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Chapter 21

Translational Implications of a Whole-Body Approach to Brain Health in Autism: How Transduction between Metabolism and Electrophysiology Points to Mechanisms for Neuroplasticity

Martha R. Herbert*

Abstract

Autism has been viewed as a highly heritable neurobiological condition of mysterious but presumably genetic origin, which involves lifelong neurocognitive, perceptual and emotional deficits. This conceptual framing has led to a focus on searching for underlying genetic causes of differences in the autistic brain, particularly in anatomical structure, that are presumed to be hardwired into the system.

More recently, it is becoming clear that genes alone do not create autism. The more inclusive emerging view is that genes and environment interact to influence epigenetics, cell signaling and physiology.

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This formulation goes beyond the idea that a preconceptional or prenatal gene-environment interaction definitively causes a person's autism, and instead emphasizes that the interplay of all of these levels develops over time contingent upon exposures, experiences and lifestyle choices, and that the behaviors are actively produced by living cells that function differently, rather than simply being caused by static brain wiring that is different from the start.

From this vantage point it is important to look freshly at how we think about the brain, and what it is that the brain *does* to create autistic behaviors. A multi-scaled, whole-body, dynamical approach to the processes of signal generation in the brain and how these processes are shaped by ongoing dynamic interplays of multiple modulators offers previously unappreciated opportunities for improvement of brain function.

Keywords: Autism spectrum disorders; Brain; Oscillation; Multi-scale biology; Systems biology; Dynamical systems; Magnetic resonance spectroscopy; Diffusion tensor imaging; EEG; Neuromodulation; Metabolism; Mitochondrial dysfunction; Connectivity; Coherence; Neuroplasticity.

Introduction

Autism, which we will call Autism Spectrum Conditions (ASCs) rather than Autism Spectrum Disorders (ASDs) due to the neutrality of the word "condition" as compared to the judgment of deficit implied in the word "disorder" that is now in dispute both culturally and scientifically, has been viewed as a highly heritable neurobiological condition, or set of conditions, of mysterious but presumably genetic origin, which involves a host of neurocognitive, perceptual and emotional deficits. This framing has led to a focus on searching for underlying genetic causes of differences in brain, particularly in anatomical structure, that are presumed to be hardwired into the system. Researchers have also focused on developing more refined methods to characterize the nature of autism deficits to provide rigorous correlates for the genetic and brain research. Also prominent in this approach is an emphasis on pharmaceutical treatment of gene-related targets.

However, in the emerging "gene-environment-epigenetic-cell signaling-physiology" framework of dynamical multi-scale systems biology, maintaining a simple bottom-up deterministic approach is giving way to multi-scale, interactive, dynamical understandings of ASCs. *This in turn opens the way to entry points into intervention from multiple levels.*

Our framing of the role of the brain in creating and sustaining autism needs to be brought up to date with this systems approach. Therefore, in what follows we will:

- review the reasons for broader, more multisystem and more dynamical understandings of ASCs;
- look at what we already have observed about the brain from this fresh perspective, and
- offer a dynamical, process-oriented, electrophysiologically centered model of the biology that constructs the behavioral outputs we label as "autism".

The approach elaborated here emphasizes the sources of brain function plasticity that can derive from whole-body interventions that can modulate brain health. The overall point is that when we are able to transition from the belief that autism is a hardwired trait to the model that much or sometimes all of autism may be related to states that are dynamic and changeable, we will be able to make much more rapid and effective progress toward minimizing suffering and maximizing potential in this growing group of people with huge challenges but also great gifts.

Beyond Hardwired: Autism Not Born but Made

Although autism has been considered a lifelong genetically-caused neurological condition, evidence and clinical observations are pointing to a different framing of autism, namely that autism may not be totally or even mainly hardwired from genetics, but may emerge from a combination of interacting exposures and stressors,

some or many of which can be dialed back. Here are some of the considerations pointing toward this reframing of autism:

- ***Numbers of reported cases are increasing markedly***, and analyses of these trends show that this cannot be ascribed purely to increasing awareness, earlier age at diagnosis or more lenient diagnostic criteria[1,2] — and since you cannot have a genetic epidemic, at least some of these new cases must arise from "environment" — i.e., changes in our world and how we live in it.
- ***We are learning that there is more to autism than genes, brain and behavior***, because problems becoming more commonly identified in ASCs include a range of medical issues and whole-body/systemic physiological abnormalities that go beyond the disorders of early brain development previously thought to be the causes and core of autism.[3,4]
- ***We are learning that there are more contributors to behavior than brain.*** More broadly, science beyond just autism is revealing that shifts in gut, immune, endocrine and other body systems as well as microbial ecology can change the way the brain functions.[5–12]
- ***Regression really does occur***. Whereas it used to be thought that parents who claimed that their children had regressed into autism were naïve new parents who had missed earlier signs of abnormality, regression of previously essentially healthy infants and toddlers into autism is now solidly documented; this suggests that autism may develop — and contingently so, depending on the accumulation of exposures and circumstances — rather than be predetermined and hardwired prenatally or even from conception.[13–17]
- ***Regression and medical features may be related***, given the common association between these phenomena. Children who regress into autism often have a history of medical problems such as recurrent infections, gastrointestinal issues, food sensitivities, sleep disturbances, rashes and irritability.[18–20]
- ***Autism is not fixed but rather is variable***. More careful observation of individuals with autism has revealed substantial variability of severity *within* as well as between individuals — over short and

longer terms. Sometimes a good day can be turned into a bad day quickly by a food or chemical exposure. Sometimes there is improvement that is transient and goes away — improvement during fever,[21,22] clear-fluid diet before medical procedures, during treatment with some antibiotics.[23] Some children with autism who receive short courses of steroids for acute problems like asthma attacks speak much more fluently and are more interactive for the duration of the treatment. Sometimes improvement persists, even to the point of loss of diagnosis, which has now been documented in a significant minority of individuals with autism. All of this variability undermines the idea that we can treat the level of severity on any particular day as genetically hardwired. This will be discussed more extensively below.

- ***Autism can no longer be considered simply a set of "deficits,"*** since many of the aspects of human functioning previously considered deficient or absent are now known to be present. Cognitive deficiency turns out to have been greatly overestimated, in part from testing people with ASCs with tests not suited for their cognitive styles.[24,25] Certain areas of perception are stronger and more discerning in people with ASCs than in neurotypical people.[26,27] Contrary to stereotypes, there is certainly no lack of emotion, though there may be issues with its expression. Lack of speech does not at all equate with lack of intelligence or even lack of the ability to read or write; more and more people with non-verbal ASCs or with verbal apraxia (difficulties in orally producing speech) and/or motor coordination or proprioceptive challenges are able to type, some even to the point of writing books.[24,26,28]
- ***The different aspects of autism are interconnected.*** Although not everyone has the same combination of symptoms, that does not make each symptom strictly discrete and separated from the others. One piece of support for this is the often widespread impact of systems-oriented treatments and interventions, which although commonly observed needs better published documentation. Though conventional medicine thinks that treatments should target specific symptoms, various kinds of treatments targeting

resiliency more generally — whether improving diet, reducing toxicity or improving neuro-movement coordination — lead to improvement in domains not specifically targeted by the treatments. This suggests that autism is not simply a collection of discrete, independently determined symptoms, but also — or perhaps instead — involves an overall compromise in adaptive function and brain coordination that affects many neurofunctional domains at once.[29] If the latter is the case, it makes sense that improving resiliency (with the idea of improving the brain's capacity to coordinate) can have a constructive impact on many domains at once, or at least over time. This phenomenology will be explored in further detail below in the section on autism as an "emergent property" rather than a discrete entity.

To summarize the implications of the above points in a sentence, it appears that rather than being uniformly predestined and lifelong, autism can be created, can emerge, and thus can also be ameliorated or even resolved if the underlying factors driving its emergence can be overcome or dialed back.

What are These New Observations Telling Us About How Autism "Works"?

Each of the observations above indicates interactions between biological and behavioral levels of functioning.

- Increasing numbers of cases suggests that the way the brain produces behaviors is being altered by environmental influences.
- Multisystem medical issues in autism, which have been labeled as "co-morbidities" as if they were there by coincidence, may actually be integrally related to the overall set of issues that create the "autism."
- Regression into autism suggests that the overall system can be shifted so that the way the brain functions is changed over time.
- The common association of regression with medical problems suggests that these brain changes occur in relation to stressors that are changing the underlying biological "settings" of the brain.

- Day-to-day variability in autism suggests that brain function is not totally hardwired but that its ups and downs may be influenced by environment — for example, brain inflammation may be worse with chemical or allergen exposure (or even sleep deprivation), or better on an allergen-free diet or reduced stress and feeling of safety.
- Transient and persistent improvements and loss of diagnosis suggest that ***autism is a functional issue, and not necessarily a hard-wired trait*** — and that the functional problems are related to ***obstruction*** of the expression of potential, rather than an underlying deficit of potential. The association of improvement with removal of noxious triggers, such as allergens or toxic exposures, is further support for the suggestion that the physiology that modulates brain "settings" may be altered by day-to-day biological influences.
- The observation that many symptoms may improve in coordination with each other suggests that conceptualizing symptoms as discrete entities created by distinct genetic influences may not be biologically accurate.

New Directions for Research and Treatment: Whole-Body Approach to Brain

If autism is something that develops rather than being predestined by genes, a whole new set of questions arise to drive research and treatment. These questions center around the ways different systems of brain and body relate to each other — how they maintain each other, help each other, or hurt each other. This is important because we would like to identify treatments and interventions that have the strongest and most widely distributed positive impacts possible — we want *the most leverage possible* out of what we do. To get this leverage, we need to focus on clarifying critical and intrinsically translational questions such as:

- How does regression happen? What are the changes in brain and body? What triggers drive these changes?
- How do problems with medical and systems physiology throughout the body affect the brain?

- What are the health problems of brain cells and tissue that underlie or contribute to what we label as "autism"?
- In particular, how does compromise of the biological health status of the brain cells and tissues affect the electrical signaling activities of the brain?
- How does remission or recovery happen? What are the changes in brain and body? Are they like playing a movie of regression in reverse? Or are the processes different?

How a Whole Body Approach Reframes the Role of the Brain in Autism

The issue I will focus on most centrally is the implications all of these observations and questions have on our understanding of the brain in autism. ***If*** we simply assume that autism is "hardwired" into the brain, ***then*** we look for the genes that "create" the wiring diagram, and seek treatments to ***compensate*** for the situation, believing still that at its core autism is fixed and unchangeable. It does not change things that much to shift the focus just to epigenetics, if the term is used in a generic, nonspecific way while the belief remains that the outcome is essentially hardwired (even though epigenetics is in its essence *not* hardwired but responsive to physiological and environmental stressors — or supports).

But ***if*** we notice the ways in which the brain is ***not*** fully hardwired, then we start to ***wonder and seek for*** where its flexibility and plasticity might come from. This allows us to be open to noticing and enhancing ways to maximize the expression of brain potential.

I propose that maximizing brain potential is best accomplished through a whole-body approach to the brain. My rationale is that many sources of transformation may arise from the way improvements in the health status of some levels of the brain and body ***transduce into — are transformed into*** — improved function at other levels of the system, particularly the brain.

Multi-Scale Interacting Aspects of Brain Biology and Function

Here are some of the reasons that the "genes-brain-behavior" model is an oversimplification of a remarkably more complex situation.

Problems in the body that have parallels in the brain

The challenges that the brain faces are in major part related to the problems faced by molecules, cells and tissues in other parts of the body. By now abundant research is showing that biochemical, metabolic, or energy-producing processes may work inefficiently or in an unbalanced way in people with autism spectrum conditions (as well as in a variety of other chronic conditions). Cells, tissues and organs may have difficulty with detoxification of noxious substances, or with getting rid of their garbage (such as misfolded proteins).[30] Cell membranes or internal structures like the cellular skeleton (cytoskeleton), receptors and channels in the membranes and various other cellular components may have problems with their structure or function.[31–38] These problems can include alteration of or injury to the lipid/fat composition of membranes that may lead to stiffness or frailty that impedes proper function of receptors and channels that live in the membranes, or that may lead to leakiness that compromises the separations between inside and outside of the cell, or between compartments inside the cell, that membranes are supposed to provide.[39,40] On a larger scale, people's bodies contain barriers such as the gut-blood barrier or the blood-brain barrier whose structures or functions may be compromised in ASCs (or other chronic conditions).[41–45] Cellular and tissue function, energy and resilience may be altered, depleted or hampered by inflammation or oxidative stress.[46,47] Atypical populations of organisms in the microbiome, including missing helpful organisms and/or the presence of harmful organisms, may produce substances that circulate and change the activities of cells in other parts of the body.[48–53] All of these "whole body" problems may impact the cells and tissues in the brain as well as in the rest of the body.

But a critical point for truly understanding the ***autism itself***, and not just the contributors, is that the functions of the brain are not just physical and biological like the rest of the body. If autism were purely whole-body (e.g., immune, GI) and not whole body-brain, then we would have a lot of brilliant people walking around with allergies and gastric reflux but not with brain problems. We need to understand what happens en route from body to brain to make it ***autism***.

Brain: Transduction between Physical and Informational Levels

The brain is an organ that has both organ-type functions and information-type functions. While the rest of the body also engages in energy and information activities, these activities are taken to a much higher and more complex level in the brain. However, in my opinion, brain research in autism has largely been characterized by either lack of insight or confusion regarding how these levels interact.

- On one side we have cognitive neuroscientists who look for genetic correlates of differences in information processing patterns or localization of brain activity without taking account of cellular, metabolic and tissue problems in the underlying brain tissue that prominently include inflammation, mitochondrial dysfunction or oxidative stress.
- On the other side we have tissue pathophysiology-oriented researchers who look at the cellular and biochemical changes in great detail, but do not think through how these changes actually alter the *information processing activities* of the brain so it produces the behaviors we label as "autistic."

When colleagues make the argument that a whole-body approach to autism (i.e. addressing medical and physiological problems and not just using behavioral and psychopharmacological interventions) improves the functioning and quality of life

of people with autism, what we are taking for granted without actually explaining it is that ***whole-body interventions help the brain process information better by generating better health for the cells and tissues that do the information processing***.

Therefore, I believe that it is time to explicate this linkage. To really transform treatment strategies in autism, I believe it is imperative that we bridge — translate between — these two levels. In what follows, I will look at older observations from the newer perspective of a whole-body approach to the brain.

Brain as a Physical Organ: The Poorly Explored Relationships between Anatomy and Pathophysiology

A variety of anatomical observations have been made in the brains of people with autism, both microscopically in brain tissue from people with autism who have died, and macroscopically using brain imaging technologies, such as magnetic resonance imaging (MRI), positron emission tomography (PET) or single photon emission computed tomography (SPECT).

The observations show intriguing differences between people diagnosed with autism and people with other diagnoses or with neurotypical development. However, the ways these observations have been interpreted may often be more revealing about the assumptions people have brought to this research than about what may actually be going on. From a whole body-brain vantage point, many of these observations need to be reconsidered freshly and their prior interpretations re-thought, keeping in mind our growing understanding of dynamical pathophysiology. The following sections cite some examples.

Microscopic findings

Changes in cell size and density over time

At the microscopic level, it has been known for decades that cells in the brain in ASCs may have different shapes or sizes than in

neurotypicals. For example, Bauman and Kemper have reported that neurons may be larger in children with autism compared with those in neurotypical children and smaller in adults with autism than in neurotypical adults.[54] Why might this be? Although these investigators had originally proposed that autism was created prenatally because the limbic system, which showed smaller and more tightly packed cells in their studies, forms in the brain at around the 32nd week of gestation,[55] their observation that this change in size and density occurred far into the lifetime and long past birth led them to suggest that some subtle but persistent changes might be going on in these cells, though they did not specify what these changes might be. Could processes such as inflammation or oxidative stress be slowly eating away at the robustness and resilience of these cells physically — and also functionally?

Differences in density of the fine dendritic fibers emanating from neurons

Other microscopic observations may also be related to the impacts on cells of persistent irritation from chronic tissue pathophysiology. The fibers from neurons, called dendrites, may be of different density — sometimes thicker, sometimes thinner.[56] The SHANK3 mutation is associated with more dendritic fibers, ironically juxtaposed with less neuronal "firing power" — perhaps a compensation for other factors leading to poorer synaptic activity.[57,58] Dendrite density can also be altered by seizures and epilepsy, which greatly irritate neurons. Zinc deficiency, quite common in autism,[59] can dysregulate the synaptic proSAP/Shank scaffold and might contribute to the development of ASCs.[60] Toxicants such as polychlorinated biphenyl compounds (PCBs) may lead to an overabundance of dendritic fibers by hijacking and confusing signals that regulate cellular development.[61,62] So altered physiology, possibly from environmental exposures, as well as genes can lead to these microscopic changes.

Beyond neurons: Glial cells

Up until recently, brain researchers in autism focused almost exclusively on neurons. Until the past year or two, hardly any papers or even abstracts were written by autism researchers about glial cells, a group of cells including astrocytes (or astroglial cells), microglial cells and oligodendroglial cells, which together outnumber neurons in the brain by 4–10:1, and which perform many vital metabolic, immune and signaling functions.[63] These cells may become "activated" (which among other things makes them bigger) to deal with perceived immunological, toxic, infectious or other cellular emergencies, and produce pro-inflammatory or excitotoxic chemicals in this state that can irritate the tissue. A growing number of studies have documented cellular, gene expression, or immune pattern changes in the brain tissue of people who had autism that are consistent with a state of immune activation or "neuroinflammation."[64–72] Although these changes may change gene expression, they may or may not be caused by genes. But the impact may not require a genetic cause.

Accumulation of protein waste products in the brain

There may be pile-ups of proteins like lipofuscin or amyloid-beta[73,74] that suggest either increase in production of these proteins (e.g. from excitoxocity, seizures or oxidative stress), problems with clearing out problem cellular byproducts, or both. Such aberrant protein accumulations have been identified in several studies of brain tissue from people with autism. The process of clearing waste products from the brain can occur through various process such as autophagy, which may be regulated or impeded by factors including oxidative stress that have been demonstrated in many individuals with autism. It is also dependent upon transport of these cellular waste products or "garbage" out of the brain through fluid channels recently dubbed "glymphatics" (because they are little fluid channels in the brain shaped by glial cells).[75–79] Little is known about fluid drainage in the brains of

people with autism, though a recent paper in *Science* reported that sleep drives metabolite clearance from the adult brain,[80] with glial shrinkage during sleep contributing to a 60% increase in interstitial space, greatly increasing convective fluxes and amyloid clearance during sleep, a function with which most people with ASCs have difficulty. In neurodegenerative diseases like Alzheimer's where abnormal substances like beta-amyloid pile up, we are learning that these glymphatic fluid flow systems function poorly, so that misfolded proteins fail to clear properly from the brain, speeding the development of dementia or other neurodegenerative diseases.[81]

Macroscopic findings

Regional size differences

At the macroscopic level, myriad anatomical brain imaging studies have measured the size of different parts of the brain and have found some parts to be larger or smaller in autism than in neurotypical people.[82,83] Much confusion has been generated by inconsistencies between studies — a region may be larger in autism in one study, smaller in another and no different in a third, particularly if you compare studies performed on younger vs. older people, suggesting that these differences change over time — and that different regions of the brain change in different ways, some getting larger over time and some getting smaller.[84,85] Could these brain volume differences start out as impairments of cellular function and only later change lead to macroscopically measurable changes in sizes or properties of brain structures? This question has received very little reflection in the autism brain research literature. Yet the size of a whole brain region is nothing more than the sum of the sizes of all the cellular, vascular, fluid, and extracellular "stuff" in that region.[84] So it would make sense that changes in the health status of any of these components, and not just genetics or high intensity activity, might be contributors to the differences in overall region size.

Overall brain enlargement

One of the most intriguing findings is that, especially in younger people with autism, the brain is on average larger than in neurotypical people, and this size increase cannot be attributed simply to the size of any one region,[86] though enlargement of white matter appears to contribute more to this overall size increase than enlargement of gray matter.[87–89] There are striking parallels between the phenomena of brain size enlargement and of inflammation, but on the other hand there is very little direct documentation of brain inflammation in young children reliably diagnosed with autism, because they rarely die and have their brains donated to research. Brain imaging of children might be able to contribute here, but it is difficult to detect inflammation more than by inference from magnetic resonance spectroscopy imaging which is hard to perform on young children without sedation; PET studies, mostly done on substantially older individuals in part due to risks from the technology and the need to inject radioactive ligands, are only recently being performed to measure this.[90] Many people who think that brain inflammation is likely to be a central player in ASCs think that the brain volume increase is likely to come from microglial cells, but it would not be inconsistent with their point of view if the brain enlargement also or instead originated from astrocytes or even fluid accumulation in the extracellular matrix. It does not, however, appear to come from a higher density of axons (the fibers that neurons send out to link to other neurons over short or long distances). Instead, the density of these fibers has been measured as lower on many occasions,[91] one of the several arguments against attributing brain volume increase in autism to failure of neuronal pruning early in development.[92]

Whole-body-brain take-home messages

Overall, the relationship between the macroscopic changes in total brain and brain region size and the underlying microscopic changes in cells, fluids and other substances in the brain is very

poorly understood, with most inferences, even if plausible, going beyond what can be solidly supported. Even so, here are several things we can say about the autism brain from observations to date from a whole-body vantage point:

- The finding of larger brains in autism suggests that the assumption that "bigger is better (or healthier)" may not always be correct, even though the details are not well worked out at present.
- The contributions of cell types other than neurons, and of tissue types other than brain cells (e.g. blood vessels, fluids, extracellular matrix) may be important in explaining what we are seeing — as well as how it got that way. Taking their roles into account may even possibly help us identify health improvement strategies that might give the tissues the resources they need to implement their repair capabilities.
- This phenomenon of widespread brain enlargement in association with autistic symptoms is perplexing to those who assume that the specific behaviors we use to diagnose autism must be localized in specific regions of the brain associated with those brain functions. It is less perplexing to those who think that behaviors emerge from dynamic interactions across large areas of brain. This leads nicely into considering the "other life" of the brain — information processing, and how physiological and informational functioning interact.

Brain as a System for Information Processing

The brain is not just a wet set of metabolizing cells; it is also an information processing organ. Many different types of cells and tissues participate in the metabolism, electrical signaling, energetics and physics of this information processing. Although it is often left unstated, the ability of each of these cell types to perform its roles is dependent upon the integrity of cellular structure and function, the supplies of nutritional precursors for biochemical processes and the maintenance of cellular integrity, and the absence of substances (e.g., toxicants or pro-inflammatory cytokines or other

metabolites) or other influences (e.g., radiation that interferes with smooth functioning).

Within the domain of research that focuses on brain information processing — called cognitive neuroscience — it is very easy to: (1) get caught up in thinking about one level of this information processing activity and forget about all the other levels that are going on simultaneously and are really part of the same overall process, and (2) forget about the supports for the underlying tissue substrate that makes this information processing possible. So let us remember here that information processing is the result of activities at many levels, ranging from synapses between neurons — including all the underlying processes that make this possible, through aggregations of signals that travel down fiber tracts. It is also related to waves of electrical activity that are related to glial cell as well as neuronal function. It is further related to modulation of blood flow. While thousands of scientists make careers studying these processes separately, in truth they are all integrated, all facets of getting the brain's job done. And from a whole brain-body health perspective, all individually and collectively depend upon underlying cellular health and integrity.

The following sections summarize some of the major areas that have captured people's attention.

"Structural connectivity" through fiber tracts

We know that neurons talk to each other through synapses and that bundles of neuronal processes, or axons, gather together in fiber tracts that link one part of the brain to another. We have measured differences in density, diffusivity and other properties of fiber bundles between people with autism and neurotypical people, using an MRI technique called diffusion tensor imaging (DTI). It is currently very fashionable in autism cognitive neuroscience research to study structural connectivity in this fashion, and to correlate it with fMRI measures to be discussed next. However, while it is tempting to infer that these structural changes "cause" autism, fiber bundles are not the only way that information is moved

around the brain. Furthermore, the changes in these fiber bundles are most likely quite a ways "downstream" of factors that include not just genes, but also and perhaps most fundamentally chronic, persistent irritating pathophysiological changes at the cellular level. In spite of the present emphasis on the technically low-hanging fruit of making these measures in fiber tracts, the underlying cellular disturbances rather than the looseness in the fiber tracts may be more basically "causative" of the functional differences leading to the autistic behaviors (by mechanisms to be further discussed below), with the fiber tract changes being secondary manifestations of these more primary cellular problems.

Specific regions that "light up" during brain activity

People with ASCs show differences from neurotypicals in the regions of their brains that activate (or "light up") in fMRI. Brain region activation appears to be more consistent in relation to the task being performed among neurotypical people, whereas the differences from neurotypicals in people with ASCs in the way their brains perform the same tasks may be "all over the map" (that is, "lighting up" different sets of regions from one person to the next).[93] This suggests that there may be no one "autism pattern" in brain activity. This in turn may mean that there is not really an "autism" but more likely a *process of dysregulation* that can create a wide variety of impacts — and that it is the *process* itself, and not the patterns that get created by the process (that in any case are fairly variable), which leads to what we label as "autism."

Tissue-level contributors to brain activation measured by fMRI

Brain activation as measured by fMRI studies arises from differences in brain blood flow and oxygenation.[94,95] This is driven by processes that involve not only neurons but other cells and tissues including astrocytes, otherwise known as astroglial cells, and the blood vasculature. Up until recently astroglial cells got almost no

attention in autism, except for a few studies noting that they were inflamed and that markers for astrocytes like GFAP (glial fibrillary acidic protein) were elevated in postmortem brain specimens, suggesting gliosis or glial activation and reactive cellular injury.[96] Astrocytes have little "foot processes" that surround the brain's capillaries and are part of the Blood-Brain Barrier (BBB). Although we know that there is a tendency for astrocytes to be "activated" and involved in brain inflammation (as briefly reviewed above regarding immune alterations, e.g. Vargas *et al*. (2005) path-breaking neuroinflammation paper[64]), we do not have an understanding of how that brain tissue pathophysiology impacts the blood flow changes that we measure in fMRI studies. fMRI researchers rarely discuss inflammatory and other influences upon astroglial cells and how they may impact the patterns of brain activation that fMRI is able to measure, because most autism fMRI researchers are not interested in brain inflammation or other brain tissue phenomena in autism; these "cognitive neuroscience" researchers instead focus mainly at the level of neurocognitive information processing but not much on the underlying cellular processes and cellular health prerequisites that make these information processing activities possible. Such researchers are more likely to jump directly to attempting to correlate their findings with genetics, skipping the vast intermediary domain of brain pathophysiology and how it may interfere with the cell's role in information processing.

Problems with blood perfusion of brain tissues

There are other ways of measuring brain activity that relate to the amount of blood flow, or perfusion, via different measurements, such as PET and SPECT scans. Many of these studies have shown poorer blood perfusion in people with autism, but the parts of the brain that have poorer blood flow are not particularly consistent from one study to another.[83] We know almost nothing about the relationship between these blood flow changes measured by these technologies and the underlying changes in the cellular health and function at the brain tissue level in ASCs. One reason is that autism

researchers using these techniques have generally been more interested in correlating changes with psychological function than with cellular and tissue changes (which in any case have not been solidly on the autism map for all that long, and are also not so easy to measure).

Electrical oscillations or "brain waves"

The brain also generates waves of electrical oscillations that are synchronized or desynchronized with each other in complicated ways, and that oscillate at a great range of frequencies.[97] We are beginning to learn about how these oscillations are different in people with autism as compared to neurotypicals, and that the differences are different depending on the frequency of oscillation. These types of brain wave differences cannot be directly mapped onto the differences we have identified in fiber bundle anatomy or density because they are not confined to travelling along those fiber tracts. Generation of synapses and the brain waves that represent aggregations of synaptic activity rest on underlying support systems, including energy production, blood flow, garbage disposal, and the ability of glial cells to smoothly and precisely support and fine-tune what the neurons do.

Temporal vs. spatial resolution of measurements and learning about autism as a PROCESS

Synaptic discharges between neurons occur in the time frame of milliseconds — thousandths of a second. Brain wave oscillations are also measured in milliseconds. These measurements can be made in human beings by EEG (electroencephalography) or MEG (magnetoencephalography), but NOT by fMRI or PET or SPECT. fMRI has much better *spatial* resolution than PET or SPECT, being much less blurry in its anatomical definitions than those technologies, as well as being non-invasive (generally nothing needs to be injected). But its temporal resolution is poor. The popularity of its

use goes hand in glove with the dominant belief that autism is a *fixed trait;* measurement of changes from microsecond to microsecond that we can get by using EEG or MEG will help us better understand the ways that autism is a constantly dynamical *process*.

The *process* consideration is important because if electrical oscillations and synaptic activity are occurring in the millisecond range, some of the underlying molecular signaling, chemistry, energetics and quantum physics processes are occurring at even more rapid rates.[98] This has significant implications for how we think about the multi-scale interactions producing autism and how we might more profitably think about autism research, as will be further discussed below.

Molecular and Cellular Underpinnings of Brain Information Processing

Underlying systems supporting brain function: Differences between cell types

From animal studies, in which needles can be placed to measure activity in specific cellular types or layers of the brain, we know that different types of brain cells generate different types and frequencies of oscillations. But since we cannot stick needles into the brains of living human beings to perform similar measurements, we can make only limited inferences from what we are learning about differences in brain oscillations as measured by EEG or MEG regarding underlying cellular status or health of different cell types in the brain. Yet even though we cannot be certain of many of the fine points of which cells are malfunctioning in what specific ways, from a whole-body-brain vantage point we can still look for signs of deficiency of underlying support systems (e.g., insufficient antioxidants, poor supply of essential fatty acids or insulin resistance), or excessive exposure to substances or processes (e.g. free radicals, toxicants, pro-inflammatory cytokines, radiation) that may interfere with optimal function.[99,100]

Underlying systems supporting brain function: Gap junctions and voltage-gated calcium channels

One further way that information is transmitted in the brain is through calcium waves generated by astroglial cells through their gap junctions. Gap junctions are actually tiny tunnels through the membranes of adjacent cells that create physical continuity between large numbers of astroglial cells. Chemicals pass through these tunnels generating calcium waves that relate to the brain oscillations and the regulation of how much activity is going on in particular regions of the brain, in ways that are poorly understood at present, not only for autism but more generally. Gap junction function can be modulated by other features related to pathophysiology, such as buildup of misfolded proteins or acidity.[101,102] For autism and other conditions where astroglial cells are activated or involved in neuroinflammatory processes, we have little or no data about how this pathophysiology impacts information processing.

Example: The potential impact of brain inflammation on brain signal-to-noise ratio

In the sections just preceding, one of the players that has shown up at multiple levels of the system is the astroglial cell, or astrocyte. Astrocytes play roles in synaptic regulation, propagation of chemically generated signals through the brain, capillary lumen caliber, integrity or compromise of the BBB, metabolic support of neurons and much more. Let us now add to this list the role that astrocytes play in regulating excitatory responses. Glutamate, an excitatory neurotransmitter at the neuronal synapse, is normally mopped up by astrocytes after the synaptic event occurred, but astroglial cells fail to do this efficiently when they are activated or inflamed. This pathophysiology-induced loss of function could very well be a major contributor to brain information processing differences in ASCs, but this potential relationship between cellular dysfunction, biochemistry and information has received hardly any attention.

If glutamate is indeed left hanging around in the synapse because activated astrocytes abdicate their clean-up duties, this glutamate will continue to stimulate neuronal responses.[103] The neurons are in no position to make a distinction between the persistent signals generated by this overload of glutamate (or the other excitotoxic or proinflammatory substances generated by the overall dysregulated milieu) and the information-containing signals from the environment which enter the brain via the sensory system. This "glutamate overload" leads to an increase in "noise" in the system. Moreover these same pathophysiological processes that impede post-synapse glutamate mop-up may also degrade the integrity of the myelin sheath around the axonal processes. Compromising the myelin reduces the insulation around the brain's axonal wiring system, which may further reduce the quality and speed of the signal and further increase the system's "noise" level.

In engineering there is a generic ratio, the "signal-to-noise" ratio (SNR), which indexes the quality of signal in a system. More signal is better; the converse means the system is functioning less well. An example familiar to everyone is cell phone signal: a cell phone with five bars of reception has good signal, but with two bars you get a lot of static (i.e., noise) and not much signal. With that kind of low SNR, the noise drowns out the signal making it very hard to have a useful conversation.

Some electrophysiological studies in autism have shown greater power and less coherence in signaling, which is evidence for a degraded signal-to-noise ratio.[104–107] Although more cross-disciplinary studies are needed, one can already say that this evidence may well reflect the impact of underlying cellular pathophysiology on the capacity of the brain to keep its electrical signaling strong and well-organized.

The above-described scenario of under-functioning astrocytes will also increase the "excitation/inhibition (E/I) ratio."[108] The brain needs to maintain a balance between excitation and inhibition to make the amount of signal "just right." Because this overall collection of pathophysiological processes increases pro-inflammatory and pro-excitatory processes and at the same time interferes with

inhibitory processes, it tends to increase the E/I ratio while decreasing the signal-to-noise ratio. So you get more noise and less information. This proclivity to overload could plausibly underlie behavioral manifestations in ASCs like poorer attention span, more meltdowns, and sensory irritability, as well as problems with sleep and vulnerability to seizures. Yet while researchers in autism and in neuroscience more broadly are very interested in this altered E/I ratio, they may still believe that the alterations must emanate from genes, and they very rarely consider potential contributors from other parts of multi-scale biology, particularly including these cell-based environmentally modulated pathophysiological processes that could quite plausibly be contributory, as can be seen from even this brief discussion.

Fast Tracking Progress in Autism Research: From Bottom-up to Middle-out and Multi-scale Approaches

Rather than thinking either bottom-up (genes and molecules "cause" everything) or top-down (which in autism would include the idea that behavioral therapy is the best therapy), I think that the "middle-out" approach along with a multi-scale approach,[109] both of which are increasingly discussed in the physiological and systems biological literature, will advance us more rapidly toward effective ways of helping people with autism.

The "middle-out" point of view is articulated by specialists in physiology and metabolism, most eloquently by the British muscle physiologist Denis Noble in his elegant book *The Music of Life*: *Biology Beyond the Genome*.[110] It emphasizes that the *action* is at the physiological level. The multi-scale approach emphasizes the simultaneous and complex interactions of activities across all the biological scales discussed above.[111,112] From this point of view, genes bias the way that things happen — they set up strengths and vulnerabilities — but they are by no means the sole contributors, so you cannot truly claim that they "cause" things all by themselves.

This point of view is emerging as well in the literature on just how specifically genes and environment interact. Calcium channel

dysfunction provides an example that has received some careful attention in this regard. There are a number of genes altering calcium channel function that are associated with autism, but environmental as well as genetic routes to calcium signaling dysfunction have been identified,[113] which include chemicals such as the polyaromatic hydrocarbons. PCB-95 in particular modulates the calcium-dependent signaling pathway responsible for activity-dependent dendritic growth.[61,62] Stamou and colleagues (2012) argue that once a genetic mutation has been associated with altering a critical signaling pathway and conferring risk for autism, chemicals or other environmental agents can be identified that target the same pathways and also confer ASC risk. These authors 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.[114] 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, a chemical toxicant, or electromagnetic perturbation, the functional effect is comparable because it is due to the way the calcium channel physiology changes.

The case that Stamou *et al*. (2012) make is a good example of middle-out thinking. The core point of what they are saying is that *it is the dysfunction in the calcium channel that is altering function in autism*. The gene itself does not directly alter the brain function, and neither does the environmental trigger. In both cases, it is *the impact on the physiological process* that creates the change in brain (and other) function.

A Further Problem: Heterogeneity — How Can There be So Many Routes to "Autism"?

Calcium channel dysfunction not only provides a good example for middle-out thinking, it also provides a good lead-in to a discussion of heterogeneity in autism. While some individuals with autism

have calcium channel dysfunction, others may not. At the level of genetic syndromes, over a hundred distinct syndromes have been identified where autism is a comorbidity;[115] and while there are some common themes across the genetic issues underlying these conditions, there is much we do not understand. Many people like to say that autism is a disorder of the synapse, but this actually is a rather vague statement since the synapse is hugely complicated and involves interactions of enormous numbers of proteins, neurotransmitters, receptors and also cell types (not just neurons but also astrocytes) as well as blood vessels, blood flow and extracellular matrix. There is no particular reason why the synaptic problem even needs to derive from a genetic mutation, if it is the synaptic dysfunction rather than the origin of that dysfunction that is the proximal cause of the brain and behavioral (and physiological) changes underlying the "autism." Scientists now talk about the tripartite synapse (neurons, astrocytes, blood vessels)[116] or even the quadripartite synapse (tripartite plus extracellular matrix).[117] Synaptic dysfunction could come from any of the components of this system.

Even here, with so many things capable of causing synaptic dysfunction, are we not faced with the famous "chicken-egg" problem? That is, when a complex system with many interacting parts changes the dynamics of how it operates, how do you pin down one single "cause" that "comes first"? Or does it even make sense to do that?

Okay, So What "is" the "Autism" Anyway?

After reviewing the incredibly complex multi-scale biology of autism, it is difficult to go back to the old assumption that "autism is a behavioral syndrome deriving from genetic alterations of brain development" without feeling that we are missing not just the boat but a giant ocean liner. Instead one is called to become fascinated with how all of these different types of multi-scale challenges to the organism and in particular to the brain, with different combinations of them from one person with autism to the next, *actively* create the behaviors that meet diagnostic criteria for autism.

Autism as an Emergent Property of a System with Many Shifted "Settings"

As mentioned, some neurocognitive researchers have proposed that at the cognitive level many features of autism emerge from difficulties with complex information processing.[29] Why would the system have such difficulties? It is easier to think about this from a multi-scale systems biology point of view. Cells laboring under inflammation, mitochondrial dysfunction and oxidative stress, or calcium channel dysfunction, will lose an edge of adaptability and fluidity or rapidity of response that may take away from the system's resources to coordinate information in the most complex ways possible. It is even possible that some neurons may be challenged enough to go "offline" so that they can survive, rather than burning themselves out when they do not have enough mitochondrial or astroglial support to generate energy or regenerate their metabolic integrity.

In a thoughtful article on the idea of emergence in autism, Anderson (2008) states that various "autism-related phenomena including intellectual disability, seizures, persistence of primitive reflexes, stereotypies, self-injurious behavior, savant abilities, and morphological abnormalities, among others," could potentially be emergent properties.[118] The author suggests that "consideration of the role of emergence in autistic behavior and related phenomena should complement a reductionist approach and might help illuminate the components and complexities of autism."

The multi-scale systems approach sketched above adds more substance and support to this assertion. A system laboring under various combinations of cellular challenges may produce behaviors we label as autistic simply because that is what the brain "does" when it has to conserve its resources, or when it cannot marshal and coordinate sufficient resources to get things done in the most elegant ways.[119]

One ironic and provocative twist here is that some challenges to the system, such as an increase in glutamate (e.g. from the failure of activated astrocytes to remove it from the synaptic cleft after synaptic discharge) may contribute to heightened sensitivity, intelligence

or even heightened perceptual acuity. Indeed, superior function in some individuals with ASCs compared to neurotypicals has been documented in just such domains (sometimes this may manifest as savant skills, sometimes as superior perceptual abilities, and sometimes as great and even sophisticated talents). It is just speculation at this point to attribute such findings at the neuropsychological level to underlying neurobiology; but even so, this is an interesting hypothesis worth testing, since it links disparate and seemingly contradictory but clearly co-existing features in ASCs.

From "what causes autism" to "how is autism caused"

When we move beyond genetic determinism to a multi-scale biology, middle-out approach, we see that much of what autism involves is related not to fixed "autistic states of being" but rather to the consequences of changes in interacting sets of complex ***processes*** that are working in people with ASCs at different rates, with different equilibria or set points, than they are in neurotypical people. This can include processes as disparate as cellular transport, fluid transport, mitochondrial metabolism, immune responsiveness, gut motility or electrophysiological oscillations — or all of these altered together in concert with each other.

Since there are many factors — including nutrition, activity and environmental exposures — that modulate these processes, it is quite conceivable that the cause of the regressive process leading to autism could be a cascade of events that progressively alter the way these internal processes work.

Similarly, from this perspective it becomes conceivable that improvement in functioning in autism, or even loss of diagnosis, may ensue when changes in these internal processes move in the opposite direction from the way they changed during regression.

From "how is autism caused" to "how does autism work": Dynamical process approach

From this perspective, the goal is not only to advance past a static point of view suggesting that a specific gene, a specific toxin or a

specific gene-environment interaction might "cause" autism — i.e. singlehandedly shift a system from not-autistic to autistic, but also to advance into a dynamical framework where we see how the autism emerges from ongoing processes in both brain and the whole multi-scaled physiologically-centered system.

Autism as What Emerges from the Moment-to-Moment Impact on Electrophysiology of Depleted Function of Cells Supporting Brain Electrical Activity

From this point of view, I would like to propose that the features we label as "autistic" emerge on a moment-to-moment basis from physiological processes, rather than being a product of some kind of hard-wired inborn differences in brain circuitry. Differences in circuitry would then emerge or exaggerate during development, rather than being fully "programmed in" from the start.

Specifically, since electrophysiological oscillations — aggregate patterns emerging from interrelated activities of individual synapses — underlie brain activity, and since electrophysiology is generated by cells whose physiological status is known to be altered in at least large numbers of people with autism — it therefore follows that the autism may emerge from a vast and inter-individually heterogeneous array of physiological alterations that converge upon the intersection of tissue physiology and electrophysiology to create changes. This physiologically altered system creates or generates "outputs" that we label as autistic behaviors.

Clearly this does not exclude the possibility that a certain number of individuals with autism have genetic alterations that contribute substantially to this situation, but it does help us understand why no such genes have been found in the majority of people with autism, and why ASCs are so heterogeneous as well as variable even *within* single individuals. It also follows that even in individuals with strong genetic vulnerabilities, there could be an additional overlay of environmentally modulated cellular dysfunction that is aggravating the situation but is actionable — that is, reducible through improving cellular function, even if the gene mutation itself is immutable.

Practical Implications for Conducting Research and Clinical Care?

If we can establish empirically that tissue pathophysiology is connected to electrophysiological alterations, we will be able to move the center of gravity in autism research from looking for the genes or environmental factors that "cause" autism in a bottom-up fashion, to *looking for the systems perturbations that we can modulate and correct*. We will no longer invest the bulk of our resources in an endless hunt for autism genes, betting on the assumption that identification of prior causes (genetic or environmental) is the only way to make progress. Instead, we will see that there are many entry points into the system's ***function*** through which that system can be modulated.

Lifestyle interventions for the brain: Public health implications

Particularly important is the ground-zero interface between systems physiology and electrophysiology, because by modulating physiology we may very well be able to make substantial improvements in electrophysiology — and the behaviors it generates.

To the extent that pathophysiological processes like inflammation, oxidative stress and mitochondrial dysfunction collectively influence electrophysiological activity as well as underlying synaptic function, this is good news, because we already have many practical ways to influence these types of dysfunction. Prominent among these are everyday lifestyle alterations including optimal high-nutrient-density diet, exercise and good sleep hygiene. High nutrient density food, full of antioxidants and quality lipids, can be anti-inflammatory, can reduce oxidative stress and can be restorative to mitochondria and even neuroprotective.[120,121] And whereas lack of sleep, stress, and lack of exercise produce pro-inflammatory responses, improving these domains is restorative.[122]

In the face of something as severe as autism can be, it may seem trivial to talk about these everyday interventions. But if you look at

the daily lives of individuals with autism, they are often characterized by self-restricted diets sorely lacking in fruits or vegetables and very nutrient poor;[123] they often sleep poorly not to speak of keeping the whole family awake too much; and they often exercise very little and feel stressed all the time. None of this is healthy, and all of it is actionable once we realize that there is a profound physiological and brain-health point to it. Improving lifestyle choices in these domains may decrease depletion and improve support for brain maintenance and repair functions.

What it Will Take to Implement a Public Health, Everyday Epigenetics Approach to Autism

What this really means is that we need a public health approach to autism, emphasizing achievable lifestyle interventions that could improve the quality of life at least somewhat for most people with autism, and improve it a huge amount for a significant subset of people.[124] In fact, given the rising number of people with autism and the rising costs, we really cannot afford NOT to implement such an approach.

Future Directions: Toward True Translational Research

Multi-scale biological research is therefore important not only for what new things it may teach us, but also for the rhetorical purpose of showing that a public health approach with everyday lifestyle changes aimed at epigenetic modification of gene expression is NOT crazy but instead imperative.[124]

Therefore:

1. From a research point of view, we need to integrate brain, behavior and pathophysiology research through coordinated projects employing multi-scale systems biological approaches. One way of doing this is to look at the interventions being performed by innovative clinicians on the systemic physiology to see how it affects brain electrophysiology and metabolism

(via EEG (or MEG) and magnetic resonance spectroscopy, respectively). Generation of this type of data will probably optimally come from prospective multisystem sample collection from individuals undergoing intensive and skilled comprehensive treatment of multiple aspects of their physiology, alongside animal models structured in parallel.[125]

2. By taking on transduction issues in ASCs through multi-scale study designs that truly tackle the interfaces between brain electrophysiology and metabolism, we will gain a systems level and mechanistic characterization of transformation, i.e., the passage from greater to lesser options (regression) or lesser to greater options (recovery). This may allow us to reverse-engineer more effective treatments.[99,100]
3. To do this, we need an infrastructure that captures data from both academic research and community-based clinical environments, and does so in a fashion that allows these differently skilled and differently equipped groups to meaningfully collaborate.[125,126]
4. In this fashion, we can perform "bedside-to-bench and back" translational research that may sooner rather than later transform the lives of thousands or millions of individuals with autism and spill over not just into their families but also into the lives of people with other conditions where compromised pathophysiology is interfering with optimal brain function and quality of life.
5. Importantly, we can transform this information into support for a public education campaign that can be started now and enriched as the research utilizing this approach accumulates.

Conclusion: Multi-Scale Dynamical Biology Gives Hope and Empowerment

In summary, based upon insights from multi-scale biology, and with the understanding that the processes involved in electrophysiological generation of "autism" can be modulated by lifestyle interventions that improve underlying physiology and epigenetic

regulation of gene expression, we can make a big difference now with what we already know, and we should mobilize our motivation and infrastructure to make it happen.

Executive Summary

- Autism develops through a dynamic interplay amongst genetic, environmental, epigenetic, metabolic, molecular signaling and physiological levels.
- Genetics may bias the system toward autism weakly or strongly, but even if it does so there may be an overlay of surplus physiological complications that may be actionable; if constructive choices are made, improved function and quality of life may still occur.
- Emphasis in brain research on anatomical features of the brain is not sufficient for helping us understand the developmental or dynamic features of autism.
- Many brain anatomical features may be downstream consequences of chronic, persistent tissue irritation, particularly from inflammation, oxidative stress and mitochondrial dysfunction rather than purely results of genetic differences.
- The "ground zero" of how the brain comes to generate "autism" probably lies in the interface between tissue-based physiology and electrophysiological oscillations.
- Many potential avenues of intervention exist at this "ground zero" interface, particularly through "bottom-up" or "middle-out" improvement of cellular health status through whole body-brain lifestyle changes, including high density nutrition, improved sleep, and reduction of physiological stressors and noxious exposures.
- From a dynamical systems perspective, "autism" can be reframed as what emerges from the moment-to-moment impact on the brain's generation of electrophysiological oscillations when the cells generating this oscillatory activity are depleted or otherwise dysfunctional.
- Bedside-to-bench translational research that collects data on changes across physiological and electrophysiological systems

from whole-body interventions may help us reverse-engineer the critical transitions of regression in ASCs to remission or recovery.
- It is an urgent public health matter that these avenues be pursued because the savings in unnecessary human suffering and economic cost could be huge.
- A whole-body approach to body-brain transduction is an empowering source of hope.

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