquisite tuning of organisms is influenced by the precision of functioning of these systems, with even subtle disturbances having the potential to ramify in a nonlinear fashion through a system causing larger-scale disturbances elsewhere. EMF/RFR exposures have been shown to create disturbances in calcium signaling through a variety of mechanisms, including membrane leakage (Nesin et al. 2012), alteration of calcium-binding proteins and GFAP reactivity (Maskey et al. 2012; Maskey et al. 2010), and altered ultrastructural distribution of calcium and calcium-activated ATPases after exposure (Kittel et al. 1996).. Adey (2002) provided an overview of key studies on calcium efflux and the importance of calcium in cell signalling. *"Early studies described calcium efflux from brain tissue in response to ELF exposures (Bawin and Adey 1976; Blackman et al. 1985), and to ELF-modulated RF*

fields (Bawin and Adey 1976) (Blackman 1979) (Blackman et al. 1985; Dutta, Ghosh, and Blackman 1989). 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 (Lin-Liu and Adey 1982). In the same and different cell culture lines, the growth regulating and stress responsive enzyme ornithine decarboxylase (ODC) responds to ELF fields (Byus et al. 1988; Litovitz et al. 1993) and to ELF-modulated RF fields (Byus, Pieper, and Adey 1987) (Litovitz et al. 1993) (Penafiel et al. 1997) ." (Adey 1994)

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. To explore the physiological importance of these findings, we have examined the impact of RFR exposure on a membrane-bound enzyme, acetylcholinesterase (AChE), which is intimately involved with the acetylcholine (ACh) neurotransmitter system. Neuroblastoma cells (NG108), exposed for 30 min to 147-MHz radiation, AM at 16 Hz, demonstrated enhanced AChE activity, as assayed by a procedure using 14C-labeled ACh. Enhanced activity was observed within a time window between 7.0 and 7.5 h after the cells were plated and only when the exposure occurred at power densities identified in a previous report as being effective for altering the release of calcium ions. Thus RFR affects both calcium-ion release and AChE activity in nervous system-derived cells in culture in a common dose-dependent manner."* (Dutta et al. 1992)

The prominence of these calcium signaling impacts of EMF/RFR are striking when considered in relation to ASD pathophysiology, where such alterations have been proposed as of central importance. Calcium channels play an important role in regulating neuronal excitability, whose disturbance during development has been thought by many to be potentially contributory to the development of ASDs, as well as to the often associated vulnerability to seizures. Gene alterations have been identified associated with a number of voltage-gated calcium channels in ASDs Smith, 2012 #1451}(Krey and Dolmetsch 2007; Pasca et al. 2011; Gargus 2009; Lu et al. 2012). 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 Ca2+ 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." (Palmieri and Persico 2010) 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 Ca2+ dynamics and augment Ca2+ surge. The reciprocal interactions between Ca2+ induced ROS increase and ROS modulated Ca2+ upsurge may cause a feedforward, self-amplified loop creating cellular damage far beyond direct Ca2+ induced damage." (Peng and Jou 2010)*

Environmental as well as genetic routes to calcium signaling dysfunction have been identified (Pessah and Lein 2008) including chemicals such as the polyaromatic hydrocarbons. PCB-95 in particular modulates the calcium-dependent signaling pathway responsible for activity-dependent dendritic growth {Wayman, 2012 #2550;Wayman, 2012 #2551}. 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 ASD 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 (Stamou et al. 2012). 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. Moreover if a person is subject to multiple triggers all of which have calcium signaling impacts, the gene-environment interactions may lead to impacts that could be less, the same as or more than any one contributor alone might create.

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.

It appears that 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 {Cervellati, 2009 #1449}. Changes in tight junctions have been observed upon exposure to microwave and x-ray irradiation {Palfia, 2001 #1458}.

A number of papers in the ASD research field document problems pertinent to junctions. Connexin abnormalities have been documented in neuropathological studies (Fatemi et al. 2008). and MacFabe and colleagues identified lipid alterations associated with oxidative stress, membrane fluidity and the modulation of gap junction coupling (Thomas et al. 2012). Decrease in platelet endothelial cell adhesion molecule-1 were reduced and this reduction correlated with repetitive behavior and abnormal brain growth; achesion molecules modulate permeability and signaling at the blood-brain barrier as well as leukocyte infiltration into the central nervous system (Onore et al. 2012).

EMF and RFR might also compromise biologically important barrier structures that separate blood flow from organs like the brain (Salford et al, BioInitiative Report 2012, Section 10) {Salford, 2012 #2477}. 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 this barrier into the intestines (invoking immune responses) and impacting the developing fetus {Somosy, 1993 #1470}. 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 {Salford, 1994 #2553;Salford, 2003 #2552}{Salford, 2007 #2629;Salford, 1992 #2628}{Eberhardt, 2008 #1428}{Nittby, 2009 #2307;Nittby, 2008 #2556}. 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 {Lange, 1993 #2557}. 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/cm2 are associated with production of corneal endothelial lesions and with disruption of the blood-aqueous barrier in the non-human primate eye."* (Kues et al. 1992) A recent study showing impact of high-frequency electromagnetic fields on trophoblastic connexins (Cervellati et al. 2009) 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 {Salford, 2012 #2477}.

According to a review by Zlokovic, *"BBB breakdown, due to disruption of the tight junctions, altered transport of molecules between blood and brain and brain and blood, aberrant angiogenesis, vessel regression, brain hypoperfusion, and inflammatory responses, may initiate and/or contribute to a "vicious circle" of the disease process, resulting in progressive synaptic and neuronal dysfunction and loss in disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and others."* (Zlokovic 2008). The integrity of the BBB can be compromised by oxidative stress which can lead to increased permeability (Parathath, Parathath, and Tsirka 2006). The resultant extravasation of albumin into brain parenchyma can be excitotoxic and neurotoxic (Hassel, Iversen, and Fonnum 1994; Eimerl and Schramm 1991).

The evidence suggesting possible existence of barrier function compromise in people with ASDs is largely indirect. The existence of brain neuroinflammation in ASDs has been documented in a growing number of studies (Boso et al. 2006; El-Ansary and Al-Ayadhi 2012; Young et al. 2011), and this is known to be associated with BBB permeability(Erickson, Dohi, and Banks 2012; Janigro 2012; Takeshita and Ransohoff 2012). In a review of clinical MRI findings in ASDs 19/59 showed white matter signal abnormalities (Boddaert et al. 2009), which in other settings have been associated with cerebral hypoperfusion, though not necessarily in the same locations as the hyperintensities (Vardi et al. 2011) {Brickman, 2009 #2581}. 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) (de Magistris et al. 2010; Lucarelli et al. 1995; D'Eufemia et al. 1996; Horvath and Perman 2002; White 2003; Robertson et al. 2008; Souza et al. 2012) and discussed in the context of food exposures, particularly gluten (Silva et al. 2012; Sapone et al. 2011; Visser et al. 2009; Simpson et al. 2009; Fasano 2009; Lammers et al. 2008; De Angelis et al. 2006). The reactivity to large numbers of different foods clinically observed in many children with autism has been framed by 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 (Theoharides and Doyle 2008). This reactivity could in turn feed in to aberrant immune responsivity which in turn could further amplify barrier vulnerability{Fasano, 2009 #654}.

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 (Hsiao and Patterson 2012).

4. Genetic Alterations and Reproductive Impacts

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, the overwhelming emphasis in recent decades in autism research has been on genetics, and on finding linkages between genes, brain and behavior. As mentioned earlier, this point of view also promotes more of a structural/anatomical orientation than a bioelectric/physiological orientation. Along with this emphasis it has seemed obvious to people just looking at the stubborn persistence of symptoms in affected individuals that ASDs are inborn, lifelong brain defects. From this vantage point there would be no reason to think about the transduction of pathophysiology – whether acquired or genetic or some combination – to brain and hence behavior (or, more broadly, neurocognitive function). Thus the research agenda of looking for gene-brain-behavior correlations has seemed both self-evident and sufficient.

In recent years the genetic premises of this seemingly obvious framing of autism as overwhelmingly genetic have been undermined at several levels. (The undermining of the brain premises will be discussed beyond what was covered in Part I in later sections.) First the number of reported cases is increasing, making it more difficult to maintain that ASDs are purely genetic because these increases can only be partly explained away by greater awareness or other data artifacts (King and Bearman 2009; Hertz-Picciotto and Delwiche 2009). 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, as well as 'de novo' mutations present in ASD children but not their parents and even 'boutique' mutations not shared beyond an individual family. Out of over a hundred genetic syndromes in which autism commonly occurs, it is unclear what the pertinent genetic mutations and rearrangements have in common to account for the shared association with ASDs (Anney et al. 2010; Betancur 2011). 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 (Hallmayer et al. 2011). Also of interest, a Swedish study of identical twins and schizophrenia grouped into monochorionic (shared placenta) and dichorionic (each had its own placenta) showed 60% concordance for schizophrenia diagnosis for monochorionic twins but only 10.7% concordance for dichorionic twins (Davis, Phelps, and Bracha 1995); though this work has not yet been replicated in ASD twins, in principle it opens the door to non-genetic

interpretations of any concordance figures that have generally been assumed to be indicators of heritable genetics. The authors of this study interpreted their findings as consistent with data on viral infection as a contributor to schizophrenia risk (a possibility also entertained in ASDs (Patterson 2012; Teixeira and Barichello 2012; Atladottir et al. 2012, 2012; Hornig et al. 1999)), but one could also consider the possibility of differences in the dichorionic cases in the integrity of the placental barrier.

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. There is certainly progress being made through genetic research to the identification of networks of genes and mechanisms on which genes converge (Voineagu et al. 2011), but environmental mechanisms converge on these mechanisms too (Stamou et al. 2012), and the mechanisms are what drive the impacts.

Genotoxicity

One route through which environmental impacts may influence an organism's status is by changing genes through mutation – that is, by genotoxicity. This has been proposed as a mechanism for the generation of 'de novo' mutations (found in children but not their parents) being found in ASDs (Kinney et al. 2010) and increasingly in other settings as well, making mutations something that needs to be accounted for rather than simply assuming tey are associated with normal, stable variation. Reviews and published scientific papers on genotoxicity and EMF report that both ELF-EMF and RFR exposures can be considered 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 (Ruediger 2009; Ivancsits et al. 2005; Diem et al. 2005; Blank and Goodman 2011; Phillips, Singh, and Lai 2009; REFLEX 31 May 2004; Sage and Carpenter 2009; Lai and Singh 2004). 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. Genotoxic impacts of EMF/RFR are further reviewed in the BioInitiative Working Group 2007 contribution by Lai as well as in Section 6 of the present Bioinitiative Report {Lai, 2007 #2549;Lai, 2012 #2548}.

The European research program REFLEX (Risk Evaluation of Potential Environmental Hazards From Low-Energy Electromagnetic Field Exposure Using Sensitive in vitro Methods – a 5FP EU project) documented many changes in normal biological functioning in tests on DNA at exposure levels below existing public safety standards(REFLEX 31 May 2004). Some of the key findings included:

- Gene mutations, cell proliferation and apoptosis which are caused by or result in altered gene and protein expression profiles. The convergence of these events is required for the development of all chronic diseases.
- Genotoxic effects and a modified expression of numerous genes and proteins after EMF exposure could be demonstrated with great certainty.
- Genotoxic effects produced by RF-EMF in fibroblasts, HL- 60 cells, granulosa cells of rats and neural progenitor cells derived from mouse embryonic stem cells.
- Response of cells to RF exposure between SAR levels of 0.3 and 2 W/Kg with a significant increase in single- and double-strand DNA breaks and in micronuclei frequency.
- A clear demonstration of increase in intracellular generation of free radicals in HL-60 cells accompanying RF-EMF exposure.
- The observation that the induced DNA damage was not based on thermal effects, which raises concerns about the thermal-based environmental safety limits for ELF-EMF exposure.

These impacts could be contributors to a role for genetics in ASDs that does not derive from only inheritance but also from environmental and epigenetic influences. Moreover, in the light of the great heterogeneity of genetic findings in ASD alongside the documented impacts of EMF/RFR upon many other levels of pathophysiology than simply genetics, it becomes worth reflecting whether genetics might not be the primary problem but instead, in many cases at least, just one of many levels of collateral damage from environmental impacts. Whatever genetic variants a person carries may bias their system toward specific vulnerability, or may contribute more generically by increasing entropy and molecular disorder; in either capacity they may aggravate the situation but may not be part of the main cause.

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. Although there is not a consensus at this time about the rates or causes of *de novo* mutations in ASDs, and using present methods of detection are only found in a small percentage of individuals with ASDs, given the potential contribution of environmentally triggered oxidative stress and free radical damage that we know is present in at least large numbers of people with ASDs, a serious investigation of the potential contribution of EMF and RFR to de novo mutations in ASD seems warranted, given the large increase in exposure to these phenomena accompanying the massively increased non-ionizing radiation exposures in daily life due to

electrification and the global saturation of RFR from wireless technologies (BioInitiative 2012 Report, Section 24, Public Health Implications, Sage and Carpenter) (Sage and Carpenter 2012).

Challenge to DNA repair mechanisms

Reduced DNA repair may contribute to increased risk of cancers, but it may also contribute to a variety of other diseases and disturbances of growth and development. 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 (Markova et al. 2005; Belyaev et al. 2005; Belyaev, Markova, and Malmgren 2009). Belyaev, Markova and colleagues (2005) Markova et al. (2009) 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 (Markova et al. 2005; Belyaev et al. 2005). 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 (Christophersen and Haug 2011). The high possibility that various such contributors may combine supports an 'allostatic load' model of environmental injury and genotoxicity. Also note the overlap between nutritional risk factors for oxidative stress and for impaired DNA repair mechanisms. This supports a vicious circle model where the more oxidative damage to the genome, the less the cells will be prepared to deal with it successfully. It can also work the other way around – nutrients can attenuate the degree of damage; instances of this will be discussed in the Melatonin section below.

Chromatin condensation

Chromatin condensation is another hallmark of damage from EMF and RFR. Orderly chromatin condensation is a normal part of cell division, but it can also be provoked pathologically. The work of Markova, Belyaev and others has repeatedly shown that RFR exposure can cause chromatin condensation. 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 1.0

uW/cm2) (Belyaev, Alipov, and Harms-Ringdahl 1997). Significant microwave-induced changes in chromatin conformation were observed when rat thymocytes were analyzed in-between 30-60 min after exposure to MW (Belyaev and Kravchenko 1994). This effect nearly disappeared if the cells were incubated more than 80 min between exposure and analysis.

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 (Belyaev et al. 2005; Markova et al. 2005). 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 (Belyaev, Markova, and Malmgren 2009).

Researchers have recently identified large numbers of "spontaneous genetic glitches," or de novo mutations, more likely to be transmitted by fathers than by mothers to their children (Neale et al. 2012; O'Roak et al. 2012; Sanders et al. 2012). These glitches are widely distributed across the genome, with their location rather than their size conferring risk. 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 (O'Roak et al. 2012). Whether the prominence of chromatin-related gene mutations can be related in any meaningful way to the impacts of EMF/RFR on chromatin condensation is not possible to say at this point in time and this apparent parallel between ASDs and EMF/RFR may be a pure coincidence, though an intriguing one worth looking into further, including regarding how these mutations and the chromatin-remodeling impacts of EMF/RFR exposure may interact.

Gonadal and germline impacts

De novo mutations have been shown to be more of a problem related to paternal age (O'Roak et al. 2012; Paul, Nagano, and Robaire 2011; Iossifov et al. 2012; Cantor et al. 2007; Alter et al. 2011), 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 (Agarwal et al. 2008; Agarwal et al. 2009; Wdowiak, Wdowiak, and Wiktor 2007; De Iuliis et al. 2009; Fejes et al. 2005; Aitken et al. 2005) Kumar, 2012). 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 (Aitken et al, 2004; Agarwal et al, 2007; Erogul et al., 2006). 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 (Dasdag et al. 1999; Yan et al. 2007; Otitoloju et al. 2010; Salama et al. 2009) Behari et al, 2006; Kumar et al, 2012). Of note, altered fatty acids consistent with oxidative stress have been found in sperm cells in male infertility (Zalata et al. 1998; Zalata, Hafez, and Comhaire 1995).

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* (Panagopoulos 2012). 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 (Gul, Celebi, and Ugras 2009). 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 one microwatt per centimeter squared (μW/cm2) (Magras and Xenos 1997).

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' (Silberman 2001), 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 (O'Roak et al. 2012).

5. Implications of Damage

We have reviewed parallels between ASD 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 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 ASDs and in EMF/RFR exposures. Also notable was the possibility of attenuating some of the damage through increasing antioxidant status.

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 (Derecki et al. 2012; Derecki, Cronk, and Kipnis 2012). 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 diminished through inhibition of phagocytosis. Phagocytosis involves removing debris. This suggests that while research has focused on how 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. This has potentially broad implications for other genetic disorders, as well as for conditions like ASDs which are for the most part idiopathic. Based on this study as well as on the levels of damage just reviewed, problems in cells that are pertinent to ASDs 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 pathophysiology. It is also encouraging that at least some of the damage and dysfunction was reversible by a generic cellular mechanism (phagocytosis), and this could have broad significance for idiopathic ASDs as well, along with other conditions involving related pathophysiological challenges.

B. DEGRADATION OF SYSTEM INTEGRITY

In the setting of molecular, cellular and tissue damage, one would predict that the organization and efficiency of a variety of organelles, organs and systems would also be degraded. EMF/RFR exposures yield a stressful situation of chronically interrupted homeostasis. Here 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 ASDs.

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 pathway can be targeted by environmental agents, including toxicants and drugs, as well as mutations (Wallace and Starkov 2000). This supports an allostatic load model for conditions in which

mitochondrial dysfunction is an issue, which includes ASDs 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 (Thar and Kuhl 2004). 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…"* (Aon, Cortassa, and O'Rourke 2008). These electromagnetic aspects of mitochondrial physiology and pathophysiology could very well be impacted by EMF/RFR.

There are also a variety of types of mitochondrial damage that 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 (Khaki et al. 2006; Lahijani, Tehrani, and Sabouri 2009; Esmekaya et al. 2011), mitochondrial DNA damage (Xu et al. 2010), swelling and crystallization (Lahijani, Tehrani, and Sabouri 2009), alterations and decreases in various lipids suggesting an increase in their use in cellular energetics (Chernysheva 1987), damage to mitochondrial DNA (Xu et al. 2010), and altered mobility and lipid peroxidation after exposures (Wang et al. 2002). Also noted has been enhancement of brain mitochondrial function in Alzheimer's transgenic mice and normal mice (Dragicevic et al. 2011). 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; these are intensively reviewed in Belyaev's contribution to BioInitiative 2012 in Section 15 (Belyaev 2012).

The idea that mitochondrial dysfunction might be common in ASDs met with a fair bit of consternation, and many professionals have preferred to limit their consideration to mitochondrial disorders with proven genetic mutations. However the concept of mitochondrial dysfunction is better established in other areas of medicine, with thousands

of papers and hundreds of reviews carrying "mitochondrial dysfunction" in their titles. 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 (Giulivi et al. 2010; Palmieri et al. 2010; Pastural et al. 2009). Recently published postmortem brain tissue studies that have added a new dimension of evidence for mitochondrial abnormalities in ASDs will be reviewed in the section on alteration of brain cells below.

Some have called the mitochondrial issues most commonly seen in ASDs 'secondary mitochondrial dysfunction' (Zecavati and Spence 2009; Rossignol and Frye 2011) to indicate that it results from environment insults and/or other pathophysiological dysfunction rather than directly from genetics (Hadjixenofontos et al. 2012); the already discussed potential for EMF/RFR to damage channels, membranes and mitochondria themselves could contribute in a number of ways to degrading mitochondrial function without a basis in genetic mutation, as could toxicant exposures and immune challenges. In a meta-analysis of studies of children with ASD and mitochondrial disorder, the spectrum of severity varied, and 79% of the cases were identified by laboratory not associated with genetic abnormalities (Rossignol and Frye 2011). "*Substantial percentages of autistic patients display peripheral markers of mitochondrial energy metabolism dysfunction, such as (a) elevated lactate, pyruvate, and alanine levels in blood, urine and/or cerebrospinal fluid, (b) serum carnitine deficiency, and/or (c) enhanced oxidative stress……In some patients, these abnormalities have been successfully explained by the presence of specific mutations or rearrangements in their mitochondrial or nuclear DNA. However, in the majority of cases, abnormal energy metabolism cannot be immediately linked to specific genetic or genomic defects."* (Palmieri and Persico 2010)

2. Melatonin Dysregulation

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. (Leon et al. 2005; Luchetti et al. 2010; Limon-Pacheco and Gonsebatt 2010) *"It is known that melatonin scavenges oxygen and nitrogen-based reactants generated in mitochondria. This limits the loss of the intramitochondrial glutathione and lowers mitochondrial protein damage, improving electron transport chain (ETC) activity and reducing mtDNA damage. Melatonin also increases the activity of the complex I and complex IV of the ETC, thereby improving mitochondrial respiration and increasing ATP synthesis under normal and stressful conditions."* (Leon et al. 2005) It also helps prevent the breakdown of the mitochondrial membrane potential, decrease electron leakage, and thereby reduce the formation of

superoxide anions. (Hardeland 2005) 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. (Limon-Pacheco and Gonsebatt 2010; Gupta, Gupta, and Kohli 2003)

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 (Kesari, Kumar, and Behari 2011).

Further types of adverse impacts can be seen in the next set of examples, but what is interesting is that melatonin can attenuate or prevent them. In an experiment exposing rats to MW from a GSM900 mobile phone with and without melatonin treatment to study renal impacts(Oktem et al. 2005), 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 (Imaida et al. 2000). The development of DNA strand breaks was observed in RFR exposed rats; this DNA damage was blocked by melatonin (Lai and Singh 1997). 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 (Xu et al. 2010). 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 (Ozguner et al. 2004). 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 (Ozguner, Bardak, and Comlekci 2006). 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 (Yariktas et al. 2005). 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 (Sokolovic et al. 2008).

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 (Bellieni, Tei, et al. 2012). There is an increased prevalence of ASDs in children who were born prematurely (Indredavik et al. 2010; Indredavik et al. 2008; Johnson et al. 2011; Johnson et al. 2010; Johnson and Marlow 2011; Lampi et al. 2012; Limperopoulos 2009, 2010; Limperopoulos et al. 2008; Matson, Matson, and Beighley 2011; Pinto-Martin et al. 2011). There are many potential prematurity-associated factors that could contribute to increased risk for ASDs, but electromagnetic exposure might be one of them worthy of further consideration, as it could be modified; conversely, such exposures in vulnerable infants are likely to have much broader impacts beyond reducing melatonin synthesis.

Melatonin and autism

Based on the commonality of both sleep disorders and low melatonin levels, Bourgeron (2007) proposed that synaptic and clock genes are important in ASDs, and that future studies should investigate the circadian modulation of synaptic function (Bourgeron 2007). A number of melatonin-related genetic variants have been identified as associated with ASDs. Polymorphisms, deletions and polymorphisms in the ASMT gene, which encodes the last enzyme of melatonin synthesis, have been found (Pagan et al. 2011; Jonsson et al. 2010; Melke et al. 2008), and variations have been found as well for melatonin receptor genes (Chaste et al. 2010; Pagan et al. 2011; Jonsson et al. 2010). 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 (Braam et al. 2012).

Regarding melatonin status in people with ASDs, 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 ASD 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."* (Rossignol and Frye 2011) The meta-analysis also showed that polymorphisms in melatonin-related genes in ASD 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.

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 ASD research and increasingly in clinical practice. Hopefully one contribution of an investigation of EMF/RFR links to ASDs 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 (Kuhn and Arthur 1999; Kuhn and Geddes 1999; Kuhn et al. 2011; Kuhn and Arthur 1997).

3. Disturbed Immune Function

There is by now a broad appreciation of the presence of immune disturbances in ASDs, to the point where there is an emerging discussion of ASDs as neuroimmune disorders (Bilbo, Jones, and Parker 2012; Persico, Van de Water, and Pardo 2012). Research identifying immune features in ASDs spans from genetics where risk genes have been identified to epigenetics where altered expression of immune genes is being reported as prominent in ASD epigenetics (Kong et al. 2012; Waly et al. 2012; Lintas, Sacco, and Persico 2012), 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 (Patterson 2011; Smith et al. 2007; Fox, Amaral, and Van de Water 2012). Immune disturbances in infants and children with ASD are heterogeneous, with some but not all manifesting autoimmunity (Soumiya, Fukumitsu, and Furukawa 2011; Martin et al. 2008). 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 (Croen et al. 2005). The immune system is turning out to have an important role in brain development (Bilbo and Schwarz 2012; Schwarz and Bilbo 2012; Boksa 2010). 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 ASDs causally, based on the evidence below regarding immune impacts of EMF/RFR exposure (which is also reviewed much more thoroughly by Johansson in Section 8 of the present Bioinitiative Report) (Blank 2012), it is certainly plausible that such exposures could serve as aggravating factors.

Low-intensity exposures

It is clear that the body's immune defense system responds to very low-intensity exposures. 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. We are increasingly appreciating the extent to which 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 (Johansson 2009; Johannson 2007).

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).

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 (Brown and Derkits 2010). 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 (Croen et al. 2005), and in a large study of autism cases in the Danish Medical registry (Atladottir et al. 2010) 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 appear to include oxidative stress, interleukin-6 and increased placental cytokines (Smith et al. 2007; Patterson 2009; Boksa 2010). Garbett et al. (2012) 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."* (Garbett et al. 2012). Maternal fetal brain-reactive autoantibodies have also been identified in some cases (Braunschweig et al. 2012; Braunschweig and Van de Water 2012; Fox, Amaral, and Van de Water 2012; Goines et al. 2011; Wills et al. 2009; Wills et al. 2011; Zimmerman et al. 2007).

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 (Aldad et al. 2012).

Potential immune contributions to reactivity and variability in ASDs

Immune changes in ASDs appear to be associated with behavioral change (Shi et al. 2003; Ashwood et al. 2008; Ashwood et al. 2011; Breece et al. 2012; Heuer et al. 2008), but the mechanisms are complex and to date poorly understood (Careaga and Ashwood 2012) and likely will need to be elucidated through systems biology methods that capture multisystem influences on the interactions across behavior, brain and immune regulation (Broderick and Craddock 2012), including electrophysiology.

Two of the particularly difficult parts of ASDs are the intense reactivity and the variability in assorted symptoms such as tantrums and other difficult behaviors. Children with ASDs 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 (Jyonouchi et al. 2011). 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 (Johannson 2007; Johansson et al. 2006). 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 (Johansson et al. 2006). 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 ASD symptoms (Theoharides et al. 2012, 2010), 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 (Zhang, Asadi, et al. 2012).

Seitz et al. (2005) 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 {Seitz, 2005 #2582}. Some of these symptoms are common in ASDs, 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 ASDs.

Johansson (2007, 2009) 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) (Johannson 2007; Johansson 2009). 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 (Johansson et al. 2001). In ASDs, infant and childhood rashes, eczema and psoriasis are common, and they are common in family members as well (Bakkaloglu et al. 2008).

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 ASDs – 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 ASDs and what is associated with EMF/RFR exposures.

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 Belyaev, 2012 in section 15 of the 2012 BioInitiatve Report (Belyaev 2012), as well as by Salford et al. (2012) in Section 10 (Salford, Nittby, and Persson 2012). A few examples of observations after exposure have included dark neurons (an indicator of neuronal damage), as well as alteration of neuronal firing rate (Bolshakov and Alekseev 1992), and upregulation of genes related to cell death pathways in both neurons and astrocytes (Zhao, Zou, and Knapp 2007). Astrocytic changes included increased GFAP and increased glial reactivity (Chan et al. 1999; Ammari et al. 2008; Ammari et al. 2010; Brillaud, Piotrowski, and de Seze 2007), as well as astrocyte-pertinent protein expression changes detected by Fragopoulou et al, 2012 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, (Ragbetli et al. 2010)including in two studies of the impacts of perinatal exposure {Albert, 1981 #2584;Albert, 1981 #2583}. Promotion of pro-inflammatory responses in EMF-stimulated microglial cells has also been documented (Yang et al. 2010).

Neuropathology findings in ASDs have been varied and have been interpreted according to various frameworks ranging from a regionalized approach oriented to identifying potential brain relationships to ASD's behavioral features (Amaral, Schumann, and Nordahl 2008)to identifying receptor, neurotransmitter and interneuron abnormalities that could account for an increased excitation/inhibition ratio {Levitt, 2009 #551}{Geschwind, 2007 #2586}{Anney, 2010 #423}{Casanova, 2006 #2587}{Rubenstein, 2003 #809}. 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. 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. (Bauman and Kemper 2005) 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 {Herbert, 2005 #642}.

Neuroinflammation, glial activation and excitotoxicity

Although much attention has been paid in ASD brain literature to specific regions manifesting differences in size and activity in comparison to those without ASDs, 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 ASD diagnosis, in which activated astrocytes and microglial cells as well as abnormal cytokines and chemokines were found. Other research has identified further astrocyte abnormalities include, altered expression of astrocyte markers GFAP abnormalities including elevation, antibodies, and altered signaling {Laurence, 2005 #1729;Singh, 1997 #1730}(Fatemi et al. 2008). Increased microglia activation and density as well as increased myeloid dendritic cell frequencies have also been documented. (Vargas et al. 2005; Breece et al. 2012; Tetreault et al. 2012), as has abnormal microglial-neuronal interactions (Morgan et al. 2012). Recently through use of the PET ligand PK11105 microglial activation was found to be significantly higher in multiple brain regions in young adults with ASDs (Suzuki et al.

2013). 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 (Garbett et al. 2008). 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, and an immune-glial module showing no such enrichment for autism GWAS signals (Voineagu et al. 2011).

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 ASDs may have distinctive cellular characteristics – e.g. the amygdala (Baron-Cohen et al. 2000; Dziobek et al. 2010; Hall et al. 2010; Mercadante et al. 2008; Nordahl et al. 2012; Otsuka et al. 1999; Schulkin 2007; Schumann and Amaral 2006; Schumann et al. 2009; Truitt et al. 2007; Zirlinger and Anderson 2003), which may have a larger or more reactive population of astrocytes (Johnson, Breedlove, and Jordan 2010) 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 ASD's features. More widely distributed brain tissue pathology be part of what leads to differences in ASDs in brain connectivity. However these types of tissue-function relationships have been poorly investigated. The contribution of tissue differences is one of the physical considerations covered by Belyaev (2012) in Section 15 of the 2012 BioInitiative Report {Belyaev, 2012 #2324}.

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 (Anitha, Nakamura, Thanseem, Matsuzaki, et al. 2012) or deficit of mitochondrial electron transport chain complexes (Chauhan et al. 2011), brain region specific glutathione redox imbalance (Chauhan, Audhya, and Chauhan 2012), and evidence of oxidative damage and inflammation associated with low glutathione redox status (Rose, Melnyk, Pavliv, et al. 2012). Oxidative stress markers were measured as increased in cerebellum (Sajdel-Sulkowska, Xu, and Koibuchi 2009).

Additional support for the presence of tissue pathophysiology-based changes in brains of people with ASDs comes from the various studies documenting reduction in Purkinje cell numbers (Whitney et al. 2009; Whitney et al. 2008; Bauman and Kemper 2005; Shi et al. 2009; Blatt and Fatemi 2011; Fatemi et al. 2002; Fatemi et al. 2012), possibly due to oxidative stress and an increased excitation/inhibition ratio that could potentially be acquired (Fatemi et al. 2012). 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. (Yip, Soghomonian, and Blatt 2007, 2008, 2009) A consensus statement on the cerebellum in ASDs 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."* (Fatemi et al. 2012)

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 (Dager et al. 2008). 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 (Bode et al. 2011; Cascio et al. 2012; Mak-Fan et al. 2012; Travers et al. 2012; Walker et al. 2012; Wolff et al. 2012){Sundaram, 2008 #2588} 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 (Wolff et al. 2012). 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 possibilty that emergence during the first few years of life of tissue pathophysiology disturbances such as neuroinflammation might be contributing to these trends (Herbert 2012).

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 ASD group than individuals in the neurotypical control group (Muller et al. 2003; Dinstein et al. 2012). 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 (Carrubba and Marino 2008; Marino, Wolcott,

Chervenak, Jourd'heuil, Nilsen, Frilot, et al. 2001; Marino and Frilot 2003; Carrubba et al. 2006; Carrubba et al. 2012; Marino, Nilsen, and Frilot 2003; Marino, Wolcott, et al. 2001, 2001; Carrubba et al. 2007; Marino et al. 2000){Bachmann, 2005 #2072} .

The presence of various types of tissue pathophysiology both in findings in postmortem tissue from individuals with ASDs and in documented impacts of EMF/RFR exposure are intriguing and suggest overlap in processes involved. But it is not really possible to infer any specific agent of injury from cellular responses since for the most part these are not specific but rather are stress or repair responses generic to a variety of triggers. It is important to entertain how environmental agents could contribute to brain changes in ASDs, 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 ASDs as well.

Altered development

There is some evidence for altered brain and organism development in relation to EMF/RFR exposure. Aldad et al. 2012 exposed mice in utero to cellular telophones, with resultant aberrant miniature excitatory postsynaptic currents, dose-responsive impaired glutamatergic synaptic transmission onto layer V pyramidal neurons of the prefrontal cortex (Aldad et al. 2012). 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 (Lahijani, Tehrani, and Sabouri 2009).

Although it is of great interest to characterize the changes in development associated with ASDs, 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 ASDs 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, 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 (Bellieni, Tei, et al. 2012); these exposures also impact heartrate variability . 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 1m 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., IEEE802.11b and Bluetooth Class I".*(Kuhn et al. 2012) Even exposure of the fetus to laptop computer wireless emissions through the pregnant mother's use of them may on her lap involve induction of strong intracorporeal electric current densities from the power supply possibly even more than the device itself (Bellieni, Pinto, et al. 2012).

Brain Blood Flow and metabolism

Cerebral perfusion and metabolism abnormalities have been identified in close to 2 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 (Theberge 2008). 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 {George, 1992 #2565}{Gupta, 2009 #2575}{Degirmenci, 2008 #2563}{Wilcox, 2002 #2578}{Galuska, 2002 #2564}{Ohnishi, 2000 #2571}, temporal lobes {Boddaert, 2002 #2558}{Burroni, 2008 #2559}{Degirmenci, 2008 #2563}{Galuska, 2002 #2564}{George, 1992 #2565}{Hashimoto, 2000 #2566}{Ohnishi, 2000 #2571}{Ryu, 1999 #2573}{Starkstein, 2000 #2576}{Zilbovicius, 2000 #2579}, as well as a variety of subcortical regions including basal ganglia {Degirmenci, 2008 #2563}{Ryu, 1999 #2573}{Starkstein, 2000 #2576}, cerebellum {Ryu, 1999 #2573}, limbic structures {Ito, 2005 #2568}{Ohnishi, 2000 #2571} and thalamus {Ito, 2005 #2568}{Ryu, 1999 #2573}{Starkstein, 2000 #2576} – i.e., in a widely distributed set of brain regions. It is interesting to note that even with this regional variation in localization, most of these publications showed that

cerebral perfusion was *reduced*; in the only one of those studies reporting some areas of localized hyperfusion, these areas were found in the middle of areas in the frontal pole and temporal lobe that were hypoperfused {McKelvey, 1995 #2570}, Only one study showed no difference in perfusion between autistic and control subjects {Herold, 1988 #2567}. 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 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 (Volkow et al. 2011). 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, in the right orbitofrontal cortex and in the lower part of the right superior temporal gyrus . 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, this time in the temporoparietal junction (Kwon et al. 2011).

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. (2011) ^{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. Given the types of damage at the cellular level covered in this pathophysiology section so far – including oxidative stress, membrane and barrier function damage and poorly functioning channels, which occur both in ASDs as a consequence of EMF/RFR exposure, and given the heterogeneity of localization of abnormalities in the autism perfusion papers as well as considerations of nonlinearity, it may not be so surprising that the results in the two PET studies of human impacts of EMF exposure were not consistent.

6. 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 ASD 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 synapses be generated? How well will immune-activated and thereby distracted glial cells be able to modulate synaptic and network activity? (Tasker et al. 2012; Eroglu and Barres 2010; Bilbo and Schwarz 2009; Fields 2006)

At present we are in the early stages of being able to formulate these questions well enough to address them. We do know that microglial activation can impact excitatory neurotransmission mediated by astrocytes (Pascual et al. 2012). We do know that the cortical innate immune response increases local neuronal excitability and can lead to seizures (Rodgers et al. 2009; Gardoni et al. 2011). We do know that inflammation can play an important role in epilepsy (Vezzani et al. 2011). We know less about lower levels of chronic or acute pathophysiological dysfunction and how they may modulate and alter the brain's electrophysiology.

Seizures and Epilepsy

EEG signals in ASDs are abnormal on a variety of levels. At the most severe level, EEGs show seizure activity. 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 ASDs 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. Although less than 50% of people 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.

Epileptic seizures can be both caused by and cause oxidative stress and mitochondrial dysfunction. Seizures can cause extravasation of plasma into brain parenchyma (Mihaly and Bozoky 1984; Librizzi et al. 2012; Marchi et al. 2010; van Vliet et al. 2007; Yan et al. 2005) 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 (Tore et al. 2002; Tore et al. 2001), 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 – which, as discussed above, is a lot more common in ASDs than in the general population.. EMF/RFR exposures from mobile phone emissions have been shown to modulate brain excitability and to increase interhemispheric functional coupling (Vecchio et al. 2012; Tombini et al. 2012). 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 (Carballo-Quintas et al. 2011), 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 (Varro et al. 2009). 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 (St-Pierre et al. 2007)

Sleep

Sleep involves a profound change in brain electrophysiological activity, and EEG abnormalities including disrupted sleep architecture figure in sleep challenges in ASD. 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 (Buckley et al. 2010; Giannotti et al. 2011), with these sleep problems being worse in children with ASDs who regressed than in those who did not regress into their autism {Giannotti, 2011 #1611}. 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 {Borbely, 1999 #2165}{Huber, 2003 #2166}.

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 (1996) reported an 18% reduction in REM sleep, which is key to memory and

learning functions in humans. In ASDs 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 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."* (Clinton et al. 2011) With disturbance simultaneously at so many of these levels, it is not surprising that sleep dysregulation is nearly universal in ASDs, and common in the setting of EMF/RFR exposures.

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, and often using data collected in controlled research settings with high density array equipment and carefully designed stimuli paradigms. In these settings a variety of abnormalities have been identified other than epileptic. These include 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 (Sun et al. 2012; Rojas et al. 2008){Rippon, 2007 #2585} and others showing reduction of spectral power across all bands (Tierney et al. 2012) while still others showed increased high-frequency oscillations (Orekhova et al. 2007) Abnormalities in coherence and synchronization between various parts of the brain have been found (Muller 2008; Muller et al. 2011; Wass 2011), comparable to abnormal functional connectivity measured by fMRI (Just et al. 2004) but measurable using EEG or MEG with higher temporal resolution {Duffy, 2012 #2593}{Isler, 2010 #1421}{Murias, 2007 #2591;Murias, 2007 #2590}{Coben, 2008 #2592}. Several studies have identified reduced complexity and increased randomness in EEGs of people with autism (Lai et al. 2010; Catarino et al. 2011), as well as an increase in power but a reduction in coherence (Isler et al. 2010; Mathewson et al. 2012). Some electrophysiological metrics are emerging as potential discriminators between brain signal from individuals with ASDs and those who are neurotypical, such as a wavelet-chaos-neural network methodology applied to EEG signal (Ahmadlou, Adeli, and Adeli 2010).

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 (Hinrikus et al. 2008), to increase randomness (Marino, Nilsen, and Frilot 2003;

Marino and Carrubba 2009), to alter power, to modulate interhemispheric synchronization (Vecchio et al. 2007), to alter electrical activity in brain slices (Tattersall et al. 2001) and to alter the patterns of coordination (spectral power coherence) across the major power bands (Hountala et al. 2008). Bachman et al. (2006) showed statistically significant changes in EEG rhythms and dymanics occurred in between 12% and 20% of healthy volunteers {Bachmann, 2006 #2069}. In children, exposures to cell phone radiation have resulted in changes in brain oscillatory activity during some memory tasks [97,102].

Sensory processing

At the symptomatic level issues with sensory processing are highly prevalent in ASDs. Phenomenology 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. (Robledo, Donnellan, and Strandt-Conroy 2012; Perry et al. 2007; Sacco et al. 2010) 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. Some studies have shown lower and some longer latencies of response to an auditory stimulus. Domains of perception where the performance of people with ASDs is superior to that of neurotypical individuals have been identified. (Marco et al. 2011) *"It is obvious…that sensory processing abnormalities in ASD are distributed rather than localized; sensory abnormalities in ASD obviously span multiple dimensions of latency, adaptation, magnitude and behavior abnormalities, with both enhanced and impaired behavior associated with aberrant cortical responses. Given this diversity in findings, the heterogeneity of ASD, and broad variability seen over and over again in the ASD groups almost irrespective of the study, it is hard to imagine that one single theory could account for all of these observations…. It is therefore 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."* (Kenet 2011)

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 and physical properties as well. Yet although there is some consideration of the pathophysiology-sensory function interaction (Kern et al. 2010), it has basically not been fleshed out in studies of ASDs with experimental designs integrating pathophysiological and electrophysiology.

Kenet et al. (2010) 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{Kenet, 2011 #1852}. *"Although the hearing sensitivity and brainstem auditory responses of pups were normal, exposure resulted in the abnormal development of the primary auditory cortex (A1). A1 was irregularly shaped and marked by internal nonresponsive zones, its topographic organization was grossly abnormal or reversed in about half of the exposed pups, the balance of neuronal inhibition to excitation for A1 neurons was disturbed, and the critical period plasticity that underlies normal postnatal auditory system development was significantly altered. These findings demonstrate that developmental exposure to this class of environmental contaminant alters cortical development."* (Kenet et al. 2007). This study may be particularly relevant for EMF/RFR exposures, as the noncoplanar PCBs were discussed above as targeting calcium signaling as do EMF/RFR exposures – i.e. they both converge upon a common cellular mechanism (Pessah and Lein 2008; Stamou et al. 2012), justifying exploring the hypothesis that the outcomes one might expect from EMF/RFR could be similar.

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 (Andrzejak et al. 2008; Szmigielski et al. 1998; Bortkiewicz et al. 2006; Graham et al. 2000; Saunders and Jefferys 2007). Buchner and Eger (2010), 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 (Buchner and Eger 2011).

Effects on the neonate are also evident. Bellieni et al (2008) 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 (Bellieni et al. 2008). 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 (Witter et al. 2009).

Meanwhile clinical observation and a growing body of literature support a major role for stress in ASDs (Anderson and Colombo 2009; Anderson, Colombo, and Unruh 2012; Daluwatte et al. 2012; Ming et al. 2011), with variability amongst individuals in the severity of the stress response but a tendency to have high tonic sympathetic arousal at

baseline (Hirstein, Iversen, and Ramachandran 2001; Toichi and Kamio 2003; Ming, Julu, et al. 2005; Mathewson et al. 2011; Cheshire 2012; Chang et al. 2012).

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 (Tore et al. 2002; Tore et al. 2001). Salford et al. (2012) reviewed the results:

> *"Comparing the animals, which had been subjected to ganglionectomy, to the other animals, Töre et al. made an interesting observation: as expected, albumin extravasation was more prominent in the sympathectomised sham-exposed rats as compared to normal exposed rats. This was due to the fact that the sympathectomised rats were in a chronic inflammation-prone state with hyper-development of pro-inflammatory structures, such as the parasympathetic and sensory inputs as well as mast cells, and changes in the structure of the blood vessels. Such an inflammation-prone state has a well-known effect on the BBB leakage. However, when comparing sham-exposed sympathectomised rats to GSM-exposed sympathectomised rats, a remarkable increase in albumin leakage was present in the GSM exposed sympathectomised rats compared to the sham rats.* ***In the GSM-exposed sympathectomised rats, both brain areas and the dura mater showed levels of albumin leakage resembling those observed in positive controls after osmotic shock****.[emphasis added] Indeed, 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."* (Salford, Nittby, and Persson 2012)

This dramatically greater impact on an autonomically and immunologically vulnerable set of animals raises concerns since the vulnerabilities of these animals bear some resemblance to the pathophysiological challenges of individuals with ASDs.

The interconnection between stress and brain connectivity (or coherence) in ASDs is brought out by Narayanan et al. (2010) n a pilot study testing the impact of the beta blocker propranolol on brain functional connectivity measured using functional MRI(Narayanan et al. 2010). 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{Hasselmo, 1997 #2594}, allowing it to utilize and coordinate more remote parts of its networks. This suggests that stressors such as EMF/RFR, by adding non-biologically meaningful noise to the system, might have the opposite effects, degrading coherent integration.

C. DE-TUNING OF THE BRAIN AND ORGANISM

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

While electrophysiological activity is an intrinsic property of the nervous system, electromagnetic signaling are vital parts 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 environments. Exposure to power-frequency fields far stronger than the natural environment is now universal in civilized society."* (Adey 1994)

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****."* (Adey 1994)
> Communication between cells through gap junctions, which is a means of "metabolic cooperation," is also vulnerable to disruption, as discussed earlier.

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 (Buzsaki 2006; Strogatz 2003). 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 (Strogatz 2001) (Strogatz 2003).

> *“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.”* (Strogatz 2003)

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. 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.”* (Iotti, Borsari, and Bendahan 2010)

The field of bioelectromagnetics has studied exposure to very low levels of electromagnetic frequencies.

> These exposures can alter critical properties of chemical reactions. *“In a chemical reaction, the bond breaks and each partner reclaims its electron from the bond, moving away to encounter a new partner. It is now an unattached, highly reactive free radical. Reforming a bond requires a meeting between two radicals with opposite electron spins, the union producing a singlet pair. The*

lifetime of free radicals is typically short, in the range of microseconds to nanoseconds. It is in this brief period that imposed magnetic fields may alter the rate and amount of product of a chemical reaction. Since the effect is only on the kinetics of chemical reactions, they are known as magnetokinetic effects (Steiner and Ulrich, 1989). They occur only in nonthermal states of biomolecular systems, defined as an insensitivity to random thermal interactions during the brief period of their existence (Walleczek, 1994). They are a consequence of a coherent quantum-mechanical step which accompanies free radical formation." (Adey 1994)

Not just chemical reactions but synchronous biological oscillations in cells (pacemaker cells) can be disturbed and disrupted by artificial, exogenous environmental signals, whicn 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 (Strogatz, 1987). Buzsaki in his book *Rhythms of the Brain* (2006) says "*rhythms can be altered by a wide variety of agents and that these perturbations must seriously alter brain performance."* (Buzsaki 2006)

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 sever 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 being synchronized{Strogatz, 2003 #1969}. It has even been suggested that autism itself could be due to brain desynchronization {Welsh, 2005 #528}.

2. Behavior as an "emergent property"

Although 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, to date almost no attention has been paid to testing this hypothesis in ASD or neurodevelopmental and neuropsychiatric conditions more generally. From this vantage point it would make sense to propose that the compromised whole body health status of at least many with ASDs 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 ASDs as core '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 (Anderson 2009, 2008; Sieb 2004; Smith and Thelen 2003; Custodio et al. 2007; Herbert 2012). Sleep and consciousness have also been considered 'emergent properties' (Krueger et al. 2008; Krueger and Obal 2003). 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(Juutilainen and Kumlin 2006; Juutilainen, Kumlin, and Naarala 2006; Verschaeve et al. 2006; Ahlbom et al. 2008; Hoyto et al. 2008; Juutilainen 2008; Luukkonen et al. 2009; Markkanen, Juutilainen, and Naarala 2008), 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 ASDs happen in individuals and to why there are more reported cases of ASDs than ever before (with studies showing that not all of this increase can be written off as artifact (King and Bearman 2009; Hertz-Picciotto and Delwiche 2009)).

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 ASDs 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 to strongly reduce exposures and to make aggressive constructive environmental changes – particularly in diet and nutrition, given their protective potency discussed above (Herbert and Weintraub 2012). 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.

PART III: IMPLICATIONS

A. SUMMARY

In the above review, the case has been made that ASDs 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 disorders (ASDs) 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 exposures (EMF/RFR). At the cellular and molecular level many studies of people with ASDs 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 ASDs 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 ASDs 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 ASDs, that parallels the dramatic rise in deployment of wireless technologies, a strong case can be made for aggressively investigating links between ASDs 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 ASDs 'are' and how they work. 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 improve the situation.

B. EXPOSURES AND THEIR IMPLICATIONS

Several thousand scientific studies over four decades point to serious biological effects and health harm from EMF and RFR as are intensively reviewed in the many detailed sections of this BioInitiative Report. 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.

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 other parts of this Bioinitiative 2012 update {Sage, 2012 #2595}, 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 'epidemiologially visible', there are no comprehensive and systematic global health surveillance programs that really keep up to report EMF/RFR health trends (Fragopoulou et al. 2010).

> "*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 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." (Sage and Carpenter 2009).

2. The population's exposure has increased

Given the range of physiological impacts described in Part 2, 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.

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 {Roche, 2012 #2614;Cellular Telephone Industry of America (CTIA), 2012 June #2615}. About 220,500 cell sites existed in 2008 {Reardon, 2007 #2613}{Cellular Telephone Industry of America (CTIA), 2012 June #2615}{Anonymous, 2005 May 20 #2618}. 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 radiofrequency radiation exposure. Other new RFR exposures that didn't 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 [16]. 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 {Roche, 2012 #2614;Cellular Telephone Industry of America (CTIA), 2012 June #2615}. 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 is 101%.

The annualized use of cell phones in the US was estimated to be 2.23 trillion minutes in 2008 [16] and 2.296 trillion minutes in 2010 (CITA, 2012). There are 6 billion users of cell phones world- wide in 2011 up from 2.2 billion in 2008 [17] 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 {Roche, 2012 #2614;Cellular Telephone Industry of America

(CTIA), 2012 June #2615}. 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.

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

With regard to children, 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 RF 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 close and repetitive exposures to both EMF and RFR in the home. 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 {International Agency for Research on Cancer of the World Health Organization, 2011 May #2616}{Baan, 2011 #2598} . The great utility of handheld devices as communication aids and sources of information and satisfaction for people on the autism spectrum may come with a concerning underbelly.

Exposures prior to conception or during pregnancy and infancy are also important to consider. These exposures can come from faulty wiring, proximity to power lines, or high-frequency transients from a proximate transformer on a utility pole, or internal sources of pulsed RFR in the home (examples 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 and other likely consequences needing further investigation (Bellieni et al. 2008; Bellieni, Tei, et al. 2012).

Wireless phones and laptops exposures produce extremely low frequency pulses from the battery of the wireless device {Sage, 2007 #2611}(Sage and Carpenter 2009) 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 (Sage and Carpenter 2009).

4. ASD Risk and Genomic Damage to Future Generations

Barouki and Grandjean (2012) make a persuasive case that public health interventions are critically needed in early childhood development to prevent adult diseases that appear decades later (Barouki et al. 2012). 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 to be, 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)".*

Part II of this chapter documents the detailed scientific basis for considering EMF/RFR exposures to be of significance to the ASDs crisis. 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.

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 inefficiencies, misfolded proteins, and cellular debris, as discussed in the section "Implications of Damage" at the end of the first part of Part II, regarding the rescue of a mouse model of Rett syndrome through enabling a probably generic process of microglial phagocytosis, critical to debris removal, rather than through

correcting some specific molecular defect of the synapse (Derecki et al. 2012; Derecki, Cronk, and Kipnis 2012).

In the present setting, where the argument about the pertinence of the cascade of physiological and genotoxic compromises to autism includes the degradative impact on oscillatory synchronization, it is also worth considering that oscillation is a property of living and even physical systems much more generally, and not just of brain oscillatory networks (Strogatz 2003). Under certain circumstances, phase transitions occur and synchronization emerges, often rather quickly rather than gradually – more like a state change than a gradual trend. On the other hand, as mentioned, synchronization can be lost, and there are an enormous number of ways for a system to be de-synchronized, which may relate to the heterogeneity amongst people with ASD that so vexes researchers.

In the setting of autism, a baby gestated or developing as a neonate in a milieu with excessively elevated EMF/RFR exposures is bound to have interference with the normal development processes, including the organization of information and experience in the brain. This baby's environment also often 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 {Krakowiak, 2012 #2617} which converge on inflammation, oxidative stress and other common forms of physiological dysregulation associated with or even just eating nutrient-depleted, pesticide-laden processed food. 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, or other hostile 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.

From a systems point of view, the phenomenon of 'autistic regression' may occur 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 it is a severe stressor it is not triggered simply by a single source of stress in an otherwise blissfully healthy child, but rather is the "straw that breaks the camel's back' laid atop a prior accumulation of 'allostatic load.'

C. CONCLUSIONS AND RECOMMENDATIONS

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. Other sections in the Bioinitiative 2012 update will address recommendations and guidelines for increasing the safety profile. This will undoubtedly provoke controversy. The problems will not get settled immediately, and transformation to healthier arrangements will take time.

> *"There is no question that global implementation of the safety standards proposed in the Bioinitiative 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*." (Sage and Carpenter 2009)

2. Encourage precautions right now based on present knowledge

In the meantime many people have already started taking precautionary measures, and more will wish to do so. Physicians and health care people 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.
- 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.

Undoubtedly risks and the above recommendations will be dismissed by those poised to benefit from the sale of these new systems. Many people also feel that new possibilities have opened up to themselves and the world through wireless technologies. But the public needs to know that these risks exist, that transition to wireless should not be presumed safe, and that it is very much worth the effort to minimize exposures that still provide the benefits of technology in learning, but without the threat of health risk and development impairments to learning and behavior in the classroom.

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(Herbert and Weintraub 2012), all of which can be implemented safely based upon presently available knowledge.

3. Build an environmentally physiologically centered research program in ASDs as a platform for investigating the EMR/RFR-ASD linkage

This review has been structured around the physiological parallels between ASDs 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 that can incorporate the the gene-brain-behavior agenda that has dominated ASD research into a broader framework (Herbert 2013). While the middle-out approach is an emerging framework in systems biology that can incorporate complexity and nonlinear, multileveled modeling (Cristofolini et al. 2008; de Graaf et al. 2009; Majumder and Mukherjee 2011; Vinga et al. 2010; Walker and Southgate 2009), the 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, and the physiological levels largely

left out of this linear approach are critically important to helping people with ASDs because they will help not only with understanding how environment impacts function but also with identifying leverage points.

4. Take the evidence as a call to action

Both EMF and RFR exposures are already classified as IARC 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.

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 ASDs 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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