AUTISM: A BRAIN DISORDER, OR A DISORDER THAT AFFECTS THE BRAIN?

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Summary

Autism is defined behaviorally, as a syndrome of abnormalities involving language, social reciprocity and hyperfocus or reduced behavioral flexibility. It is clearly heterogeneous, and it can be accompanied by unusual talents as well as by impairments, but its underlying biological and genetic basis is unknown. Autism has been modeled as a brain-based, strongly genetic disorder, but emerging findings and hypotheses support a broader model of the condition as genetically influenced and systemic. These include imaging, neuropathology and psychological evidence of pervasive (and not just specific) brain and phenotypic features; postnatal evolution and chronic persistence of brain, behavior, and tissue changes (e.g. inflammation) and physical illness symptomatology (e.g. gastrointestinal, immune, recurrent infection); overlap with other disorders; and reports of rate increases and improvement or recovery that support a role for modulation of the condition by environmental factors (e.g. exacerbation or triggering by toxins, infectious agents, or other stressors, or improvement by treatment). Modeling autism more broadly encompasses previous work, but also encourages the expansion of research and treatment to include intermediary domains of molecular and cellular mechanisms, as well as chronic tissue, metabolic and somatic changes previously addressed only to a limited degree. The heterogeneous biologies underlying autism may conceivably converge onto the autism profile via multiple mechanisms that all somehow perturb brain connectivity. Studying the interplay between the biology of intermediary mechanisms on the one hand and processing and connectivity abnormalities on the other may illuminate relevant final common pathways and contribute to focusing the search for treatment targets in this biologically and etiologically heterogeneous behavioral syndrome.

Key Words: Autism – Brain – Complex systems – Connectivity – Gene-environment interaction

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Introduction

While autism is defined behaviorally, it is clear both that it is biologically based and that better understanding of its biology is critical at this juncture. The purpose of the discussion that follows is to shed light on two contrasting sets of often unstated assumptions underlying autism research, which represent alternative vantage points within the autism community's multiplicity of perspectives. These will be characterized here as the "strongly genetic, brain-based" model and the "genetically influenced, systemic" model. The focus here will be upon the impact of underlying assumptions upon how one constructs and investigates the relationship between the phenotypic profile of atypical language, social reciprocity and hyperfocused or repetitive behaviors that define the autism behavioral syndrome (American Psychiatric Association 1994) and the underlying biology. The argument will be made that the second of the two perspectives, that is systems-oriented, is more inclusive and is capable of building upon and broadening the foundations laid by the first.

One of the most critical questions in autism today is how to address the heterogeneity of the behavioral syndrome. Autism is heterogeneous in its behavioral features, and it is also both known and presumed to be heterogeneous biologically. Because autism is defined only behaviorally, the definition neither implies nor excludes any particular underlying etiology or disease course. Given the multiple known diseases associated with autism (e.g. tuberous sclerosis, fragile X, *in utero* rubella etc.) that do not share the same biology, and the presumed multiple other not yet identified biological underpinnings in the vast majority whose autism is now classified as "idiopathic," we are faced with the challenge of how to sort out the subgroups and multiple pathways to autism. Within this overall challenge there are two particularly important questions: a) what adap-

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tations to investigative methodology need to be made to discern and understand rather than average away these differences? And b) given that effective treatment and prevention should be the ultimate goal of every activity in the autism world, how can we optimize our chances for identifying treatment targets, even if any one such target only applies to a subset of autistic individuals with the appropriate biological underpinnings?

Another core question devolving from autism's heterogeneity relates to what features may be necessary and what simply sufficient for autism. It may be that the closest we can come at present to an underlying common mechanism in autism is the hypothesis of some kind of abnormality in brain connectivity—i.e. the structural and/or functional factors related to brain connections and coordination—that eventuates in observable behaviors. Yet we are only at the beginning of investigating brain connectivity in autism, so we do not know if impaired connectivity is found in all subgroups of autism, or if different subgroups have different patterns of impaired connectivity. Furthermore, we do not know how many different kinds of underlying molecular, cellular, metabolic and tissue perturbations may lead to a connectivity disturbance sufficient to produce autism. It is quite conceivable that there may be substantial heterogeneity at many of those underlying levels, and perhaps even greater genetic (and environmentally triggered) heterogeneity beneath all of these intermediary levels.

These unanswered and complicated questions lie at the heart of much of the public debate in which autism is currently enmeshed. Questions about whether or not there is an increasing incidence of autism, whether or not (or to what extent and in what ways) environmental factors contribute to autism, whether physical symptoms in autism are coincidental or a core part of the condition, and whether (and if so in what ways) it is treatable all have as an underlying substrate the question of disease model. This paper condenses a range of complex considerations and opinions into a contrast between a "strongly genetic, brain-based" model and a "genetically influenced, systemic" model, in order to highlight the assumptions underlying two approaches to autism that differently (though sometimes complementarily) construct research, treatment and policy. Genes are important in both vantage points; the core issue relates to how to weight and approach the intermediary pathways between genes and behavior—that is, the mechanisms by which genes (and gene-environment interactions) influence brain and behavior, and the factors that may modulate these intermediary mechanisms. The argument will be made that carefully articulating these intermediary mechanisms will maximize the potential for investigations to yield insight into subgrouping the heterogeneity and identifying treatment targets to alleviate the suffering and limitation that, along with an atypical but potentially fertile neurocognitive profile, can accompany autism.

Models of autism

Autism has commonly been described as a *brain-based disorder*, and as a disorder that is strongly genetic. However, to date no single or small number of specific genes appears to be strongly associated with autism, and thus many investigators argue for a shift to a study of complex genetic contributors (Veenstra-Vanderweele et al. 2004), while others have also turned to the way that genetic influences interact with environmental factors (Keller and Persico 2003). Clearly the brain is affected in autism—many changes have been documented; and clearly autism genetics plays a strong role. Yet at the present time we have not established the mechanisms by which the behaviors we call autism are shaped neurobiologically, and we also do not know the nature of the genetic mechanisms that may cause it. Moreover, the phenomenology of autism has many facets: the biological issues in autism are not confined to the brain, given abnormalities in peripheral biomarkers and in other organ systems, prominently gastrointestinal and immune, that are common fellow travelers with autism behaviors. In addition there appears to be a role for environmental as well as genetic factors, particularly given growing reports of increasing numbers that have not been definitively explained away. While behavioral abnormalities must certainly be associated with changes in the brain, the underlying disease process may not be restricted to this association or this organ of the body. Given the limits to our current understanding and the critical questions that remain open, it would thus be more conservative to describe autism, instead, as a *behavioral syndrome with a biological basis and systemic features, influenced by genes and gene-environment interactions*. (See Table 1)

The proposed shifts, from "brain based" to "systemic" — and, regarding genetics, from "strongly genetic" to "genetically influenced," which gives more room for epigenetics, stochastic effects, pleiotropy, epistasis, variable expressivity and gene-environment interactions—both have a basis in considerations in cell and molecular biology that are not confined to autism or neurodevelopmental disabilities. Physiologically active molecules and signaling mechanisms as well as patterns of gene expression do not respect the boundaries between brain and body or between organ systems. Common mechanisms are found "centrally" and "peripherally"—that is, the same molecules are players in multiple systems and pathways throughout the brain and body. Many new pathways for mutual influence between brain and body are being identified. Environmental factors act on the same molecular and cellular mechanisms as do genes.

Within what we are here calling the "brain based, strongly genetic" model, research attention has been directed toward genes, brain and behavior. The "genetically influenced, systemic" model proposes a more explicit and systematic approach for addressing the intermediary mechanisms through which genetic factors would operate on higher-level brain and behavioral systems. (See Figure 1.) This framing encourages study of mechanisms that may impact both brain and body. Careful characterization of such mechanisms may help in the identification of candidate genes—particularly given the confound that multiple genes might impact the same mechanism; such heterogeneity could be parsed rather than averaged out if common mechanisms were known. Such an approach might add much to behavioral measures in identifying endophenotypes and more homogeneous subgroups.

Table 1. *Two disease models of autism*

STRONGLY GENETIC, BRAIN-BASED	**GENETICALLY INFLUENCED, SYSTEMIC**
AUTISM IS A BRAIN-BASED DISORDER	*AUTISM IS A DISORDER (OR BETTER, SYNDROME OR CONDITION) THAT AFFECTS THE BRAIN (AND MORE)*

Table 1A. *Specificity and pervasiveness*

Autism happens when a group of independent behavior-causing genes aggregate in the same individual.	Autism happens when pervasive processing abnormalities are severe enough that brain dysfunction crosses a threshold to produce processing alterations that manifest as the set of defining behavioral deficits.
Each autistic behavior is based in a specific brain region or neural system, as determined by corresponding genes.	Autistic behaviors are systems consequences of widespread processing and connectivity abnormalities that preferentially target mental functions with a strong requirement for coordinated activity (which include the three defining impaired domains in autism).
Abnormalities in specific brain regions are due to the specific genes that influence those regions.	Regional changes in the brain that alter neural systems functioning may be due to local tissue properties that heighten vulnerability to more pervasive influences rather than to direct and delimited targeting of those specific regions. Such regional changes in autism would be a secondary consequence of factors whose influence is more widely distributed.
Neural systems problems are due to abnormalities in functionally relevant brain regions.	Neural systems problems may be due either to general network alterations or to problems in connections between regions (nodes) as well as to local abnormalities.
Defects in brain systems that govern functions such as language, reward or face processing lead to connectivity problems.	Connectivity problems lead to defects in specific and distributed brain systems, such as those participating in language, reward and face processing.
The heterogeneity in autistic behavior between individuals is accounted for by a corresponding heterogeneity in genetics.	Autism is a set of behaviors that are a final common pathway arising from a class of information processing abnormalities that may have heterogeneous biological underpinnings (whose heterogeneity contributes to variability in the phenotype).
Specific genes are associated with specific behaviors.	Genes do not map directly onto behaviors. Biologically, genes affect pathways and mechanisms that may change tissue properties. Altered tissue can have altered connectivity and processing capacities that lead to an altered behavioral profile.
Behaviors are primary entities with specific causes.	Behaviors may represent secondary compensations for or responses to sensory and processing challenges.
If core endophenotypes underlying behaviors can be identified, their utilization in research should increase the likelihood of identifying genes associated with autism.	Because abnormalities in intermediary metabolism can provide another set of endophenotypes that will help identify autism subgroups (since metabolism is associated with pathways and mechanisms closely linked to genetic vulnerabilities), metabolic measurements should be an important component of profiling autistic individuals.
Autism overlaps with other disorders such as language impairment or obsessive-compulsive disorder because of specific shared genes related to the traits that are shared.	Autism overlaps with other disorders because of commonalities in underlying pathophysiology that have multifaceted impacts on tissue, connectivity and processing properties; these overlaps may be related to shared genetic features or may represent “final common pathways.”

Table 1B. *Comorbidities*

Secondary symptoms in autism are coincidental. Autism is rooted in brain changes due to genetic factors, and symptoms in autism (like GI and allergy/immune problems, sleep problems, etc.) are coincidental and "secondary."	Somatic symptoms are not really "secondary" but rather may be integrally related to what have been considered "core" or defining symptoms, and both are likely to derive from the same or related underlying pathophysiology.
Bodily symptoms such as gastrointestinal or immune problems contribute to autism by causing pain and discomfort but are unrelated to core autism symptoms.	Bodily symptoms are manifestations of signaling and metabolic derangements that may have widespread effects and may even be upstream of some changes in the brain. They are integrally related to what we now call autism; their treatment may improve brain conditions that lead to autistic behaviors.

Table 1C. *Determination and vulnerability*

Genes cause autism.	Genes create vulnerabilities of variable intensity to second hits from the environment without which some children might not develop autism.
Autism genes target the brain.	Autism genes target signaling and metabolic pathways. Signaling and metabolic changes may affect the brain among other things such as other systems that may affect the brain indirectly or secondarily.
Autism is caused by "hard-wired" changes in early brain development that are largely due to abnormal genetics.	a) The impact of genetics may be considerably modified by epigenetics and stochastic factors during *in utero* and postnatal development. b) Autism may be partly or entirely due to chronic alterations in tissue properties of the brain such as inflammation, oxidative stress or hypoperfusion. Such changes may alter brain development, but we do not have the evidence to exclude the possibility that chronic tissue changes may be sufficient in themselves to cause autism, even without altering the "hard-wired" features of the brain.
Rate increases make no sense in this largely genetic disorder, so they must be due to increased awareness and altered diagnostic criteria.	Unchanged genetic vulnerability plus an increase in environmental triggers is consistent with the possibility that some of the rate increase is real.
The null hypothesis that there are no rate increases should form the basis of research hypotheses until definitive evidence has been gathered that there is an environmental role.	Hypotheses derived from an environmentally modulated model need to be operationalized now and may provide critical insights into the nature and treatment of autism.

Although there are other ways of construing the mechanisms of genetic influence on the brain, some authors have argued that research should be focused upon how specific genes and localized brain regions or neural systems will be associated with specific behaviors (Dawson et al. 2002). Such associations may be found (although they have not to date been identified in a fully consistent manner). A "genetically influenced, systemic" model would expand the research agenda to also include a systems approach. In a systems framework, hypotheses are generated that reflect how specific behaviors may emanate from widespread alterations of multi-leveled complex interacting systems parameters. This systems orientation is more consistent with models of widespread underlying processing abnormalities, such as "weak central coherence" (Frith and Happe 1994) or, when considering the underlying biology, a theory of "underconnectivity" (Just et al. 2004), and it may prove useful in addressing the functional implications of the anatomical phenomenon of early brain enlargement in autism. Such systems-oriented perspectives are also often more explicitly developmental, in that they address the important role of developmental windows in shaping outcome, and

Table 1D. *Timing and tissue*

Regressive autism is due to the unfolding of genetic programming and/or prenatal events.	Regressive autism may be a consequence of cumulative alterations based on metabolic changes such as immunological or redox imbalances, possibly related to an accumulation of environmental exposures or stressors, that reach a tipping point or threshold beyond which brain connectivity decompensates.
Post-natal brain enlargement is interesting but hard to correlate with specific diagnostic features.	Brain enlargement could be due to pervasive and chronic tissue changes, and it may be an anatomical underpinning of impaired connectivity.
Autism is a static encephalopathy with a fixed core neurobiological, or brain, abnormality resting upon hard-wired architectural alterations in tissue that may be otherwise healthy.	Autism can have features of metabolic encephalopathy. Abnormalities in autism may come from sustained neuromodulator abnormalities in tissue with chronic ongoing disease and maladaptive processing patterns.

Table 1E. *Treatment*

Since autism is a static encephalopathy with a fixed, genetically programmed core neurobiological, or brain, abnormality, treatment can lead to better adaptation, but autism is inherently incurable.	The encephalopathic features of autism may rest on chronic tissue abnormalities and maladaptive processing patterns, and may be treatable and even reversible. Abnormalities in autism may come from sustained neuromodulator and/or processing and connectivity abnormalities that may be amenable to reduction by properly targeted interventions.
Altering behaviors may be aided by therapies that target specific behaviors.	Altering behaviors may be aided by changing the nature of information processing through therapies that challenge sensory or social-emotional networks.
Due to the strong genetic influence underlying brain changes in autism, there is very limited neural plasticity and interventions are much less effective if not begun very early in life.	Treatment early in life is optimal, but treatment of chronic medical problems at later ages may also yield substantial benefit at the level of tissue health (including in the brain) and brain function.
Non-pharmacological biomedical interventions in autism are implausible and irrational.	Treatment targets for chronic and environmentally mediated, as well as some genetically based, metabolic changes in autism may point to pathway-related interventions such as enzyme cofactors (e.g. vitamins and minerals) that are GRAS (generally recognized as safe) that should be assessed and implemented in a rigorous and objective but also expedited fashion.
Because autism is brain based, psychopharmacological medications constitute the reasonable domain within which to seek and develop biomedical treatments for autism.	Biomedical treatment targets may be found in any pathway or pattern that contributes to degrading tissue, connectivity and/or processing in the autistic brain, or that leads to symptoms in any part of the body. Improvement at any of these levels may alter system properties to improve brain functioning, behavior, health and quality of life for autistic individuals.

pay more systematic attention to the modulation of genetic influences during development by epigenetic (not strictly genetic), as well as stochastic (chance) processes. A systems-oriented approach can also encompass the apparent biological heterogeneity of autism, because the notion of "final common pathway"—that is, many roads or mechanisms leading to a smaller number of outcomes—is intrinsic to this perspective.

The shift to a focus that is more inclusive of intermediary mechanisms can allow a reorientation of the investigative mind in autism. A "systemic" approach that considers biological factors affecting but also go-

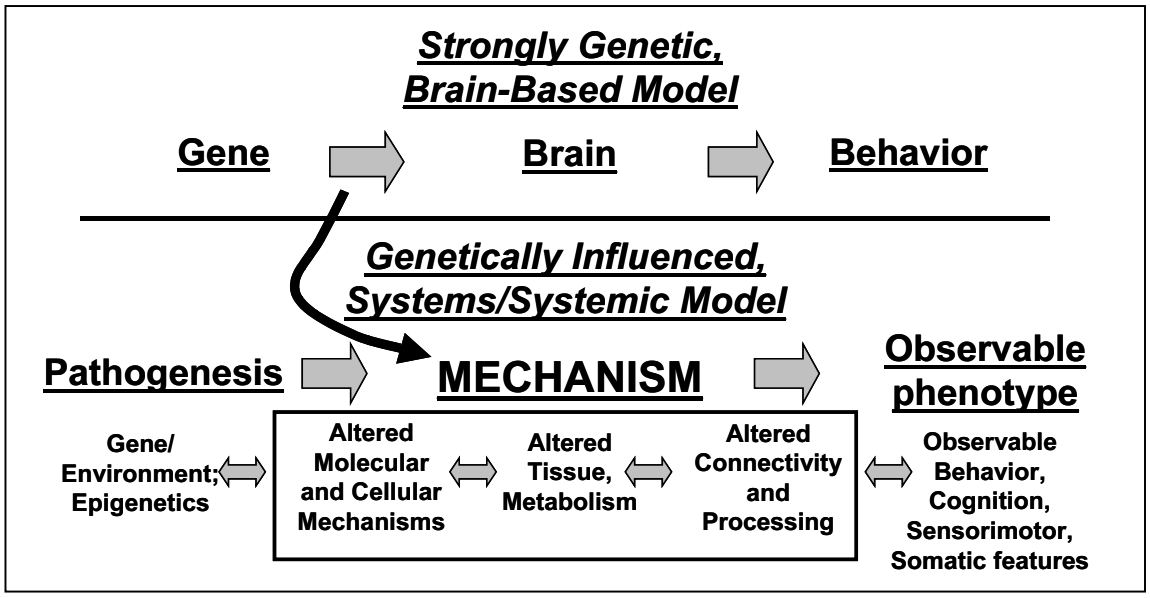

Figure 1. *In this comparison of the "strongly genetic, brain-based" model with the "genetically influenced, systemic" model, the second model breaks out and articulates linkages and classes of mechanisms that are implicit but not elaborated in the first model. The mechanisms elucidated in this manner may point toward strategic treatment targets.*

ing beyond the brain may be more likely to parsimoniously identify underlying disease mechanisms that ramify in various ways throughout the organism, rather than attempting to track down independent causes and correlates for each of a set of aggregated features and symptoms. A "genetically influenced" approach includes strong genetic effects, but broadens the investigation to identify mechanisms that can be targeted by genes but also by various environmental factors or by gene expression as modulated by environmental influence. It follows that whereas an approach guided by observable behavioral traits, particularly when they are considered to be independent of each other, may be more likely to address symptoms, a biological systems approach is oriented toward seeking underlying biological disease mechanisms—and these may potentially lead to treatment targets that strategically address the core upstream root of multiple downstream manifestations (Figure 2).

An interesting case in point is the phenomenon of brain hypoperfusion in autism, certainly a tissue phenomenon but one with functional significance. If one reads autism brain perfusion studies from the "strongly genetic, brain-based" perspective, with an eye toward finding the brain localization for autistic behaviors, one finds substantial variability across findings—temporal, parietal and frontal, anterior cingulate and right hemisphere hypoperfusion having been noted (Mountz et al. 1995, Chugani et al. 1996, Zilbovicius et al. 2000, Boddaert and Zilbovicius 2002, Zilbovicius et al. 1995, Chiron et al. 1995, Haznedar et al. 1997, Haznedar et al. 2000). But if one reads these studies from the "genetically influenced, systemic" perspective, with an eye for underlying biological disease mechanisms, one then notes that low perfusion has been documented in at least eight SPECT studies as well as in some PET studies, with lack of difference from controls being rare and *hyper*-perfusion virtually never being reported (George et al. 1992) (in contrast to glucose metabolism imaging studies, where inter-study variability has included findings of increase as well as decrease in that measure) (Rumsey et al. 1985, Herold et al. 1988, Schifter et al. 1994, Mountz et al. 1995, Ryu et al. 1999, Starkstein et al. 2000, Hashimoto et al. 2000, Ohnishi et al. 2000, Kaya et al. 2002, Wilcox et al. 2002). That is to say, a systemic orientation notes that localization may vary, but brings to the foreground that the underlying theme of perfusion reduction is constant.

While low perfusion would suggest to someone with a biological orientation that underlying tissue changes might be impairing perfusion, not one of these psychologically oriented published studies contained any reflection about what might be driving this low perfusion phenomenon at the level of brain tissue, of neurobiology. The regulation of perfusion may be modulated by task, context, motivation and other information processing factors that could be altered in the setting of an atypical neurocognitive profile; but these factors work through tissue-level signaling processes, and at the tissue level there may be disease processes that affect tissue functioning. Yet neither the domain of underlying neurobiology nor the possibility that an underlying systemic pathology might contribute to modulating the perfusion entered the discourse in any of these papers.

However, once such tissue- and systems-level pathophysiological processes become objects of interest, they suggest disease mechanisms, but even more, they can point to potential treatment targets. But whether one shifts toward an interest in pathophysiological questions is a function of one's underlying assumptions. If one's underlying model of autism in-

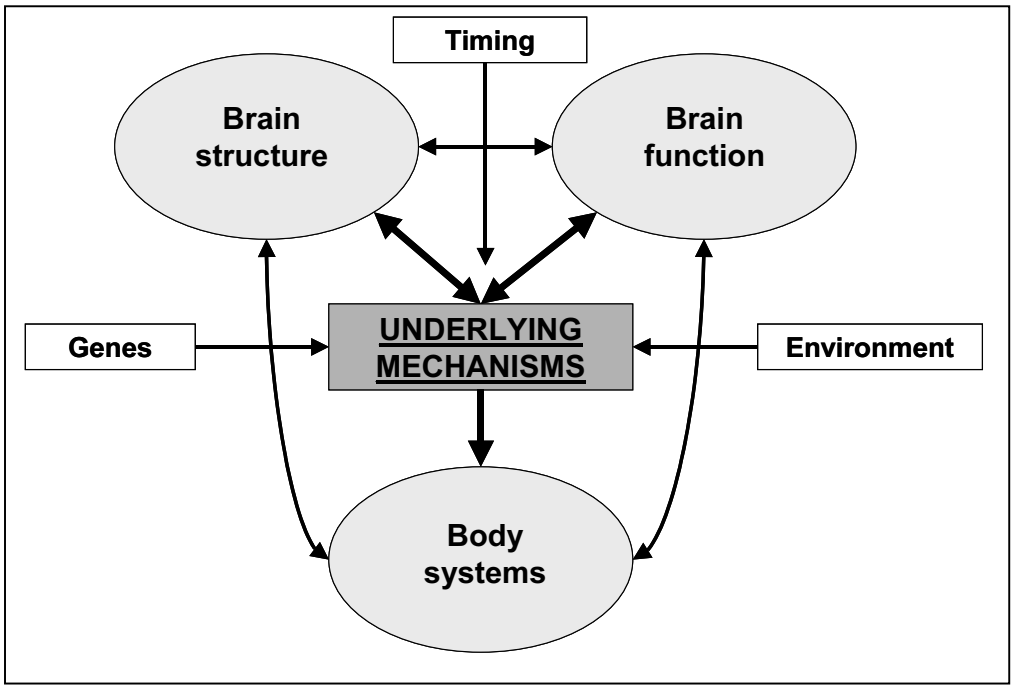

Figure 2. *Common underlying mechanisms, influenced by genes and environments in specific developmental windows, may underlie phenotypic features at multiple levels of the organism.*

cludes the assumption that the disorder is based on a hard-wired brain alteration, or one exclusively determined by genes, or that it is a psychologically or motivationally driven abnormality in a brain whose tissue is normal and healthy, or that specifically located brain lesions must underlie specific deficits, one would not consider the possibility of systemic pathophysiology. Instead, one might implicitly assume that the underlying tissue substrate and the regulatory mechanisms governing perfusion are different than in typically developed individuals in a manner due to inborn brain architectural alterations that are unchangeable. But from the vantage point of a systems approach, such implicit assumptions seem limiting in how they miss an important or potentially even critical dimension of the problem—namely, reflection on the dimensions of systems and of physical disease-related tissue mechanisms as contributors (and indeed as dynamic contributors) to structural and functional changes.

A recent paper documenting chronic neuroinflammation and microgliosis in autistic brains (Vargas et al. 2005), however, raises the possibility that chronic tissue changes with potentially treatable features could underlie this hypoperfusion. This recent paper among other things documents perivascular microgliosis, that is, inflammatory activity around brain blood vessels. Oxidative stress, evidence of which has also been found in autism as discussed later in this paper, might also lead to oxidative inhibition of muscarinic receptors controlling small vessel vasodilation (Elhusseiny and Hamel 2000, Fukuyama et al. 1996). While the relationship of such possible mechanisms to hypoperfusion documented in SPECT and PET studies of course needs to be studied rather than assumed, and while other mechanisms could be at play, these mechanisms can plausibly be entertained as *potential* causes of hypoperfusion. The issue here is not establishing the specific mechanism but rather highlighting the importance of including *orientation* toward tissue and systems mechanisms in thinking about brain changes in autism.

Testing the comparative utility of these formulations could be operationalized experimentally—both psychologically by varying task parameters, and systemically/biomedically by performing treatment trials targeting biological factors that may drive tissue-based hypoperfusion—and assessing perfusion and connectivity changes in each class of interventions. If biomedical interventions improving perfusion were found also to increase functional connectivity, this would suggest a new class of biomedical treatment targets that would complement existing, symptom-oriented behavioral interventions.

Moreover, the genetic component in this phenomenon of hypoperfusion could be very usefully construed within the "genetically influenced, systemic" disease model as a set of factors that confer vulnerability to the underlying tissue pathology driving the hypoperfusion—and not only to modulation of the behaviorally-related distribution of this tissue change. This more inclusive formulation would arise from explicit appreciation, encouraged by systems thinking, of the loose rather than tight couplings between pathogenesis, brain and behavior (Morton and Frith 1995)—i.e., that factors related to biological pathogenesis affect behavior, but only indirectly and in a fashion mediated by a range of other intermediary considerations (Johnson et al. 2002, Thomas and

Karmiloff-Smith 2002, Karmiloff-Smith and Thomas 2003, Herbert and Ziegler 2005). (See Figure 1.) For example the distribution of tissue impact of an altered molecular or cellular mechanism (e.g. regional differences in vulnerability to immune system perturbation) may overlap with a behaviorally related neural system but may not map uniquely or specifically onto that behavioral system. This non-specificity of the mapping of mechanism onto behavior may be one reason for the great range of what have been called "comorbidities" in autism.

The importance of aiming for a detailed breakout of the multiple intervening levels between the dominant landmarks of gene, brain and behavior is that becoming oriented toward such tissue intermediary metabolism and underlying processing mechanisms can help expand the dimensions of brain plasticity that are considered in autism research and treatment. Talking about "pathogenesis, mechanism and observable phenotype" includes everything from the "gene, brain, behavior" model but adds a variety of new dimensions. Addressing these extra dimensions may suggest avenues toward developing treatments that might alter tissue as well as behavioral features in autism, or that may be more strategic in their modes of transforming cognitive processing. If the health or activity patterns of brain tissue in autism could be improved, one might see improved receptivity to behavioral interventions, and perhaps some spontaneous amelioration of behavioral symptoms (such a speculation is testable but has not been carefully investigated to date). If it were possible to identify emerging chronic metabolic tissue and processing pathophysiologies—and to treat them before they crossed a threshold into decompensation and autistic regression—then prevention, in at least some cases of this condition, might become a real possibility. If incorporation of a tissue and intermediary metabolism orientation facilitated clinical improvement in even a modest subset of autistic individuals or prevention of even a modest number of cases, then the utility of aiming to incorporate this orientation would be validated in practice.

The emergence of a systems model from recent autism findings

A systems-oriented model of multi-leveled and pervasive biological underpinnings in autism has been emerging both implicitly and explicitly in a growing multi-faceted literature reviewed below. These emerging findings, directions of inquiry and theories in autism research include:

a. Widespread and pervasive brain tissue changes such as brain enlargement, widespread white matter volume increases and neuroinflammation that do not strictly localize in a pattern consistent with neural systems presumed to be implicated in autistic behaviors,
b. models of underlying processing abnormalities that are network rather than region-based,
c. genetic and anatomic overlaps between autism and other disorders previously thought to be distinct,
d. postnatal brain and behavior changes in a disorder that was previously assumed to be due to genetically determined *in utero* events,
e. the identification of chronic, ongoing brain tissue changes such as neuroinflammation and oxidative stress in a disorder that was previously assumed to derive from early hardwired changes in neural architecture,
f. common patterns of comorbid physical illnesses (gastrointestinal, immune, etc.) in many autistic individuals in a disorder that was thought to be brain-based,
g. reports of sharp increases in rates in a disorder thought to be strongly genetic, and
h. scattered cases of improvement and recovery in a disorder thought to be incurable.

These findings involve ways of approaching cause and change, timing and development, and structure-function relationships that both grow from and invite greater differentiation of thinking at the levels of underlying mechanisms. When genetics is placed into more explicit interplay with environmental factors, and when the focus is expanded from brain to organism/systemic biology, these anomalous features can be incorporated comfortably into an integrative model of autism.

A. Pervasive changes in the autistic brain

BRAIN ANATOMY: Various regional brain changes are frequently associated with autism, particularly in the cerebellum (Courchesne et al. 1988, Courchesne 1999, Courchesne et al. 1994, Gaffney et al. 1987) or the limbic system (Aylward et al. 1999, Haznedar et al. 1997, Haznedar et al. 2000, Howard et al. 2000) although these have been variably replicated (Filipek 1995, Kemper and Bauman 1998, Bailey et al. 1998, Palmen et al. 2004, Piven and Arndt 1995, Courchesne et al. 1995). From the vantage point of a model that seeks or assumes regional anatomical localization of specific functions, it has been perplexing that the most consistently replicated anatomical finding in autism is a change that can be characterized not as regional but as *pervasive:* an upward shift in the distribution of head circumference, (Bailey et al. 1993, Aylward et al. 2002, Fidler et al. 2000, Miles et al. 2000, Rapin 1996) brain weight (Bauman and Kemper 1985) and brain volume (Courchesne et al. 2001, Piven et al. 1995, Sparks et al. 2002) in younger autistic individuals (Redcay and Courchesne 2005, McCaffery and Deutsch, 2005). The finding of increased volume in brains that look clinically normal in standard MRI scanning acquisitions does not have precedent in the neurological literature, and it does not fit standard models of brain-behavior correlation (Herbert 2005). As the existence of this brain enlargement trend has become established, several studies have gone on to show that the volume changes, while pervasive rather than localized in the brain, are non-uniformly scaled, with the volume increase being driven most strongly by an increase in white matter (Courchesne et al. 2001, Carper et al. 2002, Cody et al. 2001, Herbert et al. 2003a). Moreover the scaling of white and gray matter volume differences from controls changes over time, with both gray and white matter being increased in the youngest subjects identified (Courchesne et al. 2001, Hazlett et

al. 2005), and with an apparent greater persistence of white matter volume increases into mid-childhood (Herbert et al. 2003a), although here the data are more sparse. Yet even this non-uniformity poses a challenge to localization-oriented approaches, because the change is widespread and not clearly localized to any functionally associated region or particular neural system. Genetic influence could lead to such widespread brain changes, but to appreciate this possibility, thinking about genetics, which has advanced to an appreciation of the importance of continuously distributed, non-dichotomous traits (Dawson et al. 2002) would also need to relax assumptions about localization and association of genes with specific functional deficits to which genetics is currently frequently coupled in models of autism (Dawson et al. 2002, Herbert and Ziegler 2005).

BRAIN FUNCTION STUDIES: In addition, while functional brain imaging studies seeking specific loci to correlate with specific behavioral deficits have yielded inconsistent results, studies are accumulating that show circuitry abnormalities with a *pervasive* character. For example, regarding inconsistent localization, while several studies have reported failure to activate the fusiform face area (FFA) during face processing (Schultz et al. 2000, Critchley et al. 2000, Pierce and Courchesne 2000), the aberrations from the typical pattern are not consistent between individuals within studies (Pierce et al. 2001), and two studies even found that autistic subjects did indeed activate the FFA during a face-processing task (Hadjikhani et al. 2004, Dalton et al. 2005). On the other hand, when one interrogates functional imaging findings not for changes in specific regions but for indications of common *patterns* of difference from the typical (Herbert 2004), one finds an atypical *distribution* of activation (Belmonte and Yurgelun-Todd 2003, Belmonte et al. 2004b), over-activation in early stimulus-driven stages processing but less than typical activation in higher-order processing centers, which may lead to (and/or reflect) an impairment in complex processing and be associated with the decreased covariance of activity that has been noted among regions that are normally coordinated (Horwitz et al. 1988, Starkstein et al. 2000), or the less than normal coordination that has been noted among the multiple components of a neural system (Luna et al. 2002, Just et al. 2004, Castelli et al. 2002). The finding that the brains of autistic individuals tend to engage in local rather than global processing (Ring et al. 1999, Hubl et al. 2003, Hall et al. 2003) may also be consistent with an abnormal coordination among components of distributed neural systems (Koshino et al. 2005). This lack of coordination among regions, or "underconnectivity" (Just et al. 2004), appears to be a widespread, *pervasive* rather than localized phenomenon, and moreover a property emergent from poor synchronization or coordination rather than a failure of some putative central coordinating mechanism or region. Belmonte (Belmonte et al. 2004a) and Courchesne (Courchesne and Pierce 2005a) also have also advanced models wherein local overconnectivity and long-range underconnectivity could be co-involved in the altered information processing patterns seen in autism. Such a pervasive connectivity problem invites association with pervasive findings at other levels, such as white matter enlargement or neurometabolic abnormalities like neuroinflammation, as well as synaptic or interneuron abnormalities, although such associations have not to date been clarified in specific research programs.

It may also be the case that the exceptional talents found in some autistic individuals may be related to the shifts in processing characteristics that alter connectivity, or compensatory adaptive responses to such alterations (Belmonte 2005), in that such atypical connectivity may facilitate the amplification of certain types of perception and focus beyond the level achieved by individuals with more typical neurocognitive processing. These talents include not only savant skills (e.g. calendar skills), but also high levels of artistic, musical, mathematical, writing and scientific creativity (Pring 2005, Heaton and Wallace 2004, Gould 1998). While the study of autism as an alteration of processing style should not compete with or take way from the study of impairments associated with autism, neither should it be neglected. The presence of such talents in some individuals may be rich with clues about the nature of autism, and from the vantage point of the current discussion these capabilities may also rest upon processing style differences that are widely distributed or pervasive.

BRAIN FUNCTION SYMPTOMATOLOGY. Autistic individuals have long been known to suffer frequently from a range of challenging issues beyond the defining trio of behavioral features, including seizures, sleep disorders, anxiety, and movement incoordination. These problems suggest nervous system abnormalities that are more pervasive than specific neural systems to which one might localize deficits in specific cognitive domains.

B. Models of pervasive or network-based processing alterations

The number of published systems-oriented approaches to the understanding of behavior and cognition has been increasing in recent years. Some early models of processing abnormalities include weak central coherence (Hill and Frith 2003), impaired complex processing (Minshew et al. 1997), underconnectivity (Just et al. 2004), and neural network abnormalities (Cohen 1994, Gustafsson 1997, McClelland 2000). Each of these models posits a more pervasive processing perturbance as underlying the autism behavioral phenotype, with the behaviors that cluster together to define the autism phenotype emerging as a consequence of these processing problems in vulnerable domains. Shah and Frith noted a reduced effort needed to segment a "gestalt" whole, suggesting that the "whole" was constituted less strongly for them—meaning that they showed "weak central coherence." Cohen (Cohen 1994, Cohen In press) has proposed a neural network model in which either too many or too few neuronal connections, as documented in neuropathological literature, would lead to overemphasis on specific details but an inferior capacity for generalization. Brock (Brock et al. 2002) proposed that a reduction in the integration of specialized local neural networks in the brain associated with a deficit in temporal binding would lead to

abnormal processing consistent with "weak central coherence." Deutsch has discussed how similar processing deficits may result from heterogeneous genetic influences (Deutsch 2003). McClelland has proposed that hyperspecificity in autism derives from abnormalities in neural nets (McClelland 2000). Minshew describes autism as a late information processing disorder with sparing of early information processing (Minshew et al. 1997); her colleague Just attributes language impairment in autism to underconnectivity, involving a lower degree of information integration and synchronization across large-scale cortical networks (Just et al. 2004). The research program of this group has also significantly oriented toward designing studies to dissect multiple impairments in autism, including working memory, abstract reasoning, and postural control, to show how an impairment of integrative information processing can critically contribute to issues seen in autism in each domain. (Minshew et al. 2004) A research program oriented toward discriminating between pathway and complexity-specific hypotheses has also been emerging in other centers (Bertone et al. 2003, Pellicano et al. 2005a), including a demonstration that the performance of high functioning autistic subjects is superior for a first-order visual task but inferior for a higher-order task, with higher order tasks requiring greater neuro-integrative complex processing (Bertone et al. 2005).

The operationalization of these models into experimental design so that their hypotheses may be tested is itself complex (Happe et al. 2001, Pellicano et al. 2005b), and this approach has not won over all members of the autism research community; but it is a developing theme and research agenda that addresses a variety of issues not encompassed by other paradigms, including potential brain mechanisms that may be related to systemic biological abnormalities in autism. Moreover, the idea that deficits may be due to impaired cortical coordination is also emerging in other fields such as Alzheimer's and schizophrenia (Bressler and Kelso 2001). Both simulations and experiments are yielding data supporting the idea that the problem lies not necessarily in any one cortical area or function, but may derive from altered circuitry, network dynamics, and supporting metabolic processes.

These types of pervasive network and processing based alterations raise the question of what types of biological mechanisms would lead to such changes, as well as the question of what types of interplay of genetic and environmental influences could trigger such mechanisms. It is quite conceivable that this level of perturbed processing is the closest we will come to convergence on commonality of underpinnings to the behaviors we use to define the autism syndrome. If this proves to be the case, then the convergence will remain abstract (i.e. convergence upon a common *pattern* of connectivity disturbance) rather than concrete (i.e. a specific gene or biological mechanism or environmental agent causing this disturbance).

C. Relevance to other disorders: is autism on a spectrum with other neurodevelopmental disorders?

While autism is *defined* by a set of behaviors, the behaviors are distributed continuously rather than discretely (Dawson et al. 2002). There is thus overlap both with the normal range and with other diagnostic entities. Neuroimaging (Herbert et al. 2003b, Herbert et al. 2004, De Fosse et al. 2004, Herbert et al. 2005) and genetic studies (Kjelgaard and Tager-Flusberg 2001, Tomblin et al. 2003, Bishop 1989) show much overlap between autism and developmental language disorder (or specific language impairment). Many children with autism are hyperactive or have obsessions or compulsive behaviors, while many children with ADHD or OCD have autistic features (Goldstein and Schwebach 2004, Bejerot et al. 2001, Kano et al. 2004). Genetic studies suggest intriguing overlaps (Johnson 2003), such as between autism, Tourette's syndrome and various autoimmune diseases (Becker et al. 2003). Similar *in utero* infection and maternal antibody factors may be involved in the pathoetiology of a variety of neurodevelopmental and neuropsychiatric disorders (Hornig et al. 2002, Behan and Geschwind 1985, Dalton et al. 2003). Thus considerations related to autism may also be relevant to a broader spectrum of disorders. This is a challenge to rethink the significance of the specificity of autism's definition. What constrains the relationships between specificity, continuously distributed symptoms and overlap?

D. Postnatal changes in autism

BRAIN VOLUME INCREASE: A number of studies have shown that the large head and brain sizes so commonly found in autism are not generally present at birth, but emerge over the first few years of life (Redcay and Courchesne 2005). Unusual growth trajectories have been discerned both by retrospective head circumference studies (Lainhart et al. 1997, Courchesne 2002, Dementieva et al. 2005) and by MRI volumetrics (Courchesne et al. 2001, Hazlett et al. 2005, Aylward et al. 2002), with average or even below average head circumference at birth and early postnatal onset of accelerated brain growth persisting during the first few postnatal years and then tapering off to the extent that in some studies the increase in brain volume relative to controls does not persist past childhood (Aylward et al. 2002).

Measurements of the distribution of this white matter enlargement even in older but pre-adolescent autistic children show a pattern of non-uniform distribution that is consistent with the post-natal overall brain and head-size enlargement. That is, the white matter increase is found in later-myelinating areas of the brain, particularly frontal lobe (Carper et al. 2002), and in the radiate (outer) zone as compared to deeper parts of white matter that do not show volume difference from controls (Herbert et al. 2004). Prefrontal lobe is most strikingly implicated, showing 37% more white matter than controls (Herbert et al. 2004). This pattern suggests what one might call an "archaeological footprint" of an age-related process that unfolds postnatally and becomes more pronounced with time—although on a cautionary note the fact that this finding appears to follow the gradient of myelination does not itself provide evidence that the underlying tissue compartment implicated in this volume change is indeed myelin; it could

instead be some other tissue component that affects or is reflected in processes involved in myelination, white matter formation or some other aspect of brain development that affects gray matter-white matter scaling.

AUTISTIC REGRESSION: It is also apparent that a significant number of children with autism have a period of apparent normality prior to experiencing a regression into autism (Lord et al. 2004, Lainhart et al. 2002), although the age, rate, and accompanying circumstances of regression seem to vary, and the precise proportion of autistic children who may be classified as having regressed is unclear. This regression involves not only the emergence of an atypical behavioral profile but also the loss of previously acquired capacities such as language, interest in social interaction and eye contact. In the last few years prospective studies of at-risk infant and toddler younger siblings of children with autism have started to yield data about early signs of autism and autistic regression (Zwaigenbaum et al. 2005, Richler et al. In press., Luyster et al. 2005, Lord et al. 2004). However measures utilized in the first round of such studies were entirely behavioral, while no tissue biomarkers (blood, urine, etc) were studied. We must therefore await future prospective studies employing a more comprehensive profile to generate data that could illuminate the metabolic or electrophysiological dynamics of autistic regression. The motivation to ask such questions is enhanced by a model of autism as "a condition that affects the brain."

NEUROPATHOLOGY: Neuropathological investigators have been divided on the timing implications of their findings. Published neuropathology studies to date are few and for the most part include limited clinical characterization, so that one frequently has no sense of the degree of functional impairment, the medical and seizure history, whether or not there was regression—or even the post-mortem interval between death and fixation, a variable that can introduce substantial artifact. Such information would be critical in evaluating the significance of autopsy findings. Nevertheless neuropathological specimens provide a unique window into tissue pathology. Certain findings such as brainstem anomalies, reduced Purkinje cell number and olivary changes have been interpreted as implying that abnormalities occurred prenatally (Kemper and Bauman 1998, Bauman and Kemper 1985, Rodier et al. 1996). Other investigators have argued that the changes seen in post-mortem autistic brain tissue (and in autistic brain anatomy as assessed by *in vivo* measurements as well) are too subtle to have occurred so early and that the findings more likely imply a late gestational or early postnatal onset (Ciaranello and Ciaranello 1995, Bailey et al. 1998). Purkinje cell vulnerability to metabolic stressors such as excitotoxicity has been argued to be a potential basis for postnatal loss of such cells (Kern 2003). More recently the Bauman and Kemper laboratory reported a post-mortem study that failed to replicate the Purkinje cell and brainstem findings that they had reported starting in the 1980s and that have been pivotal in supporting the prenatal model (Thevarkunnel et al. 2004, Kemper et al. 2004). Thus for a variety of reasons, the argument for an exclusively prenatal origin of autism has been substantially undermined in recent years.

E. Chronic tissue changes in the autistic brain and body

Tissue changes have been identified in autistic brains that are associated with chronic pathophysiological processes rather than with early aberrations in brain development. These prominently include neuroinflammation and oxidative stress, which are both final common pathways that could be a reaction to a huge number of genetic, environmental and altered metabolic processes. Nevertheless, even though they are non-specific, the recent entry of these types of chronic tissue changes into the set of autism findings makes it newly important to consider a wide range of factors and stressors that have hitherto been little investigated in autism research. One important and provocative recent study, already mentioned, has discerned signs of widespread neuroinflammation, including microglial and astroglial activation as well as inflammatory cytokine and chemokine profiles in post-mortem brain tissue from brains of autistic individuals from childhood through mid-adulthood, with inflammatory cytokines and chemokines also being found in cerebrospinal fluid obtained from living subjects (Vargas et al. 2005). It is notable that these chronic changes were not confined to childhood but were identified substantially across the lifespan. Indications of oxidative stress are also being reported in autism, both centrally and peripherally. Carboxy ethyl pyrrole, a lipid peroxidation product, has been found in post-mortem brain tissue in all young autistic subjects investigated to date, specifically in dendrites, in a study of this marker, which may have significant implications for brain connectivity (Perry et al. 2005). The investigative techniques that discerned these neuroinflammatory and oxidative stress changes had never previously been applied to autistic brain tissue.

Peripheral markers of lipid peroxidation have been measured as increased in autism as well (Zoroglu et al. 2004, Ming et al. 2005), and their increase correlated in one study with loss of previously acquired language skills in autism (Chauhan et al. 2004a). Altered phospholipid metabolism has also been reported (Chauhan et al. 2004b). Further metabolic markers of oxidative stress have been identified in autism, including abnormal levels of metabolites in the methionine transmethylation and transsulfuration pathways, signifying impaired methylation and increased oxidative stress (James et al. 2004); these findings may be associated with genetic polymorphisms conferring vulnerability (James et al. 2005). Abnormal levels of antioxidant enzymes in plasma (Yorbik et al. 2002) and in red blood cells (Zoroglu et al. 2004, Sogut et al. 2003) have also been found. Abnormal levels of nitric oxide are also associated with oxidative stress, and have been identified in several autistic cohorts (Sogut et al. 2003, Sweeten et al. 2004, Zoroglu et al. 2003). Reduced levels of antioxidant vitamins and minerals that have been reported in various autistic cohorts (Audhya and

McGinnis 2004) could be both cause—exacerbating oxidative stress, and consequence—resulting from depletion of antioxidant reserves. Reduced antioxidant levels have also been associated with various neuropsychiatric disorders, such as active affective disorder (Ozcan et al. 2004). A variety of other symptoms may be associated with oxidative stress as well. One such symptom in autism is REM sleep behavior disorder in autistic children (Thirumalai et al. 2002); this disorder is associated with Parkinsonism in later life, for which a large literature suggests a relationship between Parkinsonian neurotoxicity and oxidative mechanisms.

Oxidative stress and neuroinflammation are associated with each other and also with low energy production and excitotoxicity (Chong et al. 2005) and reduced synaptic efficiency (Bazan 2005); and impaired methylation negatively impacts multiple processes including neurotransmitter synthesis and gene regulation (Mattson and Shea 2003, Gilbert 2004). It is conceivable that the brain membrane and phospholipid abnormalities reported by Minshew in her early 31P magnetic resonance spectroscopy study (Minshew et al. 1993) could have been related to oxidative stress. In addition, the association of ongoing neuroinflammatory and oxidative stress pathophysiology with autism raises the possibility that findings in post-mortem specimens previously assumed to have a prenatal origin could at least in some cases be aggravated or changed if not caused entirely in the postnatal period. These types of chronic pathophysiology may be contributors to what Bauman and Kemper recently described as the ongoing character of autism neuropathology (Bauman and Kemper 2005), on the basis of observations such as their own work showing cells in certain regions that were large and dark in younger subjects but in older subjects were small and pale. From the current vantage point it can be suggested that such a pattern might be attributable to prolonged oxidative stress and slow neuronal damage, which has been associated with cell swelling and inflammatory reactive edema that over a long period of time might deplete the cell (Kern 2003, Vajda 2002).

DEVELOPMENTAL AND CHRONIC MECHANISMS. Of note, as the study of this class of chronic brain abnormalities—including but perhaps not limited to chronic neuroinflammation and oxidative stress—is in its infancy, its regional distribution is unknown, but it is conceivable that it would preferentially affect certain regions even though its triggers might be more widespread (Caviness 2001). The identification of this class of chronic, ongoing abnormalities also opens up new possibilities regarding the points in development at which relevant pathology may occur. For example, if inflammation or oxidative stress occurred early, they might alter signaling processes modulating brain development. The impact of oxidative stress on *in utero* development is poorly studied, but immune factors such as chemokines modulate brain development (Cartier et al. 2005), and there is some evidence that *in utero* infection and maternal antibodies, as well as early postnatal antigen exposure in immunologically vulnerable animals, are associated with abnormal brain development (Fatemi et al. 2002, Dalton et al. 2003, Hornig et al. 2004, Pletnikov et al. 2002, Patterson 2002). *In utero* nutrition, toxic exposures and maternal stress may also impact development. *In utero* events and alterations may prime the system for more catastrophic responses later on.

However, an additional class of changes beyond early or *in utero* alteration in brain anatomy or architecture is suggested by documentation that the brains and bodies of autistic individuals manifest ongoing chronic tissue abnormalities. These mechanisms may or may not be rooted in pathophysiology that begins in the womb, but in either case their presence suggests that problems occurring, actively continuing and affecting tissue later in development may also—or in some cases instead—be implicated as potential contributory biological substrates for autistic behaviors: such chronic and ongoing pathophysiological processes, individually or in combination, can potentially negatively impact the brain's chemical milieu, impairing brain signaling and connectivity. For example, excitotoxic mechanisms may be potentiated by excessive amounts of glutamate in inflamed brain tissue (Muscoli et al. 2005). The immune system may impact the central nervous system through an abundance of mechanisms including neurotransmitters, hormones, cytokines and chemokines (Dunn 2002, Barkhudaryan and Dunn 1999, Dunn et al. 1999). Neuroimmune and neuroendocrine relationships may be altered by infectious and toxic influences as well as emotional stress (Lawrence and Kim 2000). Such potential ongoing neurochemical consequences of chronic, ongoing tissue and metabolic changes point toward potential utility of the conception of "encephalopathy" in relation to at least some cases of autism.

Moreover, chronic tissue changes may progressively erode compensatory capacities until a threshold is crossed and decompensation—both behaviorally and at the cellular level—occurs. Indeed, the line of thought being presented here raises the possibility that autistic behavioral regression may have specific metabolic and tissue concomitants. Some anatomical changes identified in autism, even if they contribute to observable behaviors, may not be "primary" but rather may be the "downstream" structural traces of such underlying chronic metabolically related pathophysiology. For example, regional abnormalities in limbic system and cerebellum may be secondary to immunological disturbance or excitotoxicity (Vargas et al. 2005, Hornig et al. 2004, Kern 2003), while white matter enlargement may be downstream of increased axonal activity due to cortical noise (that could also be due, among other possibilities, to excitotoxicity) (Barres and Raff 1993, Rubenstein and Merzenich 2003), or to stimulation of oligodendrocytes by microglial activation (Hamilton and Rome 1994). Abnormal cortical columns may be a result of abnormalities during their formation early in gestation (Casanova et al. 2003), or may be related to factors involved in postnatal cortical column sculpting, such as altered nitric oxide which itself could be associated with oxidative stress mechanisms (Gustafsson 2004). While these examples are clearly at the level of speculation at this time, their incorporation of components of observations that have been made in autism supports the pursuit of this line of investigation.

F. Multisystem comorbidities and interrelationships between peripheral and central biomarkers in autism

While autism is highly heterogeneous in many respects, large numbers of affected individuals manifest similar patterns of one or more of a set of physical symptoms outside the central nervous system (CNS). Prominent among these are gastrointestinal and immune issues; in children with regressive autism, such symptoms may precede the autistic regression. Gastrointestinal disturbances that have been reported include reflux esophagitis, chronic gastritis, chronic duodenitis, constipation, reduced carbohydrate enzyme activity and chronic diarrhea (Horvath and Perman 2002, Jass 2005). Reported immune abnormalities have included autoantibodies (particularly to central nervous system proteins) (Ashwood and Van de Water 2004b) and deficits in immune cell subsets, cytokine abnormalities, impaired responses to viral infections, and prolonged and recurrent infections (Ashwood and Van de Water 2004a), as well as vulnerability factors including family history of autoimmune disease (Comi et al. 1999, Sweeten et al. 2003) and genetic variants associated with autoimmunity (Torres et al. 2001, Ashwood and Van de Water 2004b). Many of the reported gastrointestinal abnormalities are of an immune character, such as altered mucosal immunity (Torrente et al. 2002, Furlano et al. 2001, Ashwood et al. 2003, Ashwood et al. 2004); atypical immune responses to certain dietary components have also been reported (Jyonouchi et al. 2005b, Jyonouchi et al. 2005a, Murch 2005, Jyonouchi et al. 2002, Vojdani et al. 2002). CNS, GI and immune systems may all interrelate as well; for example the neurotransmitter serotonin, that has been documented in various ways as abnormal in autism, is prominent in the intestine and may be modulated by immune factors (Barkhudaryan and Dunn 1999, Ashwood and Van de Water 2004a); this type of multisystem involvement can be described for other neurotransmitters as well. An animal model of gut-brain interaction showed that inflammatory bowel disease activates areas of the brain implicated in autism (Welch et al. 2005), and in a fashion consistent with an underlying inflammatory pathophysiology. Systemic inflammation may lead to exacerbation of central nervous system inflammation (Perry et al. 2003); in one study, induction of TNF-alpha was shown to peak in serum in one hour and return to normal levels in six hours, but to persist in the brain for a month (Qin et al. 2004). Increased intestinal permeability has been found even in autistic individuals without gastrointestinal symptoms (D'Eufemia et al. 1996), and such permeability has been associated with endotoxemia that in turn may render the blood-brain barrier more permeable (Kowal et al. 2004). Inflammatory bowel disease has also been associated with neurobehavioral symptomatology (Solmaz et al. 2003). Reports of low antioxidant and anti-inflammatory nutrient levels in autistic children (Jory 2005, Audhya 2005, Yorbik et al. 2005) suggest a potential self-amplifying feedback loop between (possibly inflammation related) intestinal malabsorption—which exacerbates poor nutritional status, and low levels of nutrients—which exacerbate inflammation, oxidative stress and gut disease. The pathologies that are in turn exacerbated by inflammation and oxidative stress themselves have multiple further ramifications.

From the point of view of autism modeled as what we are here calling a "brain-based, strongly genetic" disorder, these peripheral abnormalities have seemed secondary and coincidental, and this presumably contributes to the limited attention that has been paid until recently to assessing the prevalence of these features, the predictors of their presence or absence, and the mechanisms by which these phenomena are related to CNS abnormalities in autism. They are certainly not uniformly present in every individual with autism, and the inconsistency of findings to date can support a rejection of the relevance of this domain by those who expect the specificity of autism biology to map unambiguously to the specificity of the defining behaviors. (But from the vantage point of a "genetically influenced systemic" model that construes the relationship between underlying metabolic or tissue level mechanisms and observable behaviors as one of loose coupling and final common pathways, heterogeneity is expected and inconsistency can be seen as providing opportunities to characterize distinctive subgroups). Nevertheless, mechanisms are being identified that may suggest how these peripheral abnormalities could be related to a syndrome characterized behaviorally. For example, peripheral immune chemicals affect brain function (Barkhudaryan and Dunn 1999); immune neuromodulators may affect brain development (Bajetto et al. 2001), mood and behavior (Licinio and Wong 1999, Reichenberg et al. 2001), and blood-brain barrier permeability (Abbott 2000); while peripheral inflammation can affect inflammatory markers and conditions in the brain (Qin et al. 2004, Perry et al. 2003, Perry 2004, Godbout et al. 2005). Neurochemical consequences of these peripheral tissue changes may also be implicated in features of autism symptomatology such as anxiety, sleep disturbance and seizures.

The study of multisystem abnormalities in autism is complicated by the likely great heterogeneity of the underlying biological factors that lead to final common pathways of symptomatology we are discussing here. For example, the FMR1 knockout mouse model of Fragile X is associated with overactive signaling by group I metabotropic glutamate receptors, and the animals manifest a series of symptoms and findings including anxiety, hyperactivity, seizures, sleep disturbance, repetitive behaviors, and even gut dismotility and dendritic spine abnormalities—a profile of abnormalities strikingly reminiscent of autism— (Dolen and Bear 2005, Bear et al. 2004); but the glutamate abnormality that may be the underlying mechanism could also arise in other ways and lead to this symptom complex even without this particular mutation. Conversely, autistic symptomatology in the presence of such a mutation might be exacerbated or even triggered in the setting of environmental factors such as PCB exposure that amplify glutamate signaling (Gafni et al. 2004); worthy of reflection is the possibility that such environmental factors may contribute to the development of autism in genetic conditions (e.g. Fragile X) in which autism is common but not universal. Similarly, a reduction in serotonin or serotonin efficacy might be a primary genetically related problem of serotonin receptors or serotonin synthesis but could also be sec-

ondary, for example, to immune modulation of tryptophan and serotonin metabolism (Barkhudaryan and Dunn 1999) (such as the depletion of the serotonin precursor tryptophan by the inflammation-associated kynurenin pathway) or to anti-serotonin receptor antibodies (McDougle et al. 1996, Ashwood and Van de Water 2004a). Overall, the extensive documentation of various abnormalities in autism outside of the central nervous system suggests that at least in some subgroups of autism these phenomena may be intrinsically linked, at the level of underlying disease mechanism, to the syndrome we call autism.

G. Reports of autism rate increases with their implication of non-inevitable environmental triggers and genetic vulnerability

Although autism has often been assumed to be highly genetic, it should be remembered that the monozygotic concordance only reaches 90-95% if the sib is required to meet only broad autism spectrum criteria; if both sibs meet full autism criteria the monozygotic concordance goes down to around 60%, which although high, and substantially higher than dizygotic concordance, also implies a role for environmental factors (Muhle et al. 2004). Whereas autism rates in the 1970s and 1980s were reported as 3-4 per 10,000, rates are now reported to be between 30-60/10,000, at least a tenfold increase (Fombonne 2003, Blaxill 2004, Newschaffer et al. 2005). While many say that these increases can be accounted for by altered definition and increased awareness, this has not been definitively established, and it does not appear to be due to diagnostic substitution (Croen 2003, Newschaffer et al. 2005, Rutter 2005). If the question is whether or not we are facing a serious public health problem, it would seem prudent to systematically address mechanisms through which environmental factors might lead to the autism syndrome even before we can answer this question clearly. Autism rate increases imply non-inevitable factors—i.e. environmental factors and gene-environment interactions—with resultant non-inevitable alterations in metabolism, gene expression, signaling etc., some of which may be treatable and reversible. Developmental neurotoxicology (Slikker and Chang 1998)—and also indeed developmental neuroendocrine- and neuroimmunotoxicology (El-Fawal et al. 1999)—are central here. The chronic pathophysiology of neuroinflammation and oxidative stress observed in autism are potentially non-inevitable, as they are well documented to arise from a great range of environmental factors, including but not limited to pesticides, heavy metals, infection, and air pollution (Filipov et al. 2005, Kim et al. 2002, Zurich et al. 2002, Campbell et al. 2005, Ling et al. 2004, Shanker et al. 2004, Campbell et al. 2004).

In the setting of environmental exposures that may contribute to causing or triggering (or exacerbating) autism, the role of genes may be to lead to vulnerability in pathways that are impacted by or involved in dealing with environmental agents or factors (Johnson 2003). From this point of view candidate genes would need to include environmentally responsive genes as well as genes directly involved in the central nervous system (Serajee et al. 2004, James et al. 2005, D'Amelio et al. 2005, Herbert et al. 2005). Filipek et al reported a set of mild mitochondrial abnormalities including carnitine deficiency, reduction in pyruvate, slight lactate elevation and significant elevations of alanine and ammonia (Filipek et al. 2004). The investigators carefully noted that these problems were mild compared to the levels of abnormality in many patients with documented mitochondrial mutations. Given that environmental toxins may inhibit various components of mitochondrial metabolism and lead to leakage of antioxidants from mitochondria (Emerit et al. 2004, Kitazawa et al. 2004, Mishra and Shukla 2003, Moon et al. 2005, Allen et al. 2001), the level of subtlety in these reported findings may reflect an interaction of mild genetic vulnerability with environmental insult, or may in some instances even be exclusively due to environmental factors. This consideration deserves further investigation, as we have very limited knowledge about the metabolic consequences of ongoing low-level exposure to multiple environmental agents, even though such exposures have become the norm rather than the exception (Environmental Working Group 2003). One challenge is that such investigation poses significant methodological complexities.

There is no body of evidence at present sufficient to reject the role of environmental agents, and much that suggests these are highly relevant to autism, other neurodevelopmental disorders and chronic disease more broadly. For example, in Texas, for each 1000 Ib of environmentally released mercury, there was on average a 43% increase in the rate of special education services and a 61% increase in the rate of autism (Palmer et al. 2005). Body burden studies have been showing that most people carry traces of hundreds of chemicals in their bodies (CDC 2003, Thornton et al. 2002); that cord blood from newborns, in the first study to measure toxins in this gestationally relevant body fluid, contained 287 chemicals of which 180 cause cancer in humans or animals, 217 are toxic to the brain and nervous system, and 208 cause birth defects or abnormal development in animal tests (Environmental Working Group and Commonweal 2005); and that breast milk contains multiple environmental toxicants (Landrigan et al. 2002). Low doses of chemicals, though not cytotoxic, still appear to have impacts—sometimes significant ones—at the level of molecular and cellular mechanisms (Welshons et al. 2003). These findings have not yet, however, found their way into the evidence-based clinical arena (regarding either measuring low-grade exposures or evaluating their clinical impacts). Yet studying multiple simultaneous influences is more consistent with the nature of contemporary exposures than studying chemicals one by one, given that environmental factors are not really encountered alone in the natural setting (CDC 2004). Study of combined exposures in addition addresses the synergies between chemicals that may raise disease risks differently than when substances are encountered separately (Cory-Slechta 2005, Carpenter et al. 2002). For example an animal model was designed as the first study of the influence on embryonic development of three of the pollutants found in high concentrations in the municipal water supply in Brick, New Jersey (Kreiling et al. 2005) in the course of investigating an autism cluster there (Bertrand et al. 2001). The chemicals in combination showed impact

on a developmentally important regulatory pathway (upregulating a regulatory subunit of cAMP-dependent protein kinase, a ubiquitous protein involved in neurologic pathways and a key regulator of neuronal growth in the clam embryo model, with the clams also showing increased cilia movement). It is provocative that this impact was not found from exposure to these chemicals individually or in pairwise combinations, even at levels 1,000 times those in the mixture. But in the Brick Township autism cluster investigation, interactive effects were not studied and so these chemicals were not considered to be implicated because each individually was considered below threshold in its concentration (and one might note that, given the lack of prior developmental investigation, such thresholds could have not been construed in relation to risks to embryological development).

While designing studies of chemical synergies poses methodological challenges, it appears that without such investigation our knowledge is incomplete. Yet to date investigation of the developmental neurotoxic effects of chemicals has not been required prior to marketing, and only a small handful (perhaps a dozen out of the top approximately 3,000 of the 85,000 chemicals manufactured) have been so studied even individually (Goldman and Koduru 2000). Regarding combinations, even studying just these top 3,000 chemicals in combinations of three would require 85 billion tests. Thus, while there is a potential significant impact of chemicals and other evolutionarily unprecedented factors on child health, development and neurodevelopment (Weiss and Landrigan 2000, Stein et al. 2002), data does not now exist even for most individual chemicals, while for combinations of influences a thorough understanding may be intrinsically impossible to acquire.

At the broadest level, indicators of environmental involvement in autism have status as objects for existential reflection as well as scientific investigation. A recent United Nations Millenial Ecosystem Assessment report (that has received surprisingly little publicity), produced by 1360 scientists from 95 countries (Reid and Raudsepp-Hearne 2005), warns that the planet Earth may not be counted on to support human life for more than a few generations unless we re-set our course. This challenges the default presumption of a stable biological substrate implicitly underpinning the null hypothesis that increased autism incidence is largely artifactual. If the biological substrate is instead unstable as the UN report suggests, the phenomenon of growing numbers of children with neurodevelopmental disorders is not only plausible, but would represent another class of collateral damage alongside of epidemic chronic illness, loss of biodiversity, ecosystems disruption and global warming. If the large number of scientists contributing to this UN report (strikingly large in number as a concordant voice) is even remotely on target, then we face a need for methodological reflection regarding how best to apply human intelligence in this unprecedented situation. The epidemiological, biodiversity and ecological trends may contain the message that we do not have time for the level of precision that we have been trained to demand of ourselves prior to decision making (and that in any event has already been sacrificed given the pervasive presence of chemicals and combinations of chemicals whose biological impacts have barely been studied (Government Accountability Office 2005)). If so then perhaps we ought to use scientific intelligence to identify approximate but adequate leverage points to turn the tide constructively.

With regard to environmental contributors to autism, a good approximate leverage point may involve careful study at the level of final common pathways upon which multiple potential causes may converge (Edelson and Cantor 1998, McFadden 1996)—particularly given the challenges and length of time involved in establishing one or a number of potential triggers as specific and clear contributors (Lawler et al. 2004), and the great likelihood that heterogeneity will confound our search for unambiguous evidence. Such pathways in any event are more likely to be related to treatment targets: while there may be some treatments that directly target environmental factors (chemical, infectious, etc.), it is likely that many effective treatments will work backwards from intermediary mechanisms affected by such triggering factors, improving organism functioning and possibly improving the body's ability to address such triggers (e.g. improved immune or detoxification function).

H. Evidence of improvement or recovery

There are scattered reports of improvement or recovery from autism, whether from behavioral or cognitive processing intervention, from treatment of metabolic conditions with rare association with autism, or from treatment of metabolic pathways associated with responding to toxic or immunological challenges. In addition, many individuals with autism manifest significant variability in their symptom severity, suggesting that some modulating factors may be variable rather than strictly hardwired. Symptom variability and especially recovery raise the possibility that there are features of the mechanisms underlying the autism syndrome that may change in response to intervention. Some children improve substantially and even become mainstreamed through intensive behavioral therapy (Lovaas 1987, Perry et al. 1995, Kelley et al. In press, Fein et al. In press). In children with language impairment disorders some studies suggest that sensory based training can drive marked improvements in language (Merzenich et al. 1996, Tallal et al. 1996), which is reflected in neuronal firing patterns (Temple et al. 2003). Given the evidence for overlap between language impairment and autism to be discussed below, and given the documentation of difficulties in parsing transient sound differences in some individuals with autism (Oram Cardy et al. 2005)—which is the impairment addressed by this intervention—appropriately modified training might also reorganize neuronal assemblies and connectivity patterns in autism. Modulation of autism severity by treatment in cases of documented metabolic disorder was reviewed by Page in 2000 (Page 2000) and some more examples have since been reported. Autistic symptoms are reduced in PKU by a low phenylanlanine diet, (Gillberg and Coleman 2000); in hyperuricosuric autism by a low purine diet with or without allopurinol (Coleman 1989, Gillberg and

Coleman 2000, Page and Moseley 2002); in patients with low CSF biopterin by biopterin supplementation (Fernell et al. 1997); in some hypocalcinuric autistic patients by calcium supplementation (Coleman 1989); in some patients with lactic acidemia by thiamine and/or ketogenic diet (Coleman 1989), in cerebral folate deficiency by folinic acid supplementation (Moretti et al. 2005, Ramaekers and Blau 2004), and in Smith-Lemli-Opitz syndrome by cholesterol treatments (Natowicz 2004). Johnston offered a variety of mechanisms whereby metabolic disorders, sometimes with treatable aspects, might lead to neurological changes that could underpin autism (Johnston 2000). Zimmerman framed his report of promising immunological treatments in terms of a need for a search for reasons for their apparent at least intermittent efficacy (Zimmerman 2000). James reported that her correction of oxidative stress and methylation abnormality profiles through intervention with methylcobalamin, folinic acid and trimethylglycine was accompanied by qualitative clinical improvement (James et al. 2004), and is currently proceeding with further larger studies that will include more rigorous measures of this behavioral dimension of response (as well as of associated polymorphisms as previously mentioned (James et al. 2005)). Symptom severity was reduced in a trial of high-dose vitamin C in autism (Dolske et al. 1993). In this regard but more generically, Ames models high-dose vitamin therapy as a treatment approach for a range of genetic disorders characterized by decreased coenzyme binding affinity (Ames et al. 2002). Treating intermediary metabolism may not in itself directly or specifically address causal issues or "core" issues. But the modulation of autism severity by intervention supports a model of gene-environment interaction, because it demonstrates that intermediary metabolism related to genetic influence may be influenced by targeted intervention (i.e. environmental input) in a manner that tangibly affects outcome. It also demonstrates that one may intervene in a system in various ways, not just at the most visible targets, and effect changes that ramify at multiple levels.

While a few trade parent-written books have appeared documenting autism recovery through various methods, including both behavioral and biomedical interventions (Seroussi 2002, Edelson 2003, Maurice 1994, Hamilton 2000, Adams 2005), many parents whose children have improved or recovered anecdotally state that they are happy to escape the stigma of autism and the nightmare of being told their child's condition was incurable, and thus do not wish to document what transpired or to undergo the complex emotions involved in returning to the doctors and other caregivers who offered the initial diagnoses and poor prognoses to show changes in their children that they were told could never happen. But improvement and recovery should be documented and studied; the National Cancer Institute's Best Case Series Program provides a precedent here (Lee 2004, Nahin 2002). This type of approach provides a basis for follow-up by prospective trials that do not assume all or even a majority of patients will improve, but focus on adequate pre- and post-testing of those who do and do not improve, regardless of the ratio, to identify features of responders and non-responders that may help clarify disease mechanisms and treatment targets, as well as biologically distinct subgroups.

Discussion

To be classified as autistic, an individual simply has to meet a set of carefully delineated criteria in three behavioral domains. That is all. As there are no biological markers for autism, so also there are no biological criteria for autism. There is nothing in the definition of autism that either prescribes or excludes any specific type of biology or any disease course.

Nevertheless, it is not trivial that the behaviors that define autism can be so precisely characterized, notwithstanding the heterogeneity of their expression amongst autistic individuals. Given that we expect heterogeneity, at what level are there unifying features that account for the behavioral consistencies (Herbert 2004)? The answer to this question needs to be congruent at multiple levels. That is, this answer needs to encompass and integrate behavioral, processing, tissue organizational, molecular and cellular, and genetic levels. It also needs to encompass the heterogeneity at each of these levels. Belmonte has cogently described the "fan in, fan out" character of the cascades of convergent and divergent causation involved in the multileveled class of phenomena we call autism (Belmonte et al. 2004b)—where multiple pathways funnel through final common pathways, while one or a few mechanisms lead to multiple consequences. Some class (potentially an abstractly defined class) of computational or processing abnormalities needs to be at the core, as consistently underlying the behaviors currently defining the disorder, but its formulation needs to be crafted to integrate with the various levels of biological mechanisms underlying it (Just et al. 2004)—because the processing problem is not just cognitive but also, and critically, tissue based.

From a systems point of view, some refinement or integration of the models of pervasive processing abnormalities discussed in section B above will probably emerge as a characterization of that which unifies the heterogeneity, while the specific neural circuits identified (though not necessarily consistently) in a variety of psychology and neuroimaging studies (e.g. theory of mind or face processing networks) would be expected to be incorporated into these larger systems perturbances (Hadjikhani et al. 2004, Herbert et al. 2005). That is, from the systems vantage point, the identification of specific neural circuits that function abnormally or atypically in autism does not falsify the systems model, because specific networks or components may be preferentially impacted in a systems-level alteration.

In proposing the model of "underconnectivity," Just argued that relating a complex cognitive processing impairment to a measurable widespread reduction in functional connectivity was an advance over a purely psychological or cognitive model like "weak central coherence," since these prior models did not specifically link to issues in underlying levels that might lead to this processing style. He also argued that a decentralized network perturbation model was an advance over the to date unsubstantiated presumption that some

central part of the system serves as monitor or coordinator and has a deficit in autism (Just et al. 2004). The tissue-level biological changes that in turn might impair connectivity were addressed in particular by the model of increased excitation/inhibition ratios (Rubenstein and Merzenich 2003), where cortical hyperexcitation was shown to lead to a variety of downstream consequences including processing abnormalities consistent with "underconnectivity," but also with a variety of other features frequently associated with autism such as anxiety, seizures, disordered sleep and even conceivably gut motility disorders. The identification of neuroinflammation (Vargas et al. 2005) and oxidative stress (Perry et al. 2005, McGinnis 2004, James et al. 2004), as discussed, offers a set of tissue-level changes that might eventuate in hyperexcitability and hence also underconnectivity, as do changes associated with various candidate genes.

However at each level of this hierarchy the models and data just described do a delicate dance between specificity and generality. Because Rubenstein and Merzenich were explicitly working at the level of "model" rather than reporting a specific set of data, they were most explicit about the multiplicity of specific biologies that might lead to increased excitation/inhibition ratios. Possibilities they mentioned included genetic mutations in GABA receptors, exposure to pesticides that upregulate glutamate or exposure to auditory noise in infancy and more; various other possibilities are under discussion in the research community. At the level of processing alterations and even more at the level of the behaviors eventuating from such processing abnormalities, it may well not be possible to find features that distinguish clearly among the underlying pathoetiologies that could feed into this particular final common pathway. This same issue of heterogeneity applies in relation to neuroinflammation and oxidative stress, which are themselves final common pathways that may eventuate from a large range of triggers—and yet themselves probably represent only some of the tissue and neurochemical changes that could lead to an increased excitation/inhibition ratio (or other things), which is in turn presumably only one of a variety of classes of neurochemical disturbance that could perturb processing in a fashion sufficient to lead to "autism." Given the potential heterogeneity at each level, how do we learn what is sufficient for autism—and what, if anything, is in fact *necessary?* And among factors that are sufficient, can a factor in one setting be a cause and in another a consequence? Or, in an interconnected complex system, are such chicken-egg questions just oversimplifications?

A variety of biological substrates might be suggested as potential contributors to the computational or processing perturbance that underlies autistic behaviors. These could include white matter enlargement (structural) (Herbert et al. 2004), pyramidal cell abnormalities (Courchesne and Pierce 2005b), altered connectivity secondary to abnormal cortical minicolumns (structural/neurochemical) (Casanova et al. 2003, Casanova 2004, Courchesne and Pierce 2005b), increased excitation/inhibition ratios (neuromodulator) (Rubenstein and Merzenich 2003), abnormal interneurons (microanatomical and neurochemical) (Levitt et al. 2004), neuroligin mutations that alter the excitation/inhibition ratio in the synapse (Cline 2005), neuroinflammation (microanatomical/neurochemical) (Vargas et al. 2005), lipid peroxidation (Perry et al. 2005, Chauhan et al. 2004a), membrane and synapse malfunction secondary to reduced essential fatty acid content (Vancassel et al. 2001), energetic impairments (Minshew et al. 1993, Filipek et al. 2004), and brain desynchronization due to impaired oscillatory regulation by the inferior olive (structural/electrophysiological) (Welsh et al. 2005). Amygdala and cerebellum both play roles in informational integration that could be negatively impacted if these areas were harmed in some way. There are undoubtedly various other autism findings that could also be framed in this light. Given that we are only beginning to look at autism in this manner—i.e. explicitly grappling with its heterogeneity and its processing abnormalities—we have no way of knowing whether these and other possible underpinnings of processing and connectivity alterations are related to each other or independent. It is possible that we are facing a situation where a brainstem abnormality with an early *in utero* onset (Welsh et al. 2005, Rodier 2002, Kemper and Bauman 1998) a postnatal neurochemical or white matter abnormality (Rubenstein and Merzenich 2003, Vargas et al. 2005, Herbert et al. 2004), and a variety of other findings, all result in brain desynchronization or underconnectivity sufficient to cause autism. This would mean that many of these biologies are sufficient but none are necessary. If this is the case, then while eventually we may be able to sort out these different subgroups, in the meantime we are deeply challenged at both conceptual and methodological levels. If the phenomenon is heterogeneous but less extensively so, then how do we characterize its constraints? That is, are there specific etiological features or pathogenic "bottlenecks" (or classes thereof) that are involved in all autisms? Whether it is entirely heterogeneous or substantially constrained, we will need to develop study designs that do not average away statistical significance through inadvertently combining subgroups that have similar behavioral phenotypes but diverge in their underlying mechanisms. Measurement of intermediary mechanisms may thus add greatly to behavioral distinctions in our ability to discern more homogeneous subgroups. Utilization of "best case analysis" methods in treatment trials (Lee 2004) may add an extra research probe here by allowing treatment response versus non-response to shed light upon underlying metabolic differences and thereby contribute to identifying endophenotypes.

In the setting of this level of heterogeneity, genetic research might contribute by identifying subgroups, however small, where the mechanism can be more exhaustively characterized. This gene would not have to be the exclusive cause for an abnormality in this mechanism in autism; nor would this mechanism have to be the exclusive cause of every case of autism. But if genetic research could help characterize an abnormality in a pathway that could be disturbed in another individual without that mutation, it would then be doubly useful. Potential multiple pathways to common mechanisms were discussed above, including how Fragile X and neuroligin mutations as well as PCBs and oxidative stress may all contribute to an increased excitation/inhibition ratio (Figure 3). Thus, in the light

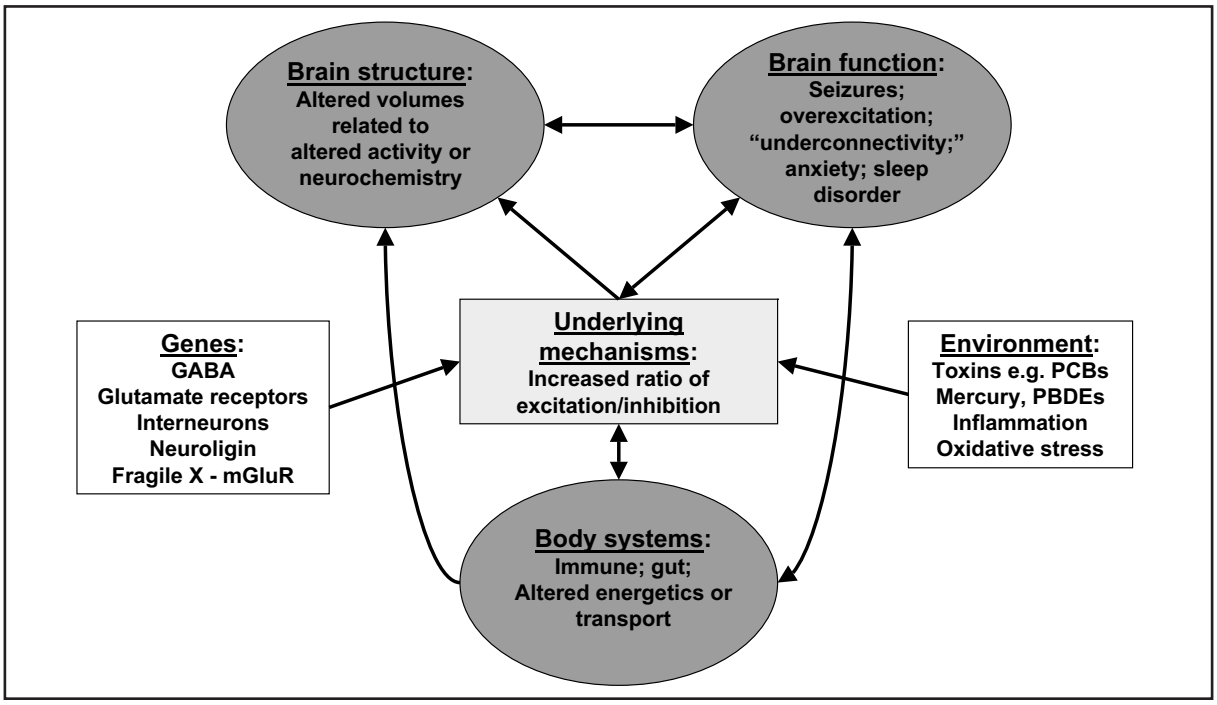

Figure 3. *The example of an increased excitation/inhibition ration is chosen as a particular case of how a common mechanisms could be driven by combinatorial effects of multiple genetic and environmental influences* (Rubenstein and Merzenich 2003).

of this dance between heterogeneity of specific mechanisms and convergence upon various common pathways, it might be better to discontinue use of the word "disorder" and describe autism instead as a syndrome or condition, because these words do not so strongly prejudice the mind to expect (here inappropriately) a unified phenomenon with consistent underpinnings. Moreover, inconsistencies between studies regarding both genetic and metabolic findings would not exclude the relevance of such findings to subgroups of individuals in a syndrome construed as heterogeneous—i.e., lack of across-the-board relevance throughout a population does not exclude relevance for a subgroup.

Looking at the range of proposed contributors to processing perturbation, one can see mechanisms that occur at a range of time scales. Some of these seem fairly hard-wired, such as alteration of white matter anatomy, while others seem susceptible to modulation. Of those that are subject to modulation, some might respond in a short time scale (conceivably neurochemical or neuroimmune features susceptible to rapid alteration), some might respond in a medium time scale (e.g. improving synaptic function by remodeling membrane lipids via essential fatty acid supplementation, a process which might take a few months, or intensive retraining of a particular facet of cognitive processing) and some might take longer (e.g. more broadly based retraining of processing pathways through behavioral intervention, or volumetric alterations due to training). One sees a set of potential mechanisms ranging from neurochemical encephalopathy to alterations in brain architecture. Since the current candidates for mechanisms that could impact connectivity include modifiable as well as unmodifiable factors, one cannot exclude the possibility that autism is curable or treatable. Any one of these mechanisms might not constitute the single underlying defect in a given case—and would almost certainly not be present in every individual with autism; but improving that which is tractable may nevertheless yield a noticeable improvement in level of functioning and quality of life. The study of biological mechanisms of regression (e.g. through metabolic as well as behavioral tracking of at risk younger siblings of autistic children) may identify targets, as may the study of intra-individual variability in severity that is so common in autism.

The balance between special or unusual talents on the one hand and frank impairment and suffering on the other in any autistic individual is likely to be a function of the range of effects of the specific underlying mechanisms and genetic vulnerabilities in each case. Were we able to distinguish among such mechanisms and vulnerabilities we could not only target therapies and treatments more precisely, but we could decompose "autism" into a series of disorders defined at the biological as well as at the behavioral level. Careful attention to the biology of the comorbidities, as well as of the special talents blessing some with autism, may be critical in leading us to biomarkers identifying subgroups. For example, individuals less afflicted by chronic tissue changes might be better candidates for an exclusively behavioral approach, while in individuals with neuroinflammation or oxidative stress abnor-

malities the rate of acquisition of new skills from behavioral therapies might increase in the setting of antinflammatory and antioxidant therapy (Granpeesheh personal communication).

In the end the model that emerges from empirical findings is unlikely to be either exclusively either pervasive or localized, though both classes of findings can probably be encompassed together more easily in a systems framework. For example, primarily localized brain changes may in some cases be sufficient to lead to autism, but even systems-wide perturbations may have impacts that are greater in specific regions or functions, leading to a localization that while secondary still has a significant functional impact. The argument here is simply that at this juncture it is important to recognize that there are a number of models in the autism research community that may weight the plausibility of research hypotheses differently, and that although the "genetically influenced, systemic" model has had less time to build a track record, it should nevertheless be recognized as providing a rational basis for undertaking investigations and treatment trials at levels that until now have been less explored. This is also an argument for more intensive focus on the intermediary levels of mechanisms that lie between gene and brain. Expansion from a brain-based to a broader systems-organism biology perspective, and from a strongly genetic to a genetically influenced and gene-environment interaction perspective, can be promoted as critical moves in the search for explanatory and treatable disease mechanisms. Identification of such mechanisms is the path to identifying specific environmental influences and/or genetic predispositions, and is much more likely to lead to identification of subgroups than behavioral measures alone. Finally, and most importantly, these intermediary biological mechanisms are the levels at which there is a particularly good chance of identifying treatment targets that simultaneously address multiple features of autism at their root.

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